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# The *Lancet* Commission to reduce the global burden of sudden cardiac death: a call for multidisciplinary action

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**Despite major advancements in cardiovascular medicine, sudden cardiac death (SCD) continues to be an enormous medical and societal challenge, claiming millions of lives every year. Efforts to prevent SCD are hampered by imperfect risk prediction and inadequate solutions to specifically address arrhythmogenesis. Although resuscitation strategies have witnessed substantial evolution, there is a need to strengthen the organisation of community interventions and emergency medical systems across varied locations and health-care structures. With all the technological and medical advances of the 21st century, the fact that survival from sudden cardiac arrest (SCA) remains lower than 10% in most parts of the world is unacceptable. Recognising this urgent need, the *Lancet* Commission on SCD was constituted, bringing together 30 international experts in varied disciplines. Consistent progress in tackling SCD will require a completely revamped approach to SCD prevention, with wide-sweeping policy changes that will empower the development of both governmental and community-based programmes to maximise survival from SCA, and to comprehensively attend to survivors and decedents' families after the event. International collaborative efforts that maximally leverage and connect the expertise of various research organisations will need to be prioritised to properly address identified gaps. The Commission places substantial emphasis on the need to develop a multidisciplinary strategy that encompasses all aspects of SCD prevention and treatment. The Commission provides a critical assessment of the current scientific efforts in the field, and puts forth key recommendations to challenge, activate, and intensify efforts by both the scientific and global community with new directions, research, and innovation to reduce the burden of SCD worldwide.**

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## Introduction

Sudden death has always generated great interest in the medical and scientific communities and in the general population. The associated trauma from sudden cardiac death (SCD) is particularly difficult for the patients' relatives who seek an explanation for the unexpected and unexplained nature of the event and fear the possibility of a similar outcome for other members of the family. An athlete collapsing suddenly on the field grabs instant public and press attention; however, the bulk of sudden deaths occur more quietly in the general population, unseen and away from the media glare.

Although acute trauma or drug overdose can cause sudden death, the focus of this Commission is on natural sudden deaths due to cardiac causes, which is commonly termed sudden cardiac death. The challenge with a sudden cardiac arrest (SCA; covering both SCD and people who have survived SCA) is that it gives no time to prepare, often occurring unexpectedly and out of hospital, and, as a result, carries poor overall survival rates (mostly under 10%).[1] Such poor survival might explain the sense of futility that has usually prevailed regarding the problem of SCD. However, thanks to many years of persistent efforts by the scientific, medical, research, and public health community, we have made substantial progress towards improved prevention and early response strategies, with SCA survival rates reaching up to 80% in some specific settings.[2,3] Presumed SCD is thought to account for roughly half of all cardiac deaths and about 15–20% of overall mortality and is therefore a public health problem of considerable magnitude.[4–6] In approximately half of individuals, SCA might be the first manifestation of cardiovascular disease, occurring unexpectedly without warning.[7–9] The epidemiology of SCD is closely linked to that of coronary artery disease, which is responsible for nearly 70% of SCDs.[10] Despite a substantial decline in mortality due to coronary artery

### Key messages

1 Sudden cardiac death (SCD) involves a complex interplay of factors; therefore, an urgent call for a clinical multidisciplinary approach and international research collaboration are essential to address this global health issue. The development of specialised sudden cardiac arrest (SCA) care teams to ensure care, teaching, and research on SCD is required.
2 Well conducted, population-based registries of SCD should be created where possible in all parts of the world to drive research and affect public-health policy decisions. Long-term consistent growth and success can be easily obtained with the inclusion and engagement of policy makers, clinicians, first responders, and community leaders.
3 Beyond the traditional medium-term and long-term approach, additional research should be directed towards the development of short-term preventive strategies aiming to prevent SCD within the minutes, hours, and days before the event. Focused studies in large cohorts of recipients of implantable cardioverter defibrillators, with continuous rhythm monitoring from the devices, will provide a unique opportunity to understand the dynamic nature of SCD and any changes of impending arrhythmias.
4 Use of big data and deep learning approaches while encompassing emerging technologies applied to large-scale populations with rigorously defined SCD endpoints should be actively explored to develop novel prediction capabilities.
5 Access to genetic testing has to be expanded and made more affordable at a global level for better identification of people at risk and to uncover new disease mechanisms. Focused studies in pharmacogenomics and epigenetics among populations at risk for SCD will help to identify new targets for therapy and movement towards precision medicine.
6 Shifting from a one-size-fits-all approach to a more individualised approach within advanced resuscitation-care research, taking into consideration underlying cause and characteristics of the SCA and patients' responses to therapy, would provide opportunity for a more comprehensive, patient-centred approach.
7 Regionalised systems of care are imperative to ensure adequate triage of patients at the time of the out-of-hospital cardiac arrest to the most appropriate facility for the level of care required. The cost-effectiveness of bringing high-level SCA teams and technology to the site of the arrest needs further exploration.
8 Accessibility to automated external defibrillators (AEDs), as well as low-dose, high-frequency training on cardiopulmonary resuscitation (CPR) within the community can greatly improve community awareness and response. AEDs should be registered, accessible 24 h a day, linked directly to the emergency medical dispatch system, include geolocation, transmit the functional status of the device, and wirelessly transmit ongoing CPR performance to local paramedics and data systems. CPR training initiatives should integrate more innovative strategies, such as apps, large group-based social media events, virtual skills practice, and a potential implementation of obligatory mandates (eg, a requirement for secondary school graduation, driving licences, and when discharged from hospital).
9 Strengthening current autopsy practices with increased availability and practice in suspected SCDs (especially in people <50 years) can provide crucial data for at-risk families. Focused research on partial autopsy substitutes, such as post-mortem imaging, might better elucidate the value of these methods in identifying arrhythmic SCD.
10 Understanding the biological, neurological, and psychological foundation of the challenges faced by survivors of SCA must become a priority to facilitate the development of effective rehabilitation programmes targeted to survivors and their family and allow the best foundation for returning to a normal life.

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disease in the second half of the 20th century,[6] prevalence has increased, especially in low-income and middle-income countries (LMICs).[11]

Efforts to reduce the burden of SCD have focused on two main areas: prevention and resuscitation. Prevention involves trying to accurately predict SCA and instituting specific measures for high-risk individuals to pre-empt its occurrence. In addition to addressing arrhythmic risk specifically among patients known to have underlying structural or electrical heart diseases, coronary artery disease prevention itself (ie, primordial prevention) will probably have a clinically meaningful effect on SCA rates at the population level, as it is the main underlying cause. By contrast, resuscitation aims to improve survival after the event by promoting strategies, such as basic life support by lay responders, early activation of emergency response, high-quality cardiopulmonary resuscitation (CPR), and rapid defibrillation, through public-access, automated external defibrillation (AED) programmes.[12]

For organisational purposes, the different aspects of SCA can be broadly considered as those pertaining to before the event (ie, pre-SCA), around the event (ie, peri-SCA), and after the event (ie, post-SCA). However, these three categories represent a continuum rather than being fully distinct from each other. This categorisation can be conceptualised as a circle (figure 1), with one aspect merging into the other. For instance, post-SCA diagnostic testing and family screening is interwoven with pre-SCA prediction, whereas short-term prevention of SCA blends into peri-SCA resuscitative procedure.

In addition to these foundational aspects, there are additional important facets to consider, such as the psychological and economic effect of SCA, genetics, ethics, family support, and societal aspects. SCD is akin to a complex puzzle with numerous pieces, requiring a multidisciplinary approach to ensure substantial effect. Although different groups have focused on specific aspects of the SCA problem, a unified perspective and a clear path forward to reduce SCA-related mortality is needed. In this Commission we considered current guidelines from professional societies and the broader scientific evidence, providing careful appraisal of the present state of evidence, important knowledge gaps, and a roadmap ahead. While most SCD research to date has been carried out in high-income countries (HICs), the Commission aims to have a global scope, challenging data and practices within this reality. Therefore, we have incorporated a specific section on LMICs in which SCD poses an increased challenge due to a relative paucity of data and scarcity of resources. This Commission, overall, encompasses aspects of patient care, research, and education at both the individual and population level with the aim of ultimately reducing the burden of SCD and improving the quality of life for survivors.

## Defining SCD: moving from a presumed mode of death to a more precise definition

When studying any disease entity, a clear, uniform definition is important to ensure consistency in research and outcomes assessment. This Commission focuses on

SCD in children and adults. Sudden death occurring in infants, sometimes known as sudden unexplained death in infancy, is a different condition and will not be addressed here. Although the term SCD implies a fatal outcome, it is often used interchangeably with SCA in which both survivors and decedents would be included.

One of the difficult issues in SCD research has been the inability to have a clear, consistent phenotype across studies. The word sudden in SCD or SCA refers to a mode of death rather than a specific cardiac disease. An implied assumption by this nomenclature is that a death that occurs rapidly is caused by a lethal ventricular arrhythmia. Thus, strategies to identify, prevent, and treat ventricular arrhythmias should be effective in reducing mortality from SCD and SCA. In epidemiological and observational studies, deaths documented to have occurred within 1 h of being witnessed alive, are considered SCD, with a supposed high rate of arrhythmic origin.[13] However, autopsy-based research suggests that more than a third of sudden deaths occurring in the field could have a non-arrhythmic cause.[14] Comparatively, patients who survive to hospital admission and discharge are more likely to have had a primary arrhythmic cardiac cause (90%).[14,15] However, restricting studies to survivors introduces some bias, given the low survival rates from SCA.

Ideally, to have a clear phenotype of arrhythmic SCD and exclude non-arrhythmic causes with a high degree of confidence, every person with suspected SCD should be monitored at the time of their death and undergo comprehensive autopsy. However, this scenario is currently unrealistic. Definitions rely on a measure of clinical judgement or adjudication, with information on timing and the best available clinical information to eliminate the individuals that probably have a non-arrhythmic cause of death (figure 2). Such adjudication is prone to error and misclassification,[16] which is an important gap that needs to be addressed in SCD research. The different terms and definitions that have been commonly used in the domain of SCD research are presented (panel 1). Conventionally, the most frequently used definition for SCD is an out-of-hospital, sudden natural death presumed to be of cardiac cause (ie, without obvious extracardiac cause), occurring with a rapid, witnessed collapse within 1 h of symptoms onset, or within 24 h of last being seen in the usual state of health if unwitnessed.[13,17–21] The inclusion of unwitnessed deaths up to 24 h, which might help to reduce bias, introduces an even greater proportion of non-arrhythmic and non-cardiac deaths than the 1 h definition.[23]

The ideal definition of SCD should be a sudden natural death where non-cardiac causes have been excluded with confidence through use of methods such as comprehensive autopsy, toxicology, and cardiac monitoring. In the absence of such evaluation, conventionally defined SCD should be considered presumed SCD. However, most global SCD research uses such presumed SCD, which undoubtedly introduces heterogeneity due to the potential mix of cardiac and non-cardiac causes, making the identification of true risk markers and prediction difficult.

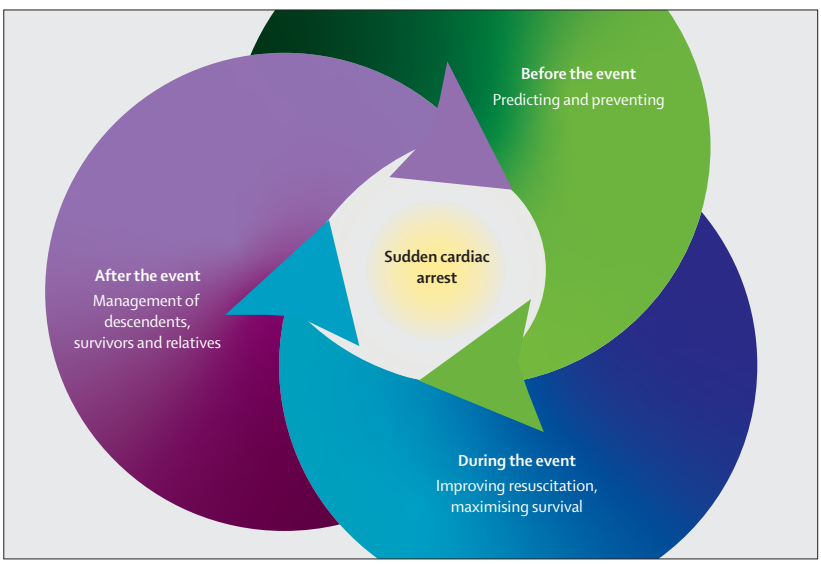


***Figure 1:*** **The circle of sudden cardiac death**
The different aspects of SCA can be broadly categorised as those pertaining to before the event, during the event, and after the event. Importantly, these issues are not distinct from each other, but represent a continuum with details from one category often merging with another (eg, post-SCA investigation is key to preventing future SCA in relatives, and rehabilitation after SCA is key for returning to a life akin to before the event). Thus, conceiving of SCA as a circle appears useful. SCA=sudden cardiac arrest.

## Burden of SCD

### Premature death from SCA

The estimated annual burden of SCD worldwide is currently 4–5 million cases every year.[24] SCD is responsible for more than half of all cardiac deaths and could account for up to 20% of overall mortality.[4,25–27] SCD results in a greater burden of premature death than any individual cancer in men or women across all age strata, with the overall mortality from SCD being second to all cancers together.[28]

In the Framingham Heart Study, SCD occurred in 358 (6·9%) of 5209 individuals aged 28–62 years over 50 years of follow-up.[6] In the Paris Prospective Study comprising middle-aged policemen, 118 (5·7%) of 2083 deaths were as a result of SCD over a period of 23 years.[29] The incidence rates of SCD range from 50 to 100 per 100 000 in the general European, Australian, and North American populations[17,30] and are slightly lower in Asia (data from Africa and South America are scarce; figure 3).[31–35] A substantial part of variations observed in SCD incidence arose from inherent differences in registry processes and definitions. Other factors, such as the socioeconomic status of populations, access to health care, risk factors for heart disease, age, sex, and ethnic background might also contribute, with a higher incidence observed in Black people than in White people.[36]

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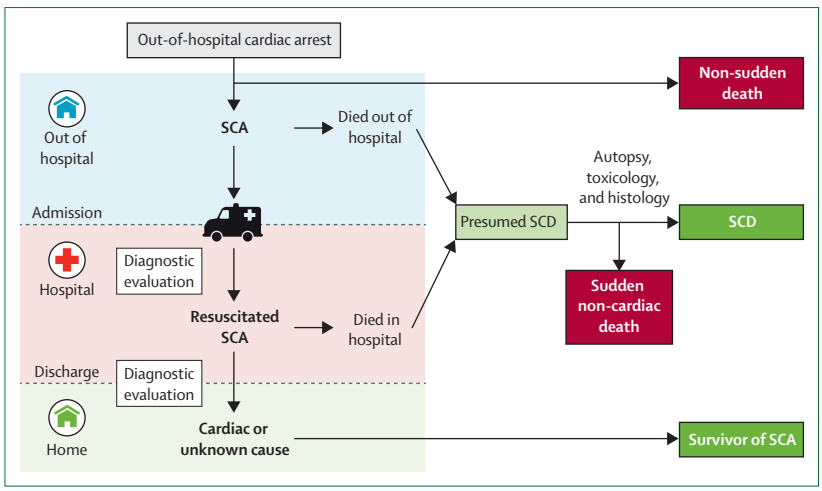


***Figure 2:*** **Challenges in differentiating sudden cardiac death from cardiac arrest**
SCDs defined entirely on adjudication could be considered as presumed SCDs because systematic misclassification of non-cardiac (eg, pulmonary embolism, acute cerebral haemorrhage, or occult overdose) and non-arrhythmic (eg, tamponade or acute pump failure) causes might occur. Comprehensive post-mortem investigation, including toxicology and histology, and even molecular autopsy have been proposed to more accurately define SCD by excluding non-cardiac and non-arrhythmic conditions. However, this proposal is not feasible in most parts of the world. SCA=sudden cardiac arrest. SCD=sudden cardiac death.

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***Panel 1:*** **Terms and definitions encountered in SCD research**[17–22]

**Sudden cardiac death (SCD)**
Sudden natural death presumed to be of cardiac cause, which occurs within 1 h of onset of symptoms when witnessed and within 24 h of last being seen alive when unwitnessed. SCD in autopsied individuals is defined as the natural unexpected death of unknown or cardiac cause.

**Sudden cardiac arrest (SCA)***
Sudden cessation of cardiac activity with haemodynamic collapse, typically due to sustained ventricular arrhythmia.

**Sudden arrhythmic death syndrome (SADS)†**
Unexplained sudden death occurring in an individual aged >1 year with negative pathological and toxicological assessment at autopsy.

*SCA covers both SCD and SCA survivors; in most literature to date, SCD includes SCA survivors if they are presumed to be of arrhythmic origin. Given potential misclassification in clinically defined SCD, the Commission recommends that sustained efforts be made worldwide to improve autopsy rates to more precisely identify SCD and develop clinical correlates to improve recognition of SCD. † When autopsy and toxicology do not reveal an alternative cause of death, SCD is unexplained and is then termed SADS. Molecular autopsy or genetic evaluation might reveal positive findings in some of these individuals.

The incidence of SCD increases with age. With a low incidence during infancy and childhood (1 per 100 000 person-years),[37–39] the incidence reaches approximately 50 per 100 000 person-years in individuals aged 50–60 years,[27,40] and 200 per 100 000 person-years in the eighth decade of life.[27] The median age of adult patients who have SCD is typically around 65–70 years.[41–43]

The epidemiology of SCD is closely related to that of coronary artery disease, which is responsible for most SCD, sharing the same important risk factors. In adulthood, men have roughly double the rate of SCD compared with women, which persists after adjustment for risk factors of coronary artery disease.[44–46] SCD most often occurs at the individual's home or residence, with cardiac arrests that occur in public places generally accounting for less than a third of cases.[41,42,47] Overall, SCD remains unwitnessed in up to 50% of cases, which poses major challenges for early resuscitation and for accurate assessment of SCD burden.[41,47,48]

A progressive decline in the incidence of out-of-hospital ventricular fibrillation and cardiac arrest treated by emergency medical services (EMS) has been noted in some areas, most likely mirroring the decline in deaths from coronary artery disease that is potentially attributable to improved lifestyle and better management of coronary artery disease.[48,49] However, because of the great increases in the prevalence of coronary artery disease in LMICs, there is a strong likelihood that the global SCD burden could increase in the near future.

## Disparities in outcomes from SCA

Although variations in incidence rates of SCA are, to a considerable extent, because of differences in definitions and surveillance methods for case ascertainment, disparities in outcomes (ie, neurological status and survival) after SCA are more certain and less likely to result from differences in data collection.

Studying geographical as well as temporal variations in SCA outcomes has been useful to realise that there is room for improvement (figure 3) and to understand key factors influencing survival.[47,50] An analysis of out-of-hospital cardiac arrest registries from 12 countries showed an overall survival to hospital discharge ranging from 6% to 22%, and survival with cerebral performance category of 1 or 2 (ie, good neurological outcomes) ranging from 2% to 20%.[51] In fact, although the overall survival from treated out-of-hospital cardiac arrest has improved over the years,[47,52,53] the percentage of SCA patients that are resuscitated and discharged in a good neurological state still differs greatly from country to country and even from region to region within the same country.[41,50,51,54] Survival also differs greatly depending on the SCA circumstances, with sports-related SCA getting up to 70% rate of survival to hospital discharge in ideal conditions,[3] but with huge disparities (up to ten-fold) in survival rates between geographical locations.[55] Successful resuscitation, especially early CPR, is more likely to occur in densely populated communities. Greater presence of first responders who can initiate immediate CPR, easier access to AEDs, shorter EMS and ambulance response times, and shorter distance to a hospital with expertise in post-resuscitation care of SCA patients all contribute to improved outcomes. Population education in basic life support, early activation of emergency response, and good lay-responder CPR have substantial impact on survival after

SCA.[56] Specific surveillance programmes, monitoring both incidence and outcomes of out-of-hospital cardiac arrest in the community, should be promoted to continuously track trends and evaluate the effect of population-level interventions and public health policies, as illustrated during the COVID-19 pandemic (panel 2).

## Before the event: predicting and preventing

Although straightforward in concept, knowledge gaps exist in accurate SCD prediction and specific preventive measures. SCD prevention can be conceptualised as a two-step approach: preventing the underlying cardiac disease causing the SCD event and preventing the actual SCD event itself among those with established heart disease. SCD prevention is also rendered difficult by the paradox in relative risk versus absolute event numbers. Although individuals with overt structural heart disease, especially those with a history of malignant ventricular arrhythmias, constitute the highest risk subgroup for SCD, these people represent a relatively small percentage of patients who have SCD in the population per year in absolute terms. Most SCD events occur in the general population in individuals without known heart disease (figure 4). Therefore, population-level approaches to studying SCD risk assessment are essential, although, in the final assessment, we need markers that are specific and unique for SCD risk at an individual level.

Therein lies the complexity of the challenge. Beyond the identification of an underlying heart condition, to ensure an accurate prediction of SCD risk, a combination of risk markers or tests (including genetics) will be required as opposed to a single marker or test. This requirement contrasts with the current method of relying almost exclusively on a single risk marker, left ventricular ejection fraction, to identify patients who might benefit from an implantable cardioverter defibrillator (ICD). Competing risk of alternative modes of mortality is also important to consider. The ICD only prevents arrhythmic SCD; thus, the mortality benefit from the ICD in any population depends not only on the absolute risk of SCD itself, but also on the proportion of deaths from SCD. Therefore, there is an urgent need to move beyond the left ventricular ejection fraction and develop multiparametric risk-assessment tools, including new markers to identify individuals at high risk of SCD and low risk of competing causes of mortality.

### *Panel 2*: Dynamic burden of sudden cardiac arrest (SCA) and need for real-time surveillance, illustrated by the COVID-19 pandemic

An association between the COVID-19 pandemic and increased rates of out-of-hospital cardiac arrest have been reported in several,[43,57–60] but not all[61–63] regions of the globe. Most studies were conducted in the emergency setting without detailed adjudication processes, and thus were focused on out-of-hospital cardiac arrest in general and not sudden cardiac death specifically. Direct effects of a COVID-19 infection, such as acute respiratory distress syndrome, can result in cardiac arrest if not rapidly treated. Cardiac arrest might also occur due to thromboembolism, direct cardiac injury, myocarditis, vascular inflammation, and arrhythmias. COVID-19 is prothrombotic and patients are at higher risk of myocardial infarction, stroke and pulmonary embolism, and acute heart failure than uninfected people, all of which can lead to SCA.[64] Meticulous analysis of patients with implantable cardioverter defibrillators during this period has not shown any increase, but rather a significant reduction in ventricular arrhythmias requiring device therapies, coinciding with measures of social isolation.[65] This finding, together with the relatively low proportion of actual COVID-19-positive patients among out-of-hospital cardiac arrest patients during the pandemic,[43,62,66] suggests that indirect effects of the pandemic might have had a considerable contribution to the increase in out-of-hospital cardiac arrest incidence. Fear of visiting hospitals prevented many patients from presenting to emergency departments or calling emergency medical services, with resultant delays in treating acute cardiovascular conditions, such as myocardial infarctions.[67–69] Furthermore, overwhelmed health-care and emergency medical services, shortages in in-hospital critical care resources, and protocol changes mandated by COVID-19 all led to delayed and suboptimal patient management, possibly contributing to worse survival. The significantly reduced increase in out-of-hospital cardiac arrest seen during the second wave of the pandemic further suggests that issues at the system and patient levels contributed more to the out-of-hospital cardiac arrest peak rather than the infection itself during the first wave.[60] Through the pandemic, we have learned that out-of-hospital cardiac arrest could actually be a valuable surrogate for population health and system efficacy in handling emerging crises similar to COVID-19 in the future.

### Predicting SCD

*Pathogenesis: from underlying cardiac disease to arrhythmia*

The commonly accepted confluence of factors in the occurrence of ventricular arrhythmias encompasses an underlying cardiac disease (ie, substrate), a transient factor (ie, trigger), and often a modulating role of the autonomic nervous system. Usual transient triggers include acute ischaemia, electrolyte imbalance, and drugs. However, although ventricular tachyarrhythmia is the classic mechanism of SCD, a gradual increase in the prevalence of patients presenting with initial pulseless electrical activity or asystole has been observed over the years, with implications for prevention with an ICD.[49,70–72]

The cause of SCD can be roughly divided into two major structural categories of heart disease, ischaemic and non-ischaemic, and a smaller non-structural category represented by pure electrical disorders, including the inherited arrhythmic diseases (figure 5).[73,74] Most SCD in the general population is attributable to coronary artery disease.[74] Non-ischaemic heart diseases include genetic

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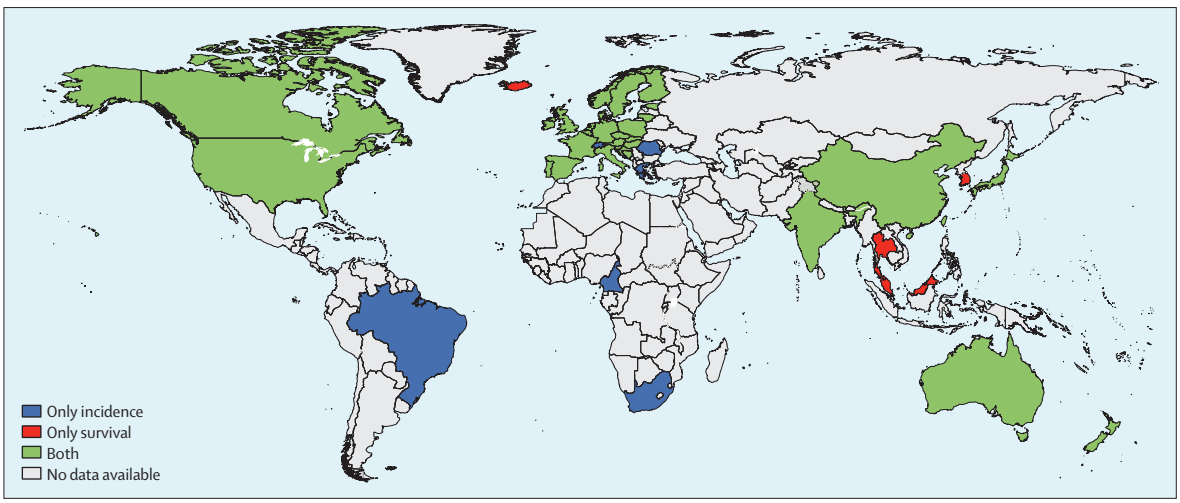


*Figure 3:* **Estimated incidence and survival at hospital discharge of paramedic-treated, out-of-hospital cardiac arrest**

cardiomyopathies, but also congenital heart disease and other acquired structural heart diseases, such as myocarditis and valvular heart disease (eg, mitral valve prolapse).[75,76]

SCD cause varies depending on sex and age, which needs to be kept in mind in prediction and prevention. Coronary artery disease is often overlooked as a cause of SCD in patients younger than 50 years, but should be considered in every case.[77–79] Generally, ischaemic cause is less prevalent among women compared with men of a similar age.[10,80] In younger patients (ie, aged <50 years), non-ischaemic structural heart diseases and channelopathies become more common, whereas left ventricular hypertrophy might account for a higher proportion of SCD among Black people than White people,[81,82] highlighting the need to delve deeper into causal differences related to age and ethnicity.[83]

Coronary artery disease-related SCD can occur in two ways: (1) acute ischaemia triggering polymorphic ventricular tachycardia or ventricular fibrillation; and (2) re-entrant arrhythmias related to scar formation secondary to previous infarction or chronic ischaemia.[80] There is variable overlap and interaction between these two mechanisms, with acute ischaemia acting as a trigger on a vulnerable substrate in some patients. SCA remains the most frequent fatal complication during the acute phase of a myocardial infarction. Additionally, population-based studies suggest that up to 40% of patients who have SCD have a myocardial infarction scar at autopsy without previous knowledge or diagnosis of the disease.[84] However, coronary-artery-disease-related SCD in the absence of myocardial scar does not necessarily imply coronary plaque disruption, because in a substantial proportion of patients there are no acute plaque events, but other myocardial pathology, such as hypertrophy and interstitial fibrosis, are found at autopsy.[85–89] Finally, another possible mechanism related to acute ischaemia might be triggered by vigorous physical exercise in a patient with severe coronary artery disease or coronary vasospasm.[78,79,84,90,91]

Non-ischaemic cardiomyopathies are partly genetically driven. Dilated, hypertrophic, and arrhythmogenic cardiomyopathies are the most well known cardiomyopathies.[92] However, hypertrophy is a common feature of most non-ischaemic cardiomyopathies and acquired conditions, such as hypertension, diabetes, kidney disease, and obesity, are the most common causes of hypertrophic heart disease leading to SCD rather than inherited hypertrophic cardiomyopathy.[73] Prominent hypertrophy and fibrosis are indeed present in most patients of SCD.[79,90] Dilated cardiomyopathy, a less common cause of SCD, can be because of various conditions, including infective, infiltrative, toxic, autoimmune, and genetic disorders.[93,94] Arrhythmogenic ventricular cardiomyopathy is a specific, inherited form of non-ischaemic cardiomyopathy related to defects in major components of the desmosomes.[95–97] Mitral valve prolapse is another example of non-ischaemic structural condition associated with SCD.[98]

Ion channelopathies, such as the long or short QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia, are rare causes of SCD in young adults (ie, aged <30 years) with a negative autopsy.[99] Idiopathic ventricular fibrillation is usually defined as ventricular fibrillation in the absence of any identifiable structural or electrical heart disease after extensive investigation;[100,101] however, diagnostic advances are likely to help recognise the cause in many of these patients and will reduce the scope of idiopathic ventricular fibrillation over time with new advances.[101–103]

### *Dynamic nature of SCD risk*

Underlying cardiac disease is often seen as a single, measurable factor in the mechanistic overview of SCD pathology and the currently used strategies for life-long prevention of SCD often take risk as a fixed variable.

However, cardiac disease is not a stable factor in the SCD cascade because the underlying substrate evolves over time, not only due to the progression or natural history of the disease process, but also due to modulating factors and therapies that can accelerate, reverse, or delay the progression of disease. For instance, the regression of electrocardiographic left ventricular hypertrophy by angiotensin-receptor blocker therapy has been shown to reduce SCD.[104] Similarly, in a stable cardiac substrate, the risk of arrhythmia could vary depending on other dynamic factors, such as circadian rhythm and environmental stressors (eg, pollution).[105]

*Predicting SCD in the general population*

Prediction of SCD in the general population without pre-existing heart disease has proven to be a daunting challenge. SCD is often a manifestation of previously undetected heart disease; therefore, strategies to prevent SCD in the general population should ideally identify people who have subclinical heart disease or cardiovascular risk factors for coronary artery disease to implement early preventive measures before SCD occurrence. Screening the asymptomatic population specifically for SCD risk is challenging at present, with no strong evidence that screening for cardiovascular disease reduces mortality because it is probably too late in the natural history to effectively intervene if cardiac disease is already established.[106] The US Preventive Services Task Force recommends against screening individuals at low risk in the population with a resting or exercise electrocardiogram (ECG) and concludes that, even in individuals at intermediate or high risk of cardiovascular diseases, there is insufficient evidence for screening.[107] Screening carries risks of anxiety, labelling, possible adverse effects of further invasive testing, and downstream effects on health-care systems and resources. However, there might be scope to consider screening for cardiovascular risk factors, especially starting at a younger age (eg, the third and fourth decades of life), which might have a long-term effect on reducing cardiovascular (including SCD) mortality. American College of Cardiology and the American Heart Association (AHA) guidelines recommend screening for traditional risk factors for atherosclerotic cardiovascular disease and apply the race-specific and sex-specific pooled cohort equations (ie, atherosclerotic cardiovascular disease risk estimator) to estimate 10-year atherosclerotic cardiovascular disease risk for asymptomatic adults aged 40–75 years. There are no recommendations from major societies regarding an approach to screening young individuals (ie, aged 18–40 years) at present, other than for hypertension;[108,109] we feel that such a strategy needs to be tested systematically in future studies. Although screening individuals at intermediate or high risk of cardiovascular disease is not unreasonable, further research is needed to test this concept. Ensuring that screening approaches are as simple and minimally invasive as possible is important to minimise potential harms of overtreatment, burdening health-care systems, and psychological effect. For instance, a simple screening strategy at a young age incorporating blood pressure, BMI assessment, and smoking status might have the potential to substantially impact cardiovascular risk in the long term.

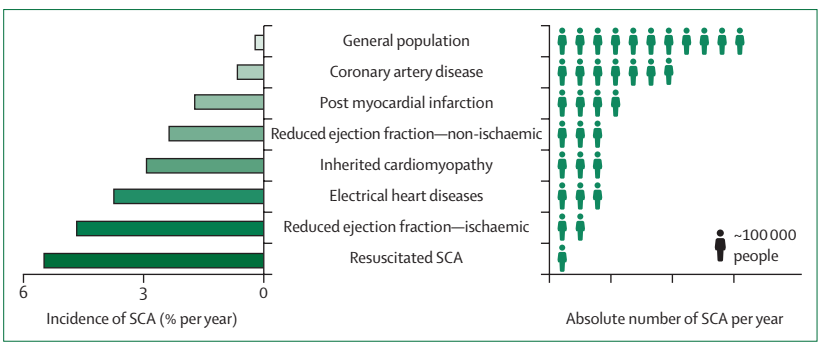


***Figure 4:*** **The epidemiological paradox in SCD: absolute risk *vs* absolute numbers**
SCD prevention is also rendered difficult by the paradox in risk versus absolute event numbers. Although individuals with overt structural heart disease, especially those with history of malignant ventricular arrhythmias, constitute the highest risk subgroup for SCD, in absolute terms these cases represent a relatively small percentage of patients who have SCD in the population per year. Most SCD events occur in the general population without known heart disease. SCA=sudden cardiac arrest. SCD=sudden cardiac death.

The fact that the usual risk factors associated with cardiovascular disease and progressive heart failure are also predictors of SCD is not surprising.[29] Similarly, biomarkers that associate with cardiovascular disease associate with SCD, even in patients without clinically recognised cardiovascular disease.[110] However, the accumulation of cardiovascular risk markers does not translate into large increments in absolute SCD risk. Most of the risk factors, ranging from genetics, clinical factors, and electrocardiographic abnormalities, are not independently powerful enough to justify the use of invasive interventions, such as the ICD.[111] Although risk scores might be useful to stratify the population, their utility for SCD prediction on an individual level is limited due to the low absolute risks of SCD, even at the highest scores and despite using a combination of multiple risk markers.[112,113] As such, novel methodologies and markers are needed for SCD-risk score development in the general population. The advent of big data and AI might confer the ability to identify subgroups of individuals at high risk of SCD by use of large-scale comprehensive analysis of SCD patients from national and administrative databases to identify markers and patterns associated specifically with SCD, which might enable preventive actions and initiatives, such as invitation for further cardiovascular screening in selected subgroups. For instance, a study showed that consumer smartwatch ECGs, acquired in non-clinical environments, can be helpful to identify patients with left ventricular dysfunction.[114] However, given the low prevalence of SCD in the general population, big data and artificial intelligence (AI) will not solve the

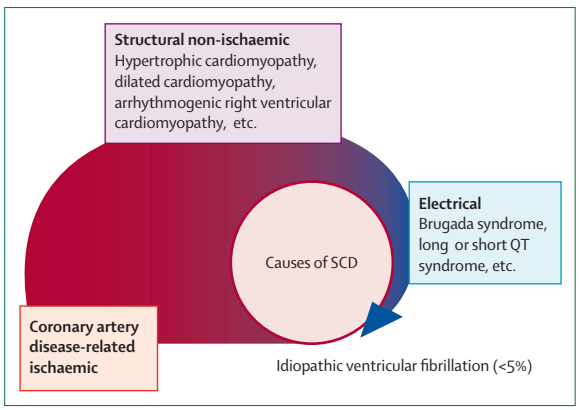


***Figure 5:*** **Spectrum of causes in SCD**
Causes underlying SCD comprise three main classes: ischaemic heart disease (eg, coronary artery disease), structural non-ischaemic heart disease (including genetic cardiomyopathies [eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, and arrhythmogenic cardiomyopathy], congenital heart disease, and other acquired structural heart diseases, such as myocarditis and valvular heart disease [eg, mitral valve prolapse]), and electrical non-structural disorders (eg, channelopathies), with idiopathic ventricular fibrillation forming a small proportion, progressively diminishing with scientific advancements, in which SCA remains unexplained after complete investigation. SCA=sudden cardiac arrest. SCD=sudden cardiac death.

issue of low positive predictive values of risk markers for events,[115] and large-scale monitoring of individuals involves large-scale ethical issues.

Although left ventricular systolic dysfunction is an advanced sign of extensive myocardial disease, the risk of lethal arrhythmias is increased even before substantial systolic dysfunction develops, with many studies showing the effect of myocardial fibrosis on the incidence of ventricular arrhythmias and SCD.[116,117] Myocardial imaging methods have greatly improved during the past decade and are able to identify even mild myocardial disease. The identification of easily obtained markers associated with subclinical myocardial disease would allow for targeted employment of novel imaging and other diagnostic methods to improve SCD risk stratification.

### *Predicting SCD in patients with established cardiovascular diseases*

The left ventricular ejection fraction remains the most universally used parameter for risk stratification in primary prevention for patients with ischaemic or non-ischaemic cardiomyopathy. However, with limited sensitivity and specificity, this parameter does not sufficiently capture the detail or the extent and characteristics of myocardial disease and is a better predictor of overall cardiovascular mortality than SCD specifically. Patients at high-risk, identified by the left ventricular ejection fraction, are also at high risk of other competing forms of cardiovascular death.[118] It is important to acknowledge that the left ventricular ejection fraction represents a continuum of risk and, therefore, a continuous risk-stratification approach is more appropriate than a dichotomous one.

Use of a cardiac MRI or other advanced imaging techniques for the detection of scar burden and type has emerged as an important risk marker with the potential to reclassify SCD risk more accurately into clinically meaningful risk categories compared with left ventricular ejection fraction alone. The absence of scar in non-ischaemic dilated cardiomyopathies identifies patients at low risk of sustained ventricular arrhythmias and SCD,[119–121] whereas scar burden and characteristics (eg, grey zone fibrosis representing transition zone between scar and viable myocardium) in ischaemic heart disease provides additional insight on SCD risk.[121–123] Indeed, in 2022, scar assessment by MRI was incorporated into guidelines for SCD risk assessment to delineate the SCD substrate at a finer degree beyond the gross assessment by left ventricular ejection fraction.[111] Randomised studies are also required to further assess whether a strategy of imaging-guided scar assessment and risk stratification can enhance SCD prevention. Indicators of myocardial scar from ECG, including newer developments such as QRS micro-fragmentation to improve precision beyond usual visual assessment, might also help enhance SCD risk prediction and deserve further study.[124,125] Considering cellular-level electrophysiological mechanisms might also be of importance. For instance, machine-learning assisted analysis of ventricular monophasic action potentials in ischaemic cardiomyopathy was seen to be useful in predicting sustained ventricular tachycardia and ventricular fibrillation.[126] The need to move towards a better and individualised risk prediction in patients with and without severely reduced left ventricular ejection fraction is being increasingly recognised and has spurred new efforts, such as the EU-funded Personalised Risk score for Implantation of Defibrillators (PROFID) project (NCT05665608). PROFID is a large European effort towards personalised prediction and prevention of SCD after myocardial infarction.[127]

For accurate prediction of SCD risk in patients with established heart disease, a combination of risk markers or tests are probably required as opposed to a single marker or test. Few scores have been introduced to identify patients at high risk of SCD. Most share the common issue of poor specificity for predicting SCD (ie, the inability to predict SCD specifically rather than overall mortality). A promising solution to address this issue might be the combination of scores designed to optimise patient selection for ICD therapy. For instance, the combined use of the Seattle Heart Failure Model and the Seattle Proportional Risk Model, containing routine clinical and laboratory variables, has been shown to better partition and quantify the treatment benefit from primary-prevention ICD therapy in patients with heart failure with reduced ejection fraction,[128–130] identifying subsets with large differences in both relative and absolute risk reduction. Other risk scores have also been proposed.[131–133]

Patients with ventricular tachycardia or ventricular fibrillation in the setting of acute ischaemia are typically

considered as having a reversible cause of SCA, with emphasis only on early revascularisation in current clinical practice. However, the future risk of SCD in such patients, the influence of the underlying substrate, such as myocardial fibrosis or hypertrophy and the time lag between myocardial infarction onset and ventricular fibrillation deserves further study. For instance, advanced myocardial imaging or genetic susceptibility might have a role in this context. Similarly, in conditions such as coronary vasospasm or myocarditis, which have been considered as potential indications for ICD implantation in European guidelines in 2022, the extent of reversibility and recurrence risk in the long-term need careful evaluation.[111] Additionally, in patients with coronary artery disease, great efforts have been made to distinguish vulnerable from stable coronary plaques, which could be a promising tool to help predict SCA in some patients. However, vulnerable plaques are associated with increased risk of myocardial infarction, but not necessarily SCD. Not all vulnerable plaque ruptures lead to myocardial infarction and not all myocardial infarction results in primary ventricular tachycardia. Better understanding of the mechanistic pathways from the vulnerable plaque to arrhythmia vulnerability is needed.

For certain non-ischaemic structural heart diseases, such as hypertrophic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy, specific multiparametric scores for risk stratification have been developed,[134–136] which are useful models to strive for in terms of improving specificity and individualising risk prediction in other conditions, including coronary artery disease.

### *Genetics for prediction of SCD*

In mendelian-inherited disorders, genetic testing can allow the identification of disease-causing variants, permitting the implementation of gene-specific preventive and therapeutic strategies and the identification and protection of affected family members through cascade screening.[137–139]

Conversely, the role of genetic testing in identifying patients at risk of common coronary artery disease-associated SCD is scarce at present. Having a family history of SCD is associated with an increased risk of dying suddenly,[29] both in the general population overall and among people with known coronary artery disease,[140,141] thereby suggesting a genetic predisposition. However, specific genetic makers for risk prediction are scarce in the setting of coronary artery disease, with some exceptions, such as familial hypercholesterolaemia, in which genetics has an important role in early diagnosis and therapy.[142]

Most of the studies performed to identify genetic variants favouring SCA in the general population assume that a sum of common genetic variants (ie, single nucleotide polymorphisms, which are alterations in a single base pair) with a small effect size is probably responsible for the genetic predisposition of SCA (figure 6A). Therefore, genome-wide association studies were performed with two main strategies: (1) directly looking for single

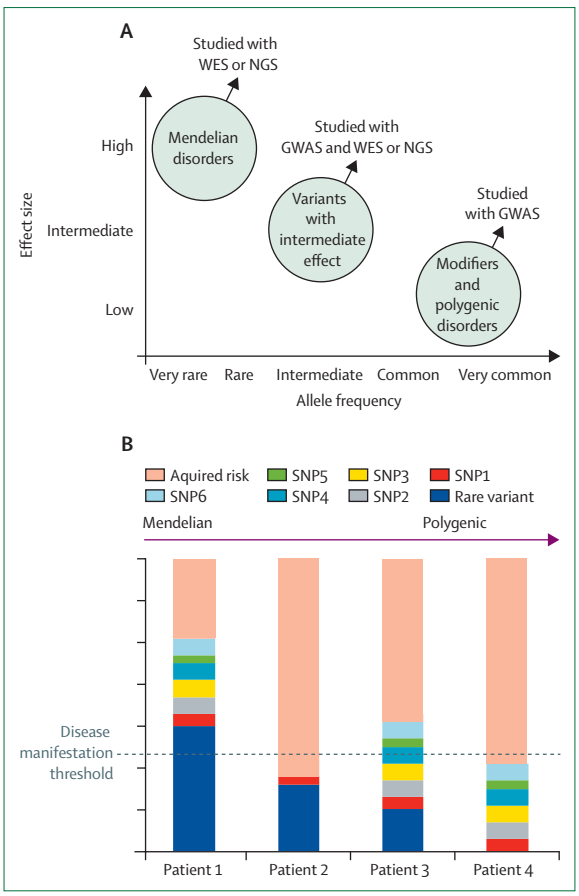


***Figure 6:*** **Genetics for prediction of SCD**
(A) Very rare variants with a strong effect size cause typical mendelian disorders. Such variants are identified with WES, WGS, or targeted NGS panels. On the opposite spectrum are polygenic disorders in which genetic predisposition is because of a sum of common genetic variants with a mild effect size. These common variants are usually identified with genome-wide association studies. Between these two extremes are conditions in which the phenotype is the result of the sum of rare and common variants. (B) Patient 1 has a rare variant with a strong effect size that, by itself, is able to cause the disease phenotype. In this patient, common genetic variants (SNPs) with a modifier role and acquired factors could act to influence the severity of the clinical manifestation (eg, a severe long QT syndrome mutation, such as the *KCNQ1*-A341V[143] or *CALM* mutation[144]). In patients 2 and 3, the patients have a rare variant with a strong effect that is, however, not strong enough to cause the disease phenotype by itself. The phenotype manifests only when acquired (patient 2) or common genetic factors with a small effect size (patient 3) are added (eg, a mild long QT syndrome mutation in which corrected QT prolongation and arrhythmic events occur only in the presence of hypokalaemia or QT-prolonging drugs). In patient 4, the phenotype is obtained with a sum of SNPs with small effect size and acquired factors (this patient could be a common SCD at the population level). Finally, SNPs could also have a protective role; therefore, there could be a patient (not represented in the figure) in whom the disease-causing variant could cause the phenotype by itself, but in the presence of protective SNPs the patient would not show the full phenotype. GWAS=genome-wide association studies. NGS=next-generation sequencing. SCD=sudden cardiac death. SNP=single nucleotide polymorphism. WES=whole-exome sequencing. WGS=whole-genome sequencing.

nucleotide polymorphisms in populations of patients with SCA (ie, cases) and without SCA (ie, controls);[145] and (2) searching for single nucleotide polymorphisms associated with risk markers of SCA and validating those single nucleotide polymorphisms in SCA cases versus controls.

The most difficult part of the first strategy is the collection of an adequate number of patients with SCA, the heterogeneity of the phenotype, and the identification of variants specific for SCA, beyond coronary artery disease. So far, the second strategy has mainly focused on the QT interval as a risk marker. Indeed, a prolonged corrected QT interval (QTc) is associated with an increased risk of SCA in patients with coronary artery disease,[146] therefore genetic variants associated with a prolonged QTc could favour SCA risk.

There are data regarding the use of genome-wide polygenic risk scores to identify individuals at high risk for coronary artery disease who can be targeted for intensive prevention efforts, which can indirectly translate into reduced SCA burden.[147,148] Although promising, the challenges to clinical translation include conclusively proving a significant, specific association of a group of variants to SCA, and having a big enough effect size for it to be clinically relevant given the multifactorial nature of SCA risk.[149]

In the past decade, the theory that mendelian disorders are always caused by very rare variants with a big effect size, and complex disorders are always caused by a sum of very common variants, each of them with a small effect size, has been questioned. Even if it is true that inherited channelopathies and cardiomyopathies are mainly monogenic, and SNPs might act by influencing clinical penetrance and severity (ie, modifier genes),[150,151] it has been recently described (eg, in Brugada syndrome) how the sum of modulating SNPs, included in the so-called polygenic risk score, could confer a large effect on disease susceptibility (figure 6B).[152,153] This observation supports the principle that common genetic variation might affect the susceptibility to a rare cardiac disorder previously assumed to be monogenic.

Just as mendelian disorders causing SCA might have a polygenic architecture in some patients,[154] it has been hypothesised and shown that SCA in the general population might occasionally be favoured by rare variants.[155,156] However, given that few SCA patients carry them, these variants can only identify a small proportion of at-risk patients.

Genetic data are not only useful to stratify SCD risk in certain conditions, but could also highlight new genes and pathways crucial to understanding SCD pathophysiology, posing the basis for the development of new and more effective therapies.[17,18,145,157,158]

The full picture might be comprehended only through a better understanding of all genetic, epigenetic, and environmental factors (including drugs) influencing SCD risk and their interplay. Genetics might influence not only drug response (ie, pharmacogenomics), but also the response to several other environmental factors that could altogether influence SCD risk. A key point to complete the picture is to have enough data from all ethnicities, because most ethnicities other than European ancestry are under-represented in genetic studies at present. Only collection of large-scale population data, both genetic and non-genetic, will move the field forward.

## Preventing SCD

Similar to prediction, SCD prevention can be envisaged in terms of reducing the burden of cardiac disease at a global level and specific prevention of SCD in different cardiac conditions. Broad interventions at a population level, such as smoking cessation and risk-factor modification for coronary artery disease, are likely to have a major impact on preventing SCD; advanced techniques, such as ICD, as currently applied, target only a small fraction of the overall population at risk and need further refinement (figure 7).

### *Lifestyle modification on a global level*

Standard risk factors for cardiovascular disease are potentially modifiable risk factors of SCD.[85,87,159,160] Emphasis on primordial prevention cannot be stressed enough and novel methods for motivating individuals to improve their cardiovascular health and fitness are required. SCD is the most striking manifestation of cardiac disease and acquires even more prominence when a celebrity has SCD. However, such tragic events are also opportunities to raise awareness among the general public through messages and videos in mass and social media to adopt heart-healthy lifestyles. A healthy diet, the cessation of smoking, and regular exercise can all reduce the risk of SCD. Additionally, although the effect of environment on SCD remains to be definitively determined, progressive urbanisation is associated with accumulation of environmental stressors. Heart-healthy city designs to address some of these stressors have been proposed. Novel urban concepts aiming to reduce private car use, promote public and active transportation with increased physical activity, and reducing $CO_2$ emissions have been proposed.[161,162] Future studies are needed to assess whether environmental measures affect SCD risk and how they interact over time with biological and traditional risk factors.

### *The role of drugs*

Pharmacotherapy to reduce SCD risk has been applied in two ways: those that modify underlying substrate and those that directly address arrhythmia. Ensuring appropriate use and adherence to therapies that address cardiovascular risk factors and coronary artery disease is important. Additionally, several drugs commonly used to treat heart failure improve cardiac remodelling and have shown a favourable effect on SCD that cannot be fully explained by any intrinsic antiarrhythmic properties.

Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and mineralocorticoid receptor

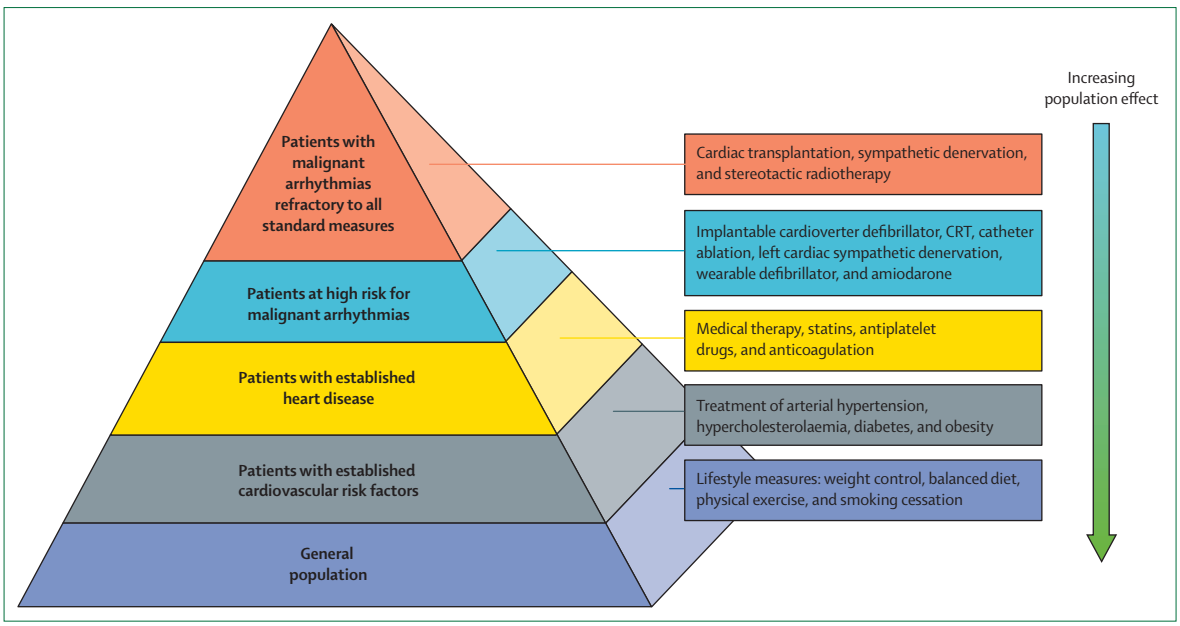


***Figure 7*: Different interventions to prevent SCD and current armamentarium to protect patients at high-risk from SCD**
The broadest interventions at the population level, such as global lifestyle measures to prevent coronary artery disease, will have the largest effect for preventing the largest number of SCD. As we move up the pyramid, advanced preventive measures (eg, implantable cardioverter defibrillator) target only a small fraction of patients at the highest risk. CRT=cardiac resynchronisation therapy. SCD=sudden cardiac death.

antagonists have been shown to improve left ventricular reverse remodelling, prevent heart failure deterioration, and improve survival (potentially with decreased SCD risk as well). Possible mechanisms include the inhibition of myocardial and vascular adverse remodelling, reduced collagen deposition and myocardial stiffness, modulation of nitric oxide synthesis, and prevention of hypokalaemia. The combination of neprilysin inhibition with an angiotensin II receptor blocker might further reduce the risk of SCD,[163] with studies showing that it reduces the burden of ventricular tachycardia, appropriate ICD shocks, and premature ventricular beats.[164]

β blockers are also effective in suppressing arrhythmia and reducing SCD in a spectrum of cardiac disorders.[165] SGLT2 inhibitors have broad-ranging effects in heart failure with both reduced and preserved ejection fraction and are associated with lower risk of new-onset atrial and ventricular arrhythmias as well as SCD in both diabetic and non-diabetic patients with heart disease.[166–168] Further studies are necessary to support this hypothesis and clarify underlying mechanisms. It is thought that statins have a modest beneficial effect on SCD, which is most likely the result of a reduction of acute coronary events complicated by arrhythmia.[169] Although it remains unclear whether statin therapy reduces the risk of arrhythmic death specifically, statin use has been associated with a reduction in the risk of appropriate ICD therapies in patients with both ischaemic and non-ischaemic cardiomyopathy.[170,171]

Antiarrhythmic therapy, such as amiodarone, is currently only indicated to treat symptomatic ventricular tachycardia, reduce the incidence of ICD shocks, and the risk of hospitalisation, but does not improve survival.[172,173] Conversely, the identification and removal of common precipitating factors for arrhythmia, such as QT-prolonging or bradycardia-inducing drugs, is also important. Existing antiarrhythmic drugs might find newer indications in other conditions, which needs further research and efforts to ensure their availability.[174,175] Some sodium-current blockers, such as mexiletine,[176] reduce risk in patients with type 3 long QT syndrome, whereas flecainide and ranolazine could potentially be of benefit.[177,178] Quinidine has specific beneficial effects in patients with Brugada syndrome.[179] There have been no major advances in conventional antiarrhythmic drugs, which requires prioritisation in future research. Although there has been some progress in therapies that prevent ventricular arrhythmias, including identification of novel targets, there is still an unmet need in this field.

### *The role of the ICD*

Large randomised trials have shown the benefits of the ICD in both primary and secondary prevention settings.[180–183] However, literature supporting the prophylactic use of the ICD in the primary prevention setting is worryingly outdated and warrants revalidation in the modern clinical context, especially considering the remarkable progress in pharmacotherapy of heart failure and advent of cardiac resynchronisation therapy.[184]

In the landmark primary-prevention ICD trials conducted in the late 1990s and early 2000s,[180,181] medical

### *Panel* 3: Clinical vignette 1: imperfections of current risk prediction

A cardiologist at a tertiary referral hospital sees two different patients. The first patient, Mr X, is a 46-year-old man who had a myocardial infarction 4 months before, has a left ventricular ejection fraction of 48%, and is relatively asymptomatic at present. On the basis of guidelines, in view of only mildly reduced left ventricular ejection fraction, the cardiologist appropriately advises him to continue optimal pharmacotherapy and lifestyle measures. The second patient, Mrs Y, is a 57-year-old woman with non-ischaemic dilated cardiomyopathy, left ventricular ejection fraction of 30%, is on heart-failure medications, has New York Heart Association class 2 symptoms, and had previously undergone implantation of a guideline-indicated primary-prevention implantable cardioverter defibrillator (ICD). Mr X collapsed suddenly 6 months later at a friend's house and was declared dead on arrival to hospital. Autopsy showed a left ventricular scar. Mrs Y is on regular follow-up for the past 10 years and has never had appropriate therapy from her ICD or documented ventricular arrhythmia on device interrogation. These patients illustrate the limitations of current guidelines based on left ventricular ejection fraction, in which some candidates at risk for sudden cardiac death would be missed, whereas some others implanted with an ICD would never receive therapy from it.

therapy was suboptimal compared with present times and resynchronisation was not used. In the 2016 DANISH trial,[184] which did not report an overall survival benefit with the ICD in non-ischaemic cardiomyopathy, compliance with guideline-directed medical therapy was very high and probably contributed to the observed absence of mortality reduction with the ICD. A progressive decline in the occurrence of SCD over the past two decades has been reported in patients with heart failure;[184] therefore, the absolute effect of ICD therapy has probably also diminished over the years. Furthermore, resynchronisation has been an important addition in the management of heart failure, which also reduces SCD risk through reverse left ventricular remodelling. Whether adding a defibrillator to resynchronisation confers additional mortality benefit is debatable, with no randomised comparisons of resynchronisation with and without associated defibrillator and cause of death analyses suggesting that SCD contributes to only a small proportion of the additional mortality observed in patients with resynchronisation alone.[185] The nature of the underlying substrate also matters, with patients with ischaemic heart disease more likely to derive additional benefit from defibrillation compared with non-ischaemic cardiomyopathy.[186] Hence, going forward, more work is needed to ensure that candidate selection for ICD targets those with the highest likelihood of benefit.[187]

Current selection criteria for the ICD are somewhat imperfect—on one hand, most recipients of ICDs never receive appropriate therapy, and on the other, many patients at high risk of SCD are not eligible for an ICD because their left ventricular ejection fraction exceeds 35% (panel 3).[188] This fact is important when considering the potential limitations of the ICD for primary prevention, including high cost, the inability to prevent ventricular arrhythmias, the morbidity and mortality associated with shocks, and the risk of device-related or lead-related complications.[189] Preferential use of the subcutaneous ICD to reduce risk of complications associated with intravascular leads might be considered in the future,[190] but more progress is needed for the development of novel, cheaper, and safer defibrillation devices, allowing concomitant cardiac pacing.[191]

The other important aspect is the issue of competing risks (figure 8), with many risk markers for SCD also being equally, or even more, predictive of non-sudden death, which might result in reduced benefit of the ICD (panel 4).[193] The benefit of the ICD also declines with increasing comorbidities (with a correspondingly increasing proportion of non-SCD mortality); for instance, patients in end-stage renal failure are very unlikely to derive a clinically meaningful survival benefit from the ICD.

Sex is also an important consideration, with studies showing that men are more likely to have SCD compared with women, because women have a lower susceptibility to ventricular arrhythmia and are less susceptible to sudden death at any age.[194] More research is needed to evaluate the magnitude of benefit of the primary-prevention ICD in women. Current evidence suggests that the primary-prevention ICD is most beneficial in relatively younger male patients (ie, aged <60 years) with ischaemic heart disease and no advanced comorbidities.[181,184]

Implantable cardioverter defibrillator and other cardiac implantable electronic devices have the potential to serve as a source of continuous monitoring, which could allow new insights into arrhythmogenesis and the ability to retest conventional markers of SCD risk in large cohorts of patients with implanted devices.[195,196] Longer battery lives or the development of rechargeable batteries would vastly improve the cost-effectiveness and reduce the risk of infection associated with the need for generator replacement. Use of the subcutaneous ICD, especially in younger, more physically active patients (ie, aged <40 years), is expected to increase over the next decade as sensitivity for the detection of ventricular fibrillation and ventricular tachycardia is enhanced and pacing ability is incorporated via a leadless approach. Other innovations for avoiding intravascular leads could be of great value in younger patients (ie, aged <40 years) in whom the conventional ICD can pose considerable morbidity in the long term. The results of an extravascular ICD with substernal lead, reported in 2022, could represent a novel solution in this regard while overcoming the limitation of no pacing with the subcutaneous ICD.[191] Optogenetics is an emerging

technology that enables modulation of electrical cellular function, which can be used to directly pace or defibrillate the heart with brief blue-light pulses. The fact that non-traumatic and pain-free optogenetic defibrillation in diseased human hearts is feasible with only epicardial illumination holds exciting possibilities for future clinical applications.[197]

*Other tools to prevent SCD*

Although catheter ablation of arrhythmia is theoretically appealing, there are limited circumstances under which ablation might prevent SCD. Pre-excitation syndrome, known as Wolff-Parkinson-White syndrome, is an example of a relatively rare cause of SCD that can be treated by catheter ablation. Other potential applications include idiopathic ventricular fibrillation triggered by premature ventricular complexes originating from the Purkinje fibres and premature ventricular complex-induced cardiomyopathy. Although prophylactic ventricular tachycardia ablation in ischaemic or non-ischaemic cardiomyopathy has not yet been conclusively shown to reduce SCD rates, ongoing research has shown some promising results in specific settings.[198–200]

Therapies directly targeting the autonomic nervous system might have an important role in the pre-emptive management of SCD. Neuromodulatory approaches, such as cardiac sympathetic denervation, have been proposed as useful adjunctive therapies for arrhythmic storms and recurrent ventricular tachycardia or ventricular fibrillation. Left cardiac sympathetic denervation is currently recognised as an option for the treatment of long QT syndrome and catecholaminergic polymorphic ventricular tachycardia,[111] and might also be of benefit in other cardiac conditions associated with a high propensity for lethal arrhythmias.[201,202] Anecdotal reports suggest substantial benefit in patients with hypertrophic or arrhythmogenic cardiomyopathy and patients after myocardial infarction at high risk for ventricular arrhythmias. Given the general safety of the procedure and potential cost-effectiveness, further studies evaluating the use of sympathetic denervation for prevention of SCD have to be pursued.

Newer technologies, such as the biological pacemaker to treat bradyarrhythmias, and biological substrate modification techniques, such as injecting exosomes to reduce ventricular scar, might bring about novel avenues for SCD prevention.[203] Immunotherapeutic strategies to reduce cardiac fibrosis, such as CAR T cells, might also be a novel alternative to conventional ablation.[204] In inherited conditions, genotype-guided risk stratification and treatment deserves further research and expansion. Genome editing with the CRISPR–Cas9 system is a particularly promising technique for targeted gene therapy, which could be of use in mendelian disorders.[205] This new technique can undoubtedly help us move towards personalised and precision medicine in the field of SCD.

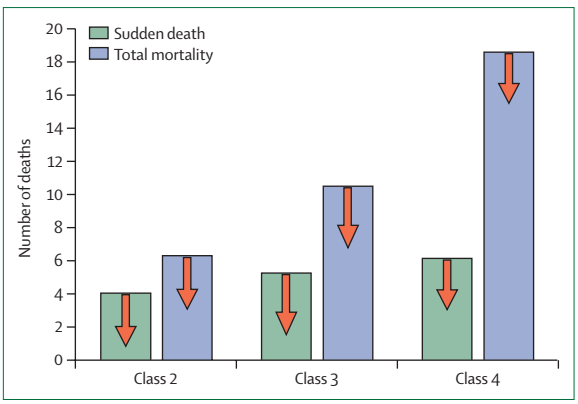


***Figure 8:*** **Understanding competing risk and the potential effect of SCD reduction by ICD on overall mortality by NYHA class in patients with heart failure**

The importance of considering competing and proportional risks of mortality in SCD prevention, illustrated by the 12-month mortality rate in the population of people with heart failure. Total mortality (blue bar) comprises non-arrhythmic cadiovascular death and non-cardiac death (neither are preventable by ICD). With increasing NYHA class, total mortality increases, but the proportion of SCD within the total mortality reduces (especially in class 4) due to an increase in other competing causes of mortality, such as progressive heart-failure death and non-cardiac death. Hence proportionate mortality reduction, achieved by the ICD (orange arrows), also reduces. Data obtained from MERIT-HF Study Group.[192] ICD=implantable cardioverter defibrillator. NYHA=New York Heart Association. SCD=sudden cardiac death.

***Panel 4:*** **Clinical vignette 2: competing risks**

A 68-year-old patient with severe renal dysfunction (on dialysis), atrial fibrillation, and ischaemic heart disease with a left ventricular ejection fraction of 25% received a transvenous implantable cardioverter defibrillator (ICD) for primary prevention of sudden cardiac death as indicated by guidelines. The patient was admitted to the intensive care unit 3 months later with severe sepsis and died after 1 week in the hospital. This patient illustrates the importance of competing risks for mortality in patients otherwise reaching criteria for ICD. Current guidelines recommend that there should be reasonable expectation of at least 1 year survival, which is rather subjective. These decisions require good clinical judgement and a multidisciplinary team approach.

Specific preventive measures depending on the underlying causes should always be considered in order to reduce SCD risk. Examples include the avoidance of extreme exertion in arrhythmogenic ventricular cardiomyopathy[96] and the use of immunosuppressive agents in cardiac sarcoidosis.[206,207] In channelopathies, specific measures, such as β blockers and sympathetic denervation for patients with long QT syndrome and catecholaminergic polymorphic ventricular tachycardia, mexiletine for patients with long QT 3, and hydroquinidine and aggressive fever management for patients with Brugada syndrome, have been shown to be beneficial.[174,177,208,209] As underlying mechanisms in specific diseases become better understood, new targets for drug therapy might emerge. Mavacamten, a myocardial

myosin inhibitor, has shown promise in reducing myocardial contractility and left ventricular outflow tract obstruction in hypertrophic cardiomyopathy and might have beneficial effects in reducing arrhythmia and SCD.[210]

In some conditions, such as with myocarditis, SCD risk is temporarily increased, but might come down with time. Alternatively, one might be in a waiting period, such as the early post-myocardial infarction period, initiation of medical therapy in a newly diagnosed cardiomyopathy, or a patient listed for heart transplant. Managing transient SCD risk in such situations is challenging because implanting a permanent transvenous ICD might be unnecessary in the long term (panel 5).

The wearable cardioverter defibrillator, or life vest, is increasingly being used in patients with a transiently increased SCD risk profile.[211–213] However, compliance is an issue with the use of the wearable cardioverter defibrillator and high rates of adherence are needed to ensure efficacy.[214] Smaller, less expensive defibrillation devices with enhanced sensitivity to detect ventricular fibrillation or ventricular tachycardia, designed to provide protection during transient periods of increased SCD risk, would be welcome in this context. The use of AEDs at home, with training on defibrillation and resuscitation provided to carers, needs to be further studied to evaluate the effectiveness in specific circumstances.[215] The potential psychological effect of prescribing a wearable cardioverter defibrillator or home AED programme on patients and caregivers needs careful consideration. Use of wearable cardioverter defibrillators could adversely affect mental health and contribute to anxiety and depression; however, studies suggest that depressive symptoms improve over time and many recipients feel safer and more confident with the protection afforded by the wearable cardioverter defibrillator.[216–218] Similarly, families of SCA survivors are generally well accepting of a home AED programme,[219] although there is some concern that it might contribute to persisting increased anxiety in caregivers such as spouses.[220]

**_Panel 5_: Clinical vignette 3: individualised risk and transient risk for sudden cardiac arrest**

A 47-year-old woman with urinary tract infection was seen by her family physician and prescribed ciprofloxacin. She collapsed in a shopping mall 2 days later and was resuscitated by paramedics with documented ventricular fibrillation. Investigations at hospital admission revealed a potassium measurement of 2·3 mEq/L and QTc prolongation (530 ms) on the ECG. After withdrawal of ciprofloxacin and potassium correction, QTc normalised to 380 ms. Molecular screening was performed and identified KCNE-D85N, a variant identified in 1% of the population, typically associated with acquired long QT syndrome. Identification of transient risk factors for QT prolongation in this case helped the managing team decide against implantable cardioverter defibrillator. The patient was advised to avoid QT-prolonging medications in the future.

*An alternative approach: short-term prevention*

Long-term SCD risk prediction has multiple limitations, including the difficulty in precisely identifying individuals at high risk, the issue of competing risk, and the imperfect technologies (eg, ICDs) used for prevention. Research efforts have focused on medium-term to long-term SCD risk on the presumption that prevention close to or around the event is not possible. However, SCD is not always completely unheralded or unexpected.[221] Approximately half of patients who have SCD report intermittent warning symptoms preceding the cardiac arrest in the minutes or hours before the actual event.[222,223] Most do not call emergency services to report these warning symptoms, but those who do show vastly improved rates of survival.[223] Thus, timely identification of individuals at high risk in the minutes, hours, or days preceding SCD with immediate pre-emptive action might be possible, opening up a potentially new framework of short-term prediction and prevention.[224] For instance, multiple clinical parameters have been shown to predict patients at high risk of SCD relating to ST elevation myocardial infarction before hospital admission (eg, younger age [<50 years], absence of obesity and diabetes mellitus, and shortness of breath),[225] which can lead to the identification of a subgroup of patients with a high probability of experiencing SCD. Such early information can be used to urge rapid responses by EMS, increasing the chances of a cardiac arrest being witnessed by EMS, or could be potentially used in the future to alert nearby lay responders via apps designed for that purpose.

We currently have limited knowledge on the exact role of transient ECG changes or non-sustained arrhythmias before SCA. Innovations in cardiac rhythm evaluation, including monitoring with mobile devices, have emerged over the past several years and could provide important insight into immediate precursors of fatal arrhythmias. Wearable ambulatory sensors have the potential to provide alerts based on ST segment or T wave changes for myocardial ischaemia or infarction,[226] and for arrhythmic events based on transient tachyarrhythmias detected by ECG.[227] Mobile devices with geolocalisation capability in conjunction with wearable sensors can help acquire timely data with immediate triggering of emergency intervention.[228] Automation of data interpretation through artificial intelligence (AI) will be crucial to deal with the large amount of information generated, but there is already some preliminary evidence that such timely data acquisition along with AI-based interpretation might allow for short-term prediction of SCA.[229,230] A single centre study showed that artificial neural networks generated with 14 parameters obtained from heart rate variability and respiratory-rate

variability analysis could predict ventricular tachycardia 1 h before occurrence with reasonable sensitivity and specificity.[230] However, AI and machine learning are subject to limitations of overfitting, data imbalance, and unreliable performance in the setting of data errors. Hence further, carefully conducted studies are required to determine the utility of such modern technologies for these and other potential scenarios.[231]

### Summary and future directions for better SCD prediction and prevention

Preventing SCD requires thorough knowledge of its underlying causes and the mechanisms leading to the final arrhythmia cascade, which involve a complex interplay of the substrate and modifying factors or triggers. Major gaps in SCD risk prediction and stratification exist, with an urgent need to have robust risk markers other than left ventricular ejection fraction. Markers, such as myocardial scar burden, scar type, and multiparametric risk scores, need further study and validation before they can be translated to the clinical arena. Additionally, future studies should consider dynamic risk and competing risk to identify the best high-yield risk indicators. Although genetic assessment is effective for monogenic conditions, our understanding of genetic risk for common SCD is still poor; large registries and multicentre collaborations will help to advance and move the field toward a more comprehensive approach that combines genotype, phenotype, and environment. Although specific risk markers that predict SCD beyond coronary artery disease will undoubtedly be valuable, SCD prevention begins at a global level with emphasis on lifestyle and overall cardiovascular disease prevention, which will then translate into meaningful reductions in SCD incidence. Impressive advances in heart-failure pharmacotherapy have reduced mortality, including SCD; however, novel therapeutics specifically addressing arrhythmia and thereby preventing SCD are an unmet need. The ICD has been at the centre of targeted efforts to prevent SCD, but gaps exist in selecting the ideal candidate for primary prevention and reducing morbidity from this therapy. New studies reassessing thresholds for the primary-prevention ICD in the current era of heart-failure pharmacotherapy are required. Catheter ablation and autonomic modulation might be valuable to prevent SCD in selected circumstances and further studies are needed to assess their efficacy for this purpose. Keeping in mind the limitations of long-term prediction for SCD, alternative frameworks, such as short-term prevention aiming to pre-empt SCD immediately before its occurrence, need to be systematically researched. Emerging technologies in varied disciplines, including genetics, AI, wearable sensors, and big data, will need to be carefully leveraged in the next decade to achieve an effective reduction in SCD burden at the population level (panel 6).

***Panel 6*: Recommendations for prediction and prevention**

- Directed studies on the identification of easily accessible surrogates that identify sudden cardiac deaths (SCDs) with a high likelihood of having an underlying cardiac arrhythmic cause can lead to improved precision of the SCD definition in large-scale population-based research.
- Comprehensive evaluation of SCD risk linked to myocardial scar, especially the importance of scar burden and heterogeneity, including border zones and channels, should be explored to further identify a useful risk marker.
- In-depth research into arrhythmia vulnerability in the setting of acute ischaemia should be strongly encouraged for a better understanding of the pathway from vulnerable plaque to myocardial infarction, and myocardial infarction to arrhythmogenesis and SCD.
- Testing of new SCD risk markers should consider the competing risk from non-SCD mortality and the proportional risk from SCD within the total mortality in a given population. The ideal SCD risk marker would be one that has specific predictivity for SCD and low or no association with non-SCD mortality.
- Established multiparametric risk scores combining variables encompassing both structural and electrical risk markers need to be developed and tested rigorously in various populations to increase the probability of identifying an adequate SCD risk marker.
- Widespread implementation of genetic analysis will provide early diagnosis of monogenic conditions and enable active exploration of polygenic risk scores for SCD related to coronary artery disease and other common heart diseases.
- Identifying and treating modifiable cardiovascular risk factors starting at early adulthood to reduce long-term SCD risk at individual and population levels should use a multidisciplinary approach to ensure full-range solutions.
- Assessing the magnitude of efficacy of the primary-prevention implantable cardioverter defibrillator (ICD) should be priority in the current era of heart failure pharmacotherapy, as well as a closer look at biological therapies aimed towards reducing myocardial fibrosis.
- Comprehensive research into novel defibrillation devices with extending battery longevity or that are rechargeable transcutaneously should be prioritised and innovations, such as optogenetic technology, should be actively pursued.
- Neuromodulatory approaches for SCD prevention, including sympathetic denervation, should be researched in well conducted trials to expand their applicability, including, as a potential one-time solution, an alternative to ICD insertion, especially in resource-constrained settings.

## During the event: improving resuscitation, maximising survival

Patients experiencing SCA continue to have an unacceptably low chance of survival. Efforts to improve survival should be multidisciplinary. To survive an SCA

event and to have the best possible outcome, a person needs the involvement of lay responders, telecommunicators, emergency medical service personnel, physicians, nurses, technicians, social workers, physiotherapists, family members, caregivers, etc. The Utstein Style is a set of guidelines for uniform reporting of cardiac arrest, first proposed for EMS in 1991,[232] endorsed by the international resuscitation community, to facilitate and structure resuscitation research and publication. During the intervening years, resuscitation science has advanced considerably and the Utstein Style has been revised.

Survival from SCA depends on a sequence of time-sensitive interventions known as the chain of survival, consisting of six interconnected links (figure 9A): (1) immediate recognition of SCA and activation of the emergency response system; (2) high-quality CPR, including telecommunicator-assisted resuscitation; (3) rapid defibrillation; (4) advanced resuscitation; (5) post cardiac-arrest care; and (6) rehabilitation and recovery.[233] The biggest effect on survival can be seen through the first to third links in the chain, affecting the greatest number of SCA patients (activation of emergency response, high-quality CPR, and early defibrillation; figure 9B). However, the research funding does not necessarily correlate with effect on survival (figure 9C) and focuses primarily on advanced resuscitation care and hospital interventions that affect a small number of patients.[235]

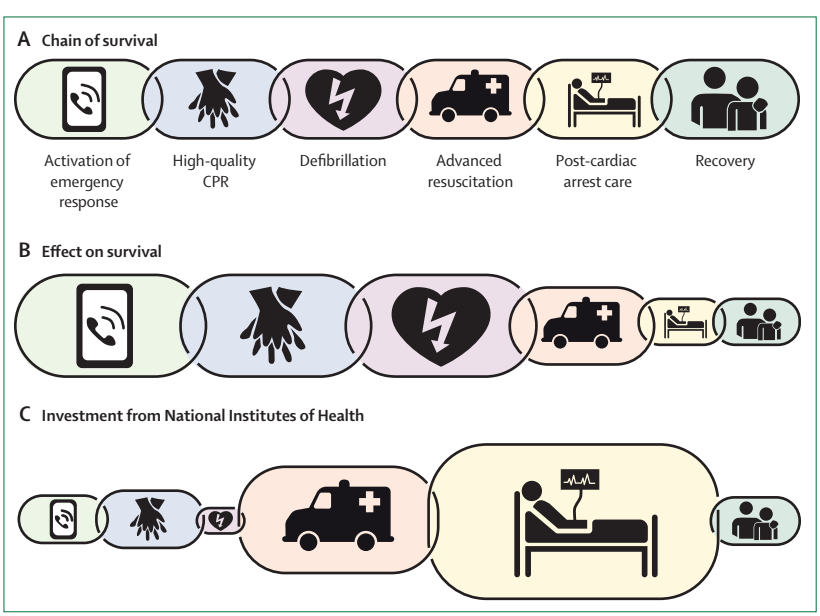


*Figure 9:* **Evaluation of SCA research funding based on chain-of-survival links**
(A) Out-of-hospital cardiac arrest chain of survival with activation of emergency response and lay-responder CPR combined into a single first link. (B) The relative effect of the individual links in the chain of survival. The size of each link represents the relative odds of survival published for each intervention. (C) National Institutes of Health research investment into chain-of-survival links. The size of each link correlates to relative number of grants awarded between financial year 2017 and 2021. Adapted with permission from Merchant et al[233] and Coute et al.[234] SCA=sudden cardiac arrest. CPR=cardiopulmonary resuscitation.

There are common epidemiological characteristics of SCA patients across countries and regions. Many of these characteristics contribute to the challenges faced by EMS and governments in implementing interventions and strategies aimed at improving outcomes. Importantly, the location of SCA is most often the patient's home, with arrests occurring in public places in fewer than 30% of events attended by EMS.[35,41,42] There are well established system factors that contribute to improved survival, including lay-responder CPR, rapid defibrillation, and short response times by EMS.[236] Individual factors include witnessed arrest, public location, younger age, and presence of comorbidities. Most survivors are patients found in ventricular fibrillation or pulseless ventricular tachycardia, and many factors that predict the likelihood of presenting in shockable rhythm are strongly aligned with survival.[1,237,238] Although incremental improvements in survival over time have been observed,[53] it has become clear that to substantially improve outcomes, a new multilevel, multidisciplinary approach is required. The Utstein group, a group of experts in resuscitation science, has proposed a formula for survival: medical science × educational efficiency × local implementation=survival.[239] Medical science includes research in SCA prevention, resuscitation, and care after arrest. Educational efficiency balances the need for training as many people as possible on resuscitation, with the latest technology and high-frequency, low-dose training methods, while keeping the messaging simple and broadly applicable.[240] Local implementation, which is the most challenging to achieve, is translating evidence-based SCA guidelines into each area with bespoke strategies. We propose key initiatives to improve outcomes after SCA, broadly categorised as individual level, resuscitation-health-system level, and community level, which, if implemented equitably and consistently, could lead to transformational change in SCA survival globally.

## Individual level interventions

Large, pragmatic, multicentre studies have evaluated some common SCA practices, from initial resuscitation with chest compressions and ventilations,[241] to advanced life support including intravenous drug administration,[242,243] and in-hospital intensive care comparing different temperature-management strategies.[244] These trials assessed the overall effect we can expect from current resuscitation practices when applied to real-life settings and show that current SCA interventions are not largely effective one-size-fits-all strategies. However, wide inclusion criteria in studies, heterogeneous patient populations, and large confidence intervals in terms of quality and timing of interventions might have hidden important yields in specific settings or patient populations. Patient-level interventions to improve outcomes for patients of SCA need to be tailored to the individual, taking into consideration underlying cause and characteristics of

the SCA and the patient's response to therapy. Therapies shown to have modest effect in large, pragmatic, randomised controlled trials might need to be re-evaluated in the setting of titrated and individualised medicine.

For any treatment to be effective for an individual having SCA it needs to: (1) be delivered before there is irreversible organ damage, (2) reach its intended target (ie, a drug needs a functioning route of administration), and (3) be supported by other aspects of life support to maintain a minimum of organ perfusion and oxygenation. During resuscitation, these prerequisites might be hard to ensure.

### *Compressions and ventilation quality*

High-quality CPR includes both effective ventilations and chest compressions with adequate depth, complete recoil, optimal rate, and minimal pauses. The importance of high-quality resuscitation is highlighted in international consensuses and guidelines, but current recommendations are still almost exclusively limited to metrics that focus on rescuer performance rather than the tailoring of actual technique to the patient being resuscitated.[245]

Mechanical CPR provides standardised support, but has not in itself been shown to improve survival compared with manual resuscitation in randomised controlled trials.[246] Despite the absence of evidence that these devices increase survival, mechanical devices have been widely implemented in many EMS systems. Because the quality of manual resuscitation during ambulance transport is severely compromised, there is an important role for ongoing mechanical CPR during transportation to further advance in-hospital treatment for some patients.[247]

Recommending standard compression and ventilation rates to all adults without considering important variations in patient size, anatomy, or underlying causes will inevitably lead to suboptimal resuscitation for every non-average patient. In more advanced clinical and experimental settings, efforts have been made to explore more tailored resuscitation. One example of a strategy that has been explored is individualising the hand position during chest compressions. Imaging studies suggest there might not be one optimal hand position as there are important variations in cardiac anatomy with sex, obesity, and cardiac disease,[248,249] and compressions delivered at the standard hand position might compress the left ventricular outflow tract in a substantial proportion of SCA patients.[250] Pilot studies evaluating variations in hand position during chest compressions by recording concurrent changes in blood pressure or end-tidal $CO_2$, which is considered an imperfect surrogate measure for cardiac output in the SCA setting, suggest there are clinically relevant variations in optimal compression sites between patients.[35,251–253]

Another example of individualised resuscitation that has been extensively tested on animals is haemodynamic-directed resuscitation in which the depth of chest compression and vasopressor doses are titrated to achieve improved coronary-perfusion pressure or diastolic blood pressures.[254,255] This concept is supported by observational data showing a correlation between higher diastolic blood pressure and favourable survival in a paediatric population resuscitated in cardiac arrest centres where haemodynamic-directed CPR was practised.[256]

Although these are preliminary, exploratory studies, they might provide important insights into how to improve outcomes through improving resuscitation quality and individualising resuscitation strategies. New technology, pairing traditional quality metrics with organ perfusion, might be key to improving patient outcomes through improving delivery. Real-time feedback during resuscitation, either in the form of audio–visual feedback with verbal prompts or a visual indication of compression depth and frequency, could also be a useful strategy to improve resuscitation quality by lay responders and for EMS by increasing cardiac compression fraction and decreasing the duration of long non-shock pauses.[257,258] However, currently there is no clear evidence that such feedback improves patient outcomes.

Future feedback devices incorporating patient signals reflecting general or cerebral perfusion (eg, capnography, near-infrared spectroscopy, or electroencephalogram [EEG]) could direct rescuer CPR personalised to the patient's physiological response. Personalisation could include adjusting hand or body position or compression depth and rate. Mechanical resuscitation is currently used as an alternative to manual resuscitation in many settings. Although these devices have not been shown to improve outcomes by providing standardised compressions, mechanical resuscitation devices might prove to be more effective if guided by individual physiological patient responses. Development of novel monitoring technology with more precise physiological signals could represent important advances in providing more effective resuscitation.

### *New defibrillation strategies*

There has been renewed interest in optimising first-shock success through novel defibrillation techniques and several new strategies are being explored. A randomised control trial in 2022 showed surprisingly high improvement in survival with double sequential defibrillation, in which two separate defibrillators are used on the same patient delivering rapid sequential shocks through both standard and anterior–posterior pad positions.[259] The trial was stopped early due to COVID-19 restrictions, but reported more than twice as many survivors to hospital discharge in the intervention group compared with standard treatment. Although the resuscitation community is enthusiastically debating the limitations and consequences of the study, there is renewed hope that both novel defibrillation strategies

and improved focus on optimal defibrillator pad placement can have an impact on cardiac arrest outcomes.

Chest compressions cause disturbances in the ECG signal and standard practice is to pause compressions for signal analysis. Development of new signal-filtering techniques have allowed for defibrillators to accurately analyse the ECG signal without pausing chest compressions. Although these filter techniques have been implemented into clinical practice, there is scarce research evaluating their usefulness. An observational before-and-after study in 2021 was the first to observe fewer pauses in chest compressions after implementation of new defibrillators with filtered rhythm analysis, but the study did not report any survival outcomes.[260] Although the effect of these filtering techniques on cardiac arrest survival has yet to be shown, this technological advancement could prove useful in future strategies exploiting information hidden in the ECG signal to develop more individualised approaches to resuscitation.

Signal analysis of the ventricular fibrillation amplitude spectral area is an example of a novel defibrillation

***Panel 7:*** **National case studies**

**Japan: National Utstein Registry**

Japan represents a unique model of a population-based national registry of out-of-hospital cardiac arrest (since 2005) in combination with continuous improvements of the emergency-medical-services system and survival after out-of-hospital cardiac arrest. Across Japan, all municipal governments provide a uniform emergency-medical-services system through fire departments that contain a dispatch centre. Dispatched emergency medical personnel includes at least one emergency life-saving technician who is trained to provide minimum advanced measures, such as intravenous access, advanced ventilation devices, and defibrillation. Furthermore, the number of public-access AEDs increased yearly and reached approximately 670 000 (5·3 per 1000 people) in 2021. Nationwide, intensive CPR training and education has been implemented by the municipal fire departments, through mandatory school CPR and AED training programmes in secondary education, and is required when obtaining a driving licence. As a result, in public locations, such as stations, schools, or sports facilities, approximately 70% of out-of-hospital cardiac arrest cases were shocked by public-access AEDs.[274,275] Continuous improvements of the emergency-medical-services system, such as shortening the time to defibrillation by emergency medical personnel and incremental increases in CPR rate and lay-responder shocks with public-access AEDs, led to 2·5-times nationwide improvement of favourable neurological outcomes (from 10·1% to 24·9%) in witnessed ventricular fibrillation out-of-hospital cardiac arrest and 2·1-times (from 2·4% to 5·1%) in witnessed out-of-hospital cardiac arrest of medical origin.[276,277]

**The Netherlands: citizen CPR and public-access defibrillation**

The Netherlands shows that the response before hospital by the public and first responders can make a true difference. With continuous public campaigns of traditional classroom CPR training, CPR rates before the arrival of EMS in the Netherlands have been high for decades (>50% in the late 90s, rising to >77% in 2017).[41] To shorten the time to defibrillation, since 2009, a professional first responder (ie, firefighter or police officer) equipped with an AED (known as dispatched AED) and qualified to perform basic life support is sent to suspected out-of-hospital cardiac arrest cases in addition to EMS. Also, since 2010, several regional systems were set up to additionally dispatch volunteer responders to either go to the patient directly or to a publicly accessible AED in the vicinity of the patient to initiate resuscitation—a system that was deployed nationwide in 2018.[278] Being the first to bring the defibrillator to the patient has now become a friendly competition between police, firefighters, dispatched volunteer responders, and EMS. A striking result of these efforts is the increasing use of AEDs: nowadays, in 60% of resuscitations for out-of-hospital cardiac arrest, an AED was attached before the arrival of EMS, which has proved to be highly effective. Survival in patients with a shockable initial rhythm had increased from 29% to 41% during a 7-year period, at least partly explained by the increased use of AEDs from 21% to 59%.[279] Implementation of the volunteer responder system is associated with reduced time to first defibrillation, increased lay-responder CPR (to 91%), and increased overall survival for out-of-hospital cardiac arrest patients in residences found in ventricular fibrillation.[280]

**Singapore: technology to save lives**

In Singapore, the technology used to alert responders is taken one step further. The myResponder app that was launched as part of the Save-a-Life initiative in 2015 not only notifies community lay responders of suspected SCAs and AED locations within 400 m,[281] but also allows users to activate EMS. This notification can reduce response time because geolocation data of the SCA can be sent directly to EMS. Volunteers are equipped with a device known as a CPRcard for feedback on CPR quality, which is placed on the chest and uses lights to indicate when the correct compression depth and rate are reached. Further enhancement of the initiative involved partnerships with taxi companies to equip taxis with AEDs. Drivers of AED-equipped taxis are notified via the myResponder app of suspected SCAs within 2 km of their location. 4 years after the initiation of Save-a-Life there had been 125 145 downloads with 46 689 registered responders. The number of registered responders in 2022 was over 111 000. The proportion of community responders who accepted notification showed an increasing trend from 11·2% in 2015 to 45·8% in 2019, and the proportion of responders who arrived at the scene of the SCA increased from 5·7% in 2015 to 24·1% in 2019.[282]

strategy in which new filtering techniques allow continuous signal-morphology analysis during chest compressions. Amplitude spectral area is predictive of whether an electrical shock can terminate ventricular fibrillation and prompt return of spontaneous circulation, offering an opportunity to tailor defibrillation therapy to individual response.[261] Current practice is to continue to shock ventricular fibrillation at set time intervals with the goal of terminating this highly energy-demanding rhythm. Tailoring defibrillations to patient responsiveness to therapy accomplishes two things: avoiding unnecessary shocks and the accompanying pauses in chest compressions, and avoiding delays in defibrillation when the patient is likely to respond earlier in the prescribed 2-min cycles. An ongoing clinical trial (NCT03237910) is underway to determine whether the ability of amplitude spectral area to predict successful defibrillation can be translated into improved outcomes for patients having cardiac arrest.

*Drugs for cardiac arrest*

Adrenaline is used to increase the perfusion of the heart and brain by redirecting blood flow and increasing the pressure gradient for coronary perfusion during SCA. Amiodarone and lidocaine are antiarrhythmics used as adjuncts in SCA in refractory ventricular fibrillation or tachycardia. Although there is theoretical rationale for their use, a 2016 clinical trial questions their effect on patient survival.[242] There are continuous efforts to identify new drugs that might be useful in cardiac arrest, most recently trials evaluating calcium, vasopressin, and steroids, but findings remain underwhelming with negative or neutral results.[262,263] Explorative studies assessing drug trials have underlined the importance of patient selection as well as timing and route of drug administration by observing potentially important differences in effectiveness depending on how and when the drugs are delivered. Intravenous administration might be more effective than intraosseous administration for some drugs, whereas early compared with late administration might have an impact for others.[264–266]

*Care after SCA and prognostication*

Most patients who have SCA and are admitted to hospital after initial successful resuscitation remain comatose and in need of care. Hypothermia was believed to be our only proven therapy to improve functional survival for these patients; however, its effectiveness has been questioned.[267] Similarly, although immediate angiography is necessary for ST-elevation myocardial infarction, the relevance of early angiography in other situations post-SCA has been called into question by randomised trials in 2019 and 2021.[268,269] In addition, randomised controlled trials on different mean arterial blood pressure and restrictive or liberal oxygen target of a $PaO_2$ did not result in different percentages of patients dying or having severe disability or coma after out-of-hospital cardiac arrest.[270,271] However, there is a signal towards titrated oxygen being detrimental to survival in key subgroups, such as those in a shockable rhythm.[272] Again, there is a suggestion that a more differentiated approach might be needed to ensure treatment is provided to those who need it, not as a one-size-fits-all approach. The theoretical benefit from hypothermia to mitigate brain injury might be offset by exposing patients without brain injury to unnecessary sedation and critical care, and procedural risks associated with urgent angiography in critically ill patients might outweigh the benefit when only a proportion have abruptly occluded coronary arteries. As clinical trials become larger and more sophisticated in their designs, there is hope that they will not only provide one-size-fits-all assessments, but also evolve into research capable of exploring and identifying specific subgroups or phenotypes of SCA that might benefit from specific treatments or treatment targets.

One of the most important interventions to improve SCA outcomes in intensive care is not to withdraw treatment too early. A comprehensive review identified bad prognosis predictors in four domains that would help in assessing when to withdraw life-sustaining therapies in catastrophic brain injury following SCA: (1) clinical examination (eg, absent pupillary and corneal reflex or presence of status myoclonus), (2) neurophysiological testing (eg, absent somatosensory-evoked potentials or presence of pathological EEG), (3) blood biomarkers (eg, elevated neuron-specific enolase during the first 72 h), and (4) brain imaging (eg, diffuse and extensive anoxic injury on brain CT or MRI). Although we have sound data to suggest poor prognosis after 72 h of unconsciousness in survivors with bad prognosis criteria within at least two of the four domains, clinicians are still challenged to assess potential residual effects from sedation and rule out any other possible reversible causes of unconsciousness. The prognostication process is often difficult and time consuming, putting considerable strain on families and health-care resources. New diagnostic tools to provide additional information on the magnitude of brain injury during the early post-cardiac arrest phase would have major therapeutic and prognostic implications. Although still imperfect as a prognostic tool, machine learning and deep learning of EEG patterns look promising and might add value in clinical decision making in predicting both good or poor neurological outcomes.[273] However, the careful consideration of the use of machine learning is extremely important to ensure poor or biased practices and self-fulfilling prophecies are not reinforced by developed algorithms. In addition, although having a rigorous process for withdrawal of life-sustaining therapy is important, the identification of patients likely to benefit from expensive and invasive organ support might become equally important as therapeutic options increase with time.

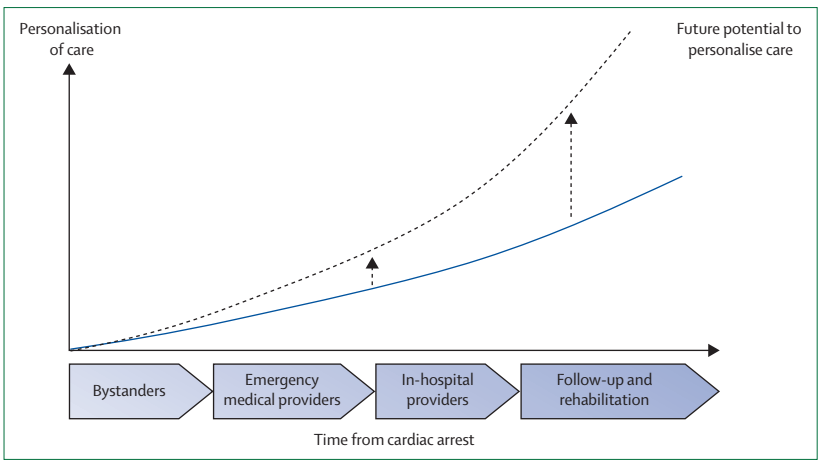


***Figure 10:*** **Opportunities for the personalisation of care after cardiac arrest**
At the earliest points in the chain of survival, a simple universal approach emphasising lay-rescuer cardiopulmonary resuscitation and public-access automated external defibrillators is needed. As we move up the chain to expert care after SCA, there is a greater scope for the personalisation of care to the individual.

*Personalisation versus simplification*

Cardiac arrest is a time-critical event in which patient survival is dependent on immediate action, predominantly by lay responders. The perfusion generated during standard CPR will not be optimal for all patients, and personalisation of resuscitation could lead to improved outcomes for individuals. However, there remains an important trade-off between keeping immediate resuscitation simple for lay responders and providing targeted, optimised, but potentially delayed complex care. Future technology might offset some of the complexity, with devices providing easy to follow, personalised feedback based on physiological signals during resuscitation. As the resuscitation and treatment of cardiac arrest progresses, there is an increased opportunity for personalisation. Whereas a lay rescuer needs very straightforward simple instructions, intensive care and rehabilitation provided by specialised health-care personnel will be increasingly personalised and guided by the patient's response and needs (figure 10).

Resuscitation research has evolved with increasing evidence from large, multicentre, randomised controlled trials. Yet out-of-hospital health-care providers are still struggling to translate the findings from these large multicentre studies to local guidance for treating their individual patients. Large, pragmatic, randomised controlled trials help us predict how system-level interventions might lead to system-level changes in outcomes, but remain a crude tool in the quest for personalised medicine tailored to each individual. We need to move away from a one-size-fits-all approach to a more refined set of strategies based on patient phenotypes to substantially advance the improvement of outcomes after SCA. However, we lack much of the mechanistic insights into cardiac arrest and our current therapies to achieve this goal.

For any treatment to be effective during cardiac arrest it needs to be delivered before there is irreversible organ damage (ie, within the therapeutic window), reach its intended target (ie, a drug with a functioning route of administration), and all other aspects of life support need to be adequate and consistent (ie, high quality of care without premature withdrawal of life-sustaining therapies). During a chaotic cardiac arrest resuscitation, these prerequisites might be as hard to ensure as they are to document, and the variations in quality of care might dwarf any intervention in the setting of a large, multicentre, pragmatic, randomised controlled trial. It is imperative that future interventions are explored in high-quality phase 2 trials that confirm whether the intervention is reaching the intended target within the therapeutic window before progressing to large, definitive phase 3 trials. Continuing to design phase 2 trials without any measurement of the intended target mechanism and progressing to large, one-size-fits-all phase 3 trials will ultimately halt the progression of resuscitation science.

*Moving from static cardiac arrest registries to real-time multisource data*

Although correct and reliable data are needed to understand causes, treatment, and outcome after an SCA, most countries do not collect data on SCA or SCD incidence and outcome (figure 3). In addition, data in established registries are often inconsistently collected with heterogeneity in how SCA, SCD, and resuscitation are defined.[283] To address the inconsistencies in SCA registration and outcome reporting, uniform terms and definitions for the registering the SCA resuscitation process were introduced as early as 1990 (ie, the Utstein Resuscitation Registry Template) and updated in 2019.[232,284] Furthermore, the Core Outcome Set for Cardiac Arrest initiative identified consensus core-outcome set domains for cardiac arrest for effectiveness trials, recommending that SCA trials should, as a minimum, include survival, neurological function, and health-related quality-of-life measurements.[285]

Still, the data collected rarely include all relevant sources (information from the dispatch centre, lay responders, AEDs, ambulance records, hospital records, personal health information, follow-up visits, patient-reported outcome measures, etc). Combining all relevant data into a high-level, secure registry is challenging and is likely to demand multidisciplinary-tailored approaches to obtain data from the entire patient trajectory—from the initial emergency call to rehabilitation and long-term quality of life among SCA survivors, while safeguarding patient privacy. However, regional resuscitation platforms or hubs that could integrate, synchronise, and analyse individual-level data in real-time would provide novel precision data to optimise quality of care at the various levels of health-care systems, provide insights to communities and policy makers responsible for public health, and provide high-granularity data to support

further clinical research. Each regional resuscitation platform could serve as a hub for working upwards towards the larger community, policy, and national levels, and downwards feeding back processed data at institutional, departmental, and individual levels. Developing a resuscitation network in which key stakeholders can interact and collaborate within and across their own institutions and regions or hubs is crucial to develop effective and sustainable strategies to reduce SCD.

The development of regional resuscitation platforms or hubs and effective networks between these regional hubs will also provide unique opportunities for research. High quality, multisource, granular resuscitation data will not only be available for novel big data or AI approaches, but will also provide prompt and reliable evaluations of interventions or changes in practice meant to reduce SCD. Established stakeholder networks and continuous high-quality data collection will also provide solid platforms for conducting randomised clinical trials, lending itself to pragmatic and adaptive trial designs that can answer clinically important questions in relevant real-word settings at a reasonable cost.

## Health-care system and community interventions

Since 1992, professional resuscitation organisations worldwide have come together in the International Liaison Committee on Resuscitation (ILCOR) to critically evaluate resuscitation science and to promote, disseminate, and advocate international implementation of evidence-informed resuscitation science. On the basis of these ILCOR reviews, international and regional resuscitation councils, such as the AHA and European Resuscitation Council (ERC), provide evidence-based resuscitation recommendations highlighting important research questions and substantial opportunities for enhancing each element of the resuscitation chain to improve survival chances.[233,286]

Although survival from SCA depends on each of the links in the chain of survival (figure 9), these links are themselves affected by complex system-level factors that might aid or detract from a successful resuscitation effort, such as strong EMS leadership, a culture of excellence, continuous resuscitation training, and quality improvement programmes designed to provide feedback and debriefing after SCA events. These elements developed by the Global Resuscitation Alliance are termed the frame of survival, which highlights elements that are often missing in systems, including political commitment and supportive legislation. The ten-step, evidence-based principles to increase SCA survival are combined with practical training sessions and access to a global network of health-care personnel implementing this approach.[287] These principles include: (1) establish a cardiac arrest registry; (2) implement resuscitation; (3) deliver high performance CPR; (4) begin rapid emergency medical dispatch; (5) measure professional resuscitation efforts with defibrillator recordings; (6) implement first-responder AED programmes, including police, firefighters, and security personnel; (7) use smart technologies to notify volunteer responders to provide early lay-responder CPR and defibrillation before the arrival of EMS; (8) make CPR training mandatory in schools and the community; (9) work towards accountability (eg, provide a publicly available annual report); and (10) work towards a culture of excellence.

### *Improving the recognition of SCA by the public and telecommunicators*

SCA can be difficult for members of the public to recognise, leading to delays in care. Given that most SCA events occur at home and are unwitnessed,[288] new wearable items, such as ECG finger rings or smart watches capable of communicating various biometric signals (eg, heart rate, respiration rate, blood saturation, skin temperature, capillary perfusion, activity, and body posture) by use of electrocardiography monitoring and photo plethysmography, could trigger an automated call to the EMS under prespecified conditions,[289] allowing the citizen to get help even before the SCA occurs.[280] Machine learning could potentially be used to ensure these algorithms are refined by the use of large volumes of data to decrease false triggers and the overload of information of EMS and health-care professionals.[224] Identifying imminent SCA by machine learning algorithms will prove to be challenging because good-quality training on unrecognised SCAs to train AI algorithms scarcely exist.

Additionally, smartphones and smart speakers have been documented to accurately identify SCA-associated agonal breathing with high sensitivity and specificity.[290] The widespread adoption of such devices presents another opportunity to identify unwitnessed SCA in domestic settings and transmit an alarm directly to the emergency dispatch centre. In addition, the use of social media to educate the public about the non-typical presentation of a cardiac arrest, such as agonal breathing and seizure activity, might improve public recognition of SCA.

In most SCA emergency calls, lay-responder CPR is not initiated before instructions from the telecommunicator.[291,292] To improve the recognition of SCA and the quality of resuscitation guidance for the lay responder, each telecommunicator needs ongoing training in early SCA recognition and personalised feedback on the provision of resuscitation instructions given in emergency calls for SCA. For quality-improvement purposes, telecommunicator audio recording can be linked with EMS data and hospital outcomes to identify training needs.[293,294] In addition, telecommunicators could be enrolled in repeated, short-duration, high-quality improvement sessions with simulation scenarios replicating real-world calls. AI in the dispatch centre could aid in minimising language barriers[295] and can also be used to listen to live emergency

calls and recognise SCA, thereby improving the sensitivity and diminishing the time for SCA recognition,[296] leading to earlier telecommunicator-assisted lay-responder CPR and the earlier dispatch of appropriate EMS. However, call-taker acceptance and meaningful integration of AI decision-support advice is crucial to implementation success. To date, such programmes have not shown clinical significance.

*Improving early CPR and defibrillation before ambulance arrival*

There has been little innovation in AED devices to the point that their communication and tracking technology is outperformed by most mobile phones, toys, and everyday household appliances. Public-access defibrillator programmes are dependent on manual steps to locate the devices, keep track of when they are moved, and check whether they are ready for use (sufficient battery, pads within expiration date, etc). Important resuscitation data from these AEDs are often not stored, and when theoretically available, the data are difficult to extract and convert to uniform formats. AEDs should include geolocation, communicate their functionality status, and offer automated wireless transmission of key data to the EMS in real time. Furthermore, the resuscitation community and consumers of AEDs should demand better functionality from manufacturers.

Targeted placement of AEDs in locations with a high incidence of out-of-hospital cardiac arrest, as recommended by the ERC and AHA,[233,286] with the flexibility of redeploying the AEDs when population movement patterns and epidemiological profiles change, are more likely to be cost-effective.[297–299] Although mathematical optimisation models for AED deployment have shown to be theoretically beneficial for the coverage of high-risk SCA,[300] translating these modelling results into real-world, improved AED coverage and survival gain has yet to be shown. In practice, most AEDs are bought by individuals or companies for local use, not by health-care authorities or communities for optimal SCA coverage to ensure more equitable access. Public-access defibrillation programmes should be complemented with public-awareness campaigns, CPR and AED training, and AED maps linked to EMS for telecommunicators to direct lay responders to the nearest AEDs.[301,302] In addition, ensuring that publicly available AEDs are registered and accessible 24 h a day, 7 days a week, and linked directly to the emergency dispatch centre increases the chance of defibrillation before the arrival of EMS and improves survival.[303]

Availability of AEDs has mainly focused on public locations, despite most SCA events occurring at home.[288] The randomised Home Automated External Defibrillator Trial, testing AED placement in the home of patients at increased risk of SCA, did not find any survival benefits compared with conventional resuscitation methods.[215] An alternative approach of placing AEDs inside selected private homes is to deploy publicly accessible AEDs in the streets of high-risk residential areas covering many people who are at risk. Activating nearby volunteer responders by text messages or smartphone apps is becoming widespread[304] and has shown the potential to increase lay-responder CPR, defibrillation, and survival, even in private homes.[280,305,306] Common for all volunteer responder programmes is a crucial mass of volunteer responders, publicly available AEDs, and continued engagement with the EMS. These app-based solutions also have considerable potential to increase public awareness, engagement, and continuous education through targeted messaging on social media.

Delivering the AED by mobile units (eg, taxi cabs with an AED on board or unmanned drones) offers the possibility to cover a larger area, increasing the chances of prompt delivery of an AED to the scene.[307] These AED delivery systems should be integrated with existing volunteer first-responder programmes, increasing the chance of early defibrillation before the arrival of EMS by local lay responders. The use of live video streaming from the lay responder's smartphone to a medical telecommunicator could improve correct hand position, compression rate, and compression depth. A simple-to-use and easy-to-carry CPR feedback device for laypersons (eg, a CPR card containing a built-in accelerometer)[308] or a smartphone app that uses the video camera to provide information on compression rate and depth could provide ongoing feedback on CPR quality to the lay responder and simultaneously transmit real-time data on hand placement, compression, and ventilation rate to the emergency dispatch centre. However, the likelihood of lay responders to use such devices in an emergency and the translation to improved outcome is yet to be shown.

During the past decade, AED deployment has spread immensely throughout most communities, whereas AED functionality has essentially stagnated. To save more lives from SCA, AEDs should be redesigned with core functionality. For example, they could alert the emergency dispatch centre and activate first-responder and volunteer-responder programmes automatically when used. AEDs could also be activated directly from the emergency dispatch centre, alerting random lay responders to retrieve the AED and bring it to the SCA location for early defibrillation while transmitting GPS data during transport. Importantly, AEDs should also be able to transmit AED data directly to the emergency dispatch centre and the retrieving hospital because this information is imperative to guide patient treatment decisions and is most often absent in current systems. Self-tests and the functional status of the device should be transmitted automatically not only to the owner of the device, but also to the regional AED register and emergency dispatch centre, because deployed but non-functional AEDs are an increasing challenge.[309] AEDs able to perform filtered real-time rhythm analysis hold the potential to guide more precise timing for effective

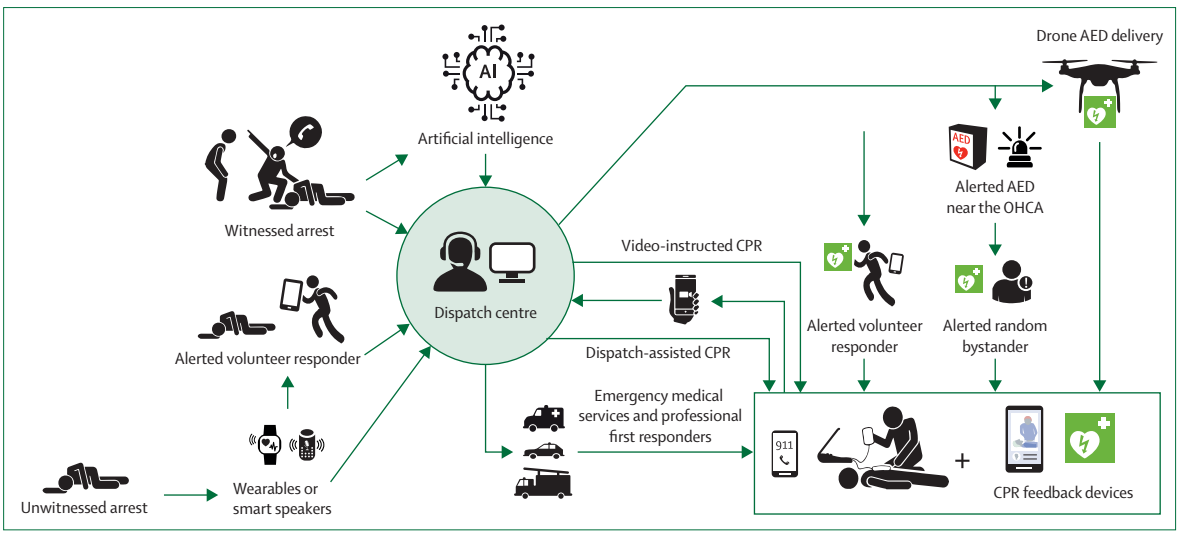


***Figure 11:*** **Technological solutions for improved resuscitation**
AED=automated external defibrillator. CPR=cardiopulmonary resuscitation. OHCA=out-of-hospital cardiac arrest.

shock delivery and improve outcomes, although clinical trials documenting the effect are scarce. Different technological solutions to improve early CPR and AED use as well as improving CPR quality through feedback systems or guidance from the dispatch centre are illustrated (figure 11).

*Delivering high-quality CPR in EMS*

SCA survival depends not only on early recognition and immediate activation of the emergency response system, but also on the quality of CPR delivered.[310] However, the quality of prehospital CPR, either by laypersons or professional responders, is often outside guideline recommendations,[311,312] hampering the chance of survival. On a system level, ongoing quality-improvement programmes should provide performance feedback to involved personnel after every cardiac arrest. Such programmes can be facilitated through initiatives such as the Resuscitation Academy, helping communities worldwide to learn how to develop and implement a plan of action to improve survival. The use of regional resuscitation platforms or hubs that could integrate and synchronise individual-level, real-time resuscitation data could fundamentally change instructions from simple CPR-metrics guidance to a dispatch centre being part of a so-called virtual resuscitation team. Merging real-time data from defibrillators and video streaming from the cardiac arrest scene would allow for online connection of resuscitation experts and treating physicians from the receiving hospital, delivering ongoing feedback for lay responders and paramedics, further improving high-performance CPR.

*Increasing access to regionalised systems of care*

Similar to stroke and trauma care, SCA is a time-sensitive condition in which matching the level of care to the type of patient will be most impactful. Regionalised systems of care, which can adequately triage patients at the time of arrest to the most appropriate facility for the level of care needed, will be imperative. Deploying resource-intensive, specialised care teams to the site of SCA and integrating appropriate interfacility transfers to specialised SCA centres with the capability to organise post-resuscitation care, including 24 h access to mechanical circulatory support, invasive treatment, neuroprognostication, and evidence-based rehabilitation of survivors, could improve patient outcome beyond what is possible in smaller centres.[313] Technologies, such as resuscitative endovascular balloon occlusion of the aorta, is feasible and might be beneficial for survival from cardiac arrest.[314] Likewise, extracorporeal membrane oxygenation for refractory cardiac arrests appears promising, but is highly dependent on careful patient selection, is costly, benefits fewer patients than early basic life-support interventions, and requires more research into which patients will benefit most from these interventions.[315]

## Roles of government, policy, public education, and engagement

Laws and legislation to assist in protecting volunteer and lay responders include the SCA Survival Act and the Community Access to Emergency Defibrillation Act in the USA,[316] the duty-to-rescue laws in Europe,[317] and the Good Samaritan laws in Australasia.[318] Government support, sound policy making, and supportive legislation are key conditions that governments should facilitate to ensure that education, implementation, and resuscitation research is possible. Access to emergency health care is an essential priority. However, it is not given in low-resource settings where an estimated 35–45% of morbidity and mortality can be averted if time-sensitive

medical conditions can be rapidly attended to.[319] There is currently good evidence for the effectiveness of prehospital systems, lay-responder CPR, AEDs, telecommunicator-assisted CPR, and other interventions for SCA, but they are insufficiently implemented and require more governmental, political, and financial support. There is also a need for education and protection of professional providers and lay responders and support for emergency research.

Currently, the bulk of research funding is directed to advanced resuscitation and care after cardiac arrest, in which decreasing numbers of patients will be affected. Figure 9C highlights the out-of-hospital cardiac arrest chain-of-survival sequence needed for survival in comparison with the allocation of research funding issued by the National Institutes of Health (NIH) in fiscal years 2017–21. Of the US$47·4 million distributed to chain-of-survival-related research, nearly 69% ($32·5 million) was awarded to advanced life-support treatment and care after cardiac arrest, leaving less than a third available for prevention and early emergency response.[234] Without proper allocation of funding, high-quality, meaningful research cannot happen; conversely, without such research output and visible, impactful results, further funding allocation is unlikely. With updated practices, appropriate steps to improve equality, and a policy shift in priorities and spending, we need to reduce the gap and provide more focus to prevention and early response. This focus will ultimately decrease the investments needed in high-tech but low-yield care after SCA and greatly reduce the burden of SCD overall. However, research funding should not be a zero-sum process, taking from one area to fund another. Instead, funding should be increased throughout all links in the chain of survival to achieve the goals of saving more lives globally.

Many countries do not yet have appropriate or comprehensive legislation or funding provision for EMS or emergency care systems. Appropriate legislation for EMS provides medical oversight of the essential elements in an EMS system: management of human resources (staffing, capacity building, etc), communication channels, community education, access to timely care, patient transportation and transfer, links to facility-based organisations, patient record keeping, emergency and preparedness response plans, and disaster management.[320] However, legislation without adequate funding for emergency services results in gaps in the provision of essential services.

Good evidence is key to driving improvements. However, research in emergency situations faces major barriers, with many countries having tight regulations regarding obtaining consent from patients to participate in research. There might also be an inconsistency across jurisdictions in the interpretation of the relevant legislation pertaining to research in emergency situations. Although concepts such as a waiver of informed consent for emergency clinical research have been legislated in some countries, there are still challenges related to data protection and privacy concerns.[321,322] In addition, barriers regarding data sharing across institutions and nations hinder scientific advancement and need to be legally resolved.

*Community CPR and AED training*

In SCA, health inequities persist on for whom an event will be recognised, when and if emergency response is activated, CPR provision, and application of an AED. These inequities vary between countries, but also at the micro level within communities, with differences in treatment and outcome between men and women and across ethnic or socioeconomic groups.[253,323–325] Also, most countries do not have legislation mandating CPR or AED training at a population level. Surveys have shown that the proportion of the population within communities who have ever been trained in CPR varies substantially and can be as low as zero.[326,327] There are gaps in how the community is currently activated to perform CPR, and without proper and repeated education, training, and awareness, existing health inequities will be magnified. A shift to a culture of action is needed to ensure that not only is training available to all residents of a community, but also that they will act in the event of an SCA. Some suggestions related to CPR training include legislation to improve training rates, targeted training for key communities where CPR and AED awareness is low, and innovative ways of delivering training to improve engagement and mitigate the decay of skills.

Increased community CPR training has been achieved through numerous initiatives, ranging from grass-roots community programmes and annual awareness campaigns to mandating training in some settings. Countries around the world have launched national CPR-awareness campaigns, such as the Restart a Heart Day[328] and Resuscitation Week in Europe,[329] Shocktober in Australia and New Zealand, CPR and AED Awareness Week in the USA, and the National Life Saving Day in Singapore.[330]

Mandatory CPR training via the school curriculum, the application process for a driving licence, industry, and the military has also been implemented in numerous countries.[308,331–334] An evaluation of the implementation of CPR training in Denmark, where legislation made CPR training mandatory in schools, was introduced in 2005 and highlighted important lessons. Despite legislation, many schools had not implemented training. The completion of CPR training was associated with factors such as awareness of the legislation, a belief that other schools were implementing training, and having a dedicated coordinator.[335] Hence, in the absence of a framework for how the training should be conducted (eg, training materials, proficiencies of instructors, delivery modes, and funding mechanisms), there is a high risk that effective, systematic implementation of CPR training could fail.[335]

Increasing community awareness and knowledge of CPR training needs to be innovative and multifactorial. There should be a shift in how training is delivered to ensure a continuous increase in lay-responder CPR rates and quality in the community. Implementing innovative training methods in addition to didactic classroom training is likely to appeal to a broader population and improve access overall. The use of virtual CPR training is yet to be fully explored, but the disruption of the COVID-19 pandemic has shown a global shift towards virtual learning. By shifting to a mastery-learning model with deliberate and repeated practice we can reduce skills decay, which can affect the likelihood of performing CPR and confidence in performance and quality. The use of innovative modes of educational delivery and instruction (eg, virtual reality, gamification, and CPR kiosks in public locations) will help bring in new learners and engage learners in different ways.[336]

There are many barriers that have been identified as to why a person chooses not to learn or perform CPR,[337] such as the financial cost of training, paucity of information, and fear of litigation. Some of these barriers can be addressed by increasing tele-communicator provision of CPR, with specific training for motivating lay responders to use innovative training delivery methods.[338] Working with community leaders and organisations can help create a culture of action. Working globally to increase CPR awareness through various modalities (eg, national strategies, apps, social media, and large events) can be another strategy to improve survival after SCA.[339] In addition, out-of-hospital cardiac arrest registry data can be used to identify high-risk neighbourhoods with a high incidence of SCA and low rates of lay-responder CPR.[340] These high-risk neighbourhoods can be targeted for focused, culturally sensitive, and tailored education and training. Reducing health inequities for SCA survival will require a multidisciplinary approach with key stakeholders and will need to adapt to the changing needs of the communities in which we are seeking to make an impact.

There are many global examples involving the public, national registries, and technological solutions showing how steps to increase survival can be implemented. Regional context determines how these different strategies can be prioritised and implemented (panel 7).

## Summary and future direction to improve SCA survival

Although incremental improvements in survival have been observed over past decades with some particularly encouraging case studies, mortality remains unacceptably high.

There remains a substantial gap in resuscitation science with respect to interventions, with most large, pragmatic trials unable to show effects on survival. Therapies shown to have marginal clinical effects in large, pragmatic, randomised controlled trials might need to be re-evaluated in the setting of titrated and individualised medicine. This re-evaluation would require consideration of the underlying cause of the SCA and the individual response to therapy, which could include individual response to novel CPR and defibrillation strategies and new drugs, taking into consideration patient factors and patient response to the delivery mode, dose, and timing. In addition, uncertainties remain in treating critically ill patients

### *Panel 8*: Recommendations for improving resuscitation and maximising survival

- Drugs given during resuscitation should be tested according to time of drug delivery and route of administration in an experimental setting. The main outcome for drug trials should be directed at improving the return of spontaneous circulation and neurologically intact survival.
- Given that precise prognostication of out-of-hospital cardiac arrest is extremely challenging, an inappropriate early withdrawal of care could contribute to low survival rates and should be avoided. Development of new strategies, including machine learning and artificial intelligence (AI), to assist clinicians with decision making in care after resuscitation has promise but needs to be explored further.
- In addition to the traditional chain of survival, use of the inner frame of survival (ie, factors within the health-care system, such as quality feedback, a culture of excellence, and strong leadership within the emergency medical services [EMS]) and outer frame (ie, factors outside the health-care system, such as legislation, political commitment, and a basic state of preventive health) will greatly benefit efforts for systems improvement.
- Novel technologies, including wearables or smartphones that can record and transmit important biometrics directly to the EMS, should be tested for the improvement of early recognition and treatment of unwitnessed sudden cardiac arrest (SCA).
- Emergency medical dispatch centers should explore how to use AI to identify SCA on live emergency calls and use virtual resuscitation teams with the involvement of resuscitation experts with access to real-time resuscitation data, which would allow high-performance feedback to paramedics and lay responders.
- Current research funding is disproportionally spent on advanced life support and care after cardiac arrest, but more funding is needed for prevention and early-response research to save more lives.
- To support research and allow for advancements in science, rational regulations for the waivering of informed consent for emergency clinical research and data sharing across institutions and international borders should be created and implemented globally.

after the return of spontaneous circulation and research around the importance of temperature, blood-pressure management, oxygenation, ventilation, and prognostication during care after SCA is essential.

Survival from SCA depends on a sequence of time-sensitive interventions and the first links in the chain of survival are likely to have the largest effect on survival on the greatest number of people. The Utstein formula for survival means that not only is broad education and new science important, but equally important is implementing what we already know for improved survival after SCA. Improvements in all the chain-of-survival links requires investment, activating communities, and leveraging emerging technology. The system also requires strong EMS leadership, and continuous quality improvement programmes designed to provide feedback and debriefing post-SCA events.

A current gap in resuscitation research is the availability of granular, patient-specific data across services, systems, and regions. Consensus-based Utstein parameters help to standardise data and provide the basics for research, quality improvement, and reporting. However, the data collected are often absent of the granularity needed to affect practice on the individual health-care provider level and rarely include all relevant sources. Investment in multisource data platforms is essential to allow the collection and synthesis of meaningful data to inform policy makers, researchers, services, and clinicians.

High-quality clinical care, integrated health systems, supportive legislation, and sound policy making are important to improve survival from SCA. Community partnership, education, and smart technology are promising ways to save more lives, but need to be delivered as part of a comprehensive strategy that focuses on equitable and consistent implementation of best practices (panel 8).

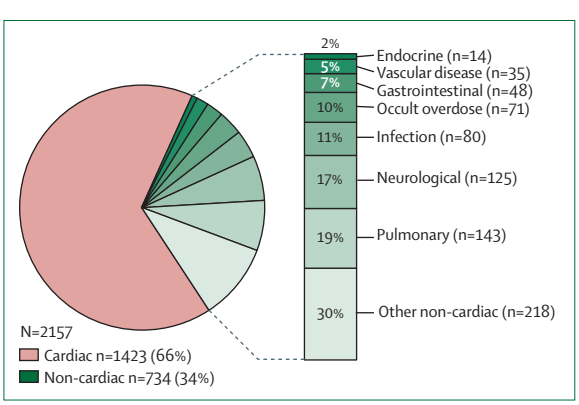


***Figure 12:*** **Autopsy-defined causes of presumed SCD: composite data from three population-based studies**
Composite data from three autopsy-based studies of presumed SCD studies: cardiac deaths N=1423 (N=315 Tseng et al;[14] N=355 Haukilahti et al;[10] N=753 Risgaard et al[341]); non-cardiac deaths N=734 (N=210 Tseng et al;[14] N=238 Haukilahti et al;[10] N=286 Risgaard et al[341]). SCD=sudden cardiac death.

## After the event: management of decedents, survivors, and relatives

Establishing the phenotype in the index case, whether by post-mortem evaluation after SCD or through diagnostic evaluations in survivors of SCA, is crucial for the prevention of recurrent events and for the subsequent assessment of SCD risk in family members. Trying to identify the cause of SCA in the index case involves comprehensive diagnostic tests, including appropriate use of genetic testing. Rehabilitation, quality of life of survivors, and psychological support of relatives are important additional aspects that have been an underappreciated area of research and clinical care.

### Evaluation after SCD

*The role of autopsy in ascertaining a cause of sudden death*

To distinguish SCD from other causes of sudden death with a high degree of certainty, a comprehensive post-mortem investigation, including autopsy and ancillary examinations, is required because more than a third of patients dying suddenly could have an underlying non-cardiac cause, such as occult overdose, neurological catastrophes, and underlying infections (figure 12).[14,341] Determining whether a sudden death is cardiac in origin, and the exact underlying cardiac cause, has major implications in terms of providing a cause of death, which is important in aiding closure, and clarifying future risk to family members. Preventive measures can be implemented when a cause is determined to be heritable and reassurance provided in individuals with non-heritable conditions (eg, myocarditis) with no perceived risk to relatives.

Although some people survive an initial SCA, fewer survive to discharge. In-hospital evaluations in initially resuscitated patients of cardiac arrest might reveal a cause in some patients, although caution is needed to infer whether a detected abnormality is truly causal or associated. For individuals who do not survive a cardiac arrest, the consensus of professional societies is that an autopsy that uses a sequential approach to evaluating the causes of death should be performed ideally in all cases of sudden death and always in people younger than 50 years (figure 13).[19,22,111,342] The full autopsy includes the macroscopic and microscopic examination of all internal organs, with a precise protocol for heart examination and sampling, post-mortem laboratory tests (eg, toxicology and biochemistry), and the storage of adequate samples for genetic testing.[22] Currently, more than half of young people dying of SCD in the ICU remain aetiologically unexplained due to early investigations not being performed.[343] Excluding overdose in sudden deaths is important. Rigorous toxicological analyses combine a drug-screening analysis with liquid chromatography tandem mass spectrometry methods[344] and an analytical method accounting for a drug's post-mortem degradation, redistribution, neoformation, or artefactual formation.[345] In individuals for whom a cardiac implantable electronic

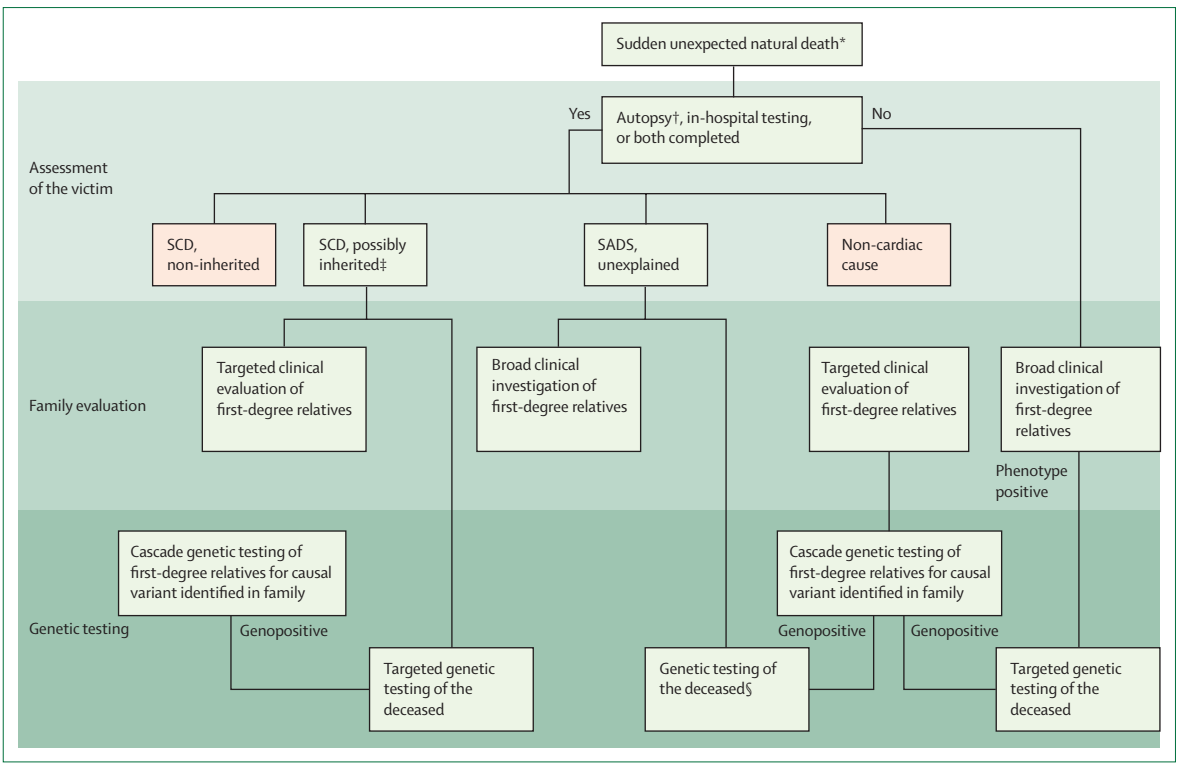


***Figure 13:*** **Evaluation of patients who have sudden unexpected death aged <50 years or with possible inherited cause**
SADS=sudden arrhythmic death syndrome. SCD=sudden cardiac death. *Including death after rescuitation. †Including toxicological and histological analyses with examination of the heart and storage of adequate samples. ‡Based on all available information. §Primary electrical disease genes and consider cardiomyopathy genes.

device is present, a complete interrogation helps identify the terminal rhythm and rare instances of device failure (ie, battery and hardware) that can potentially guide future improvements in design and refinements to programming.[346]

Circumstances and medical history should also be carefully considered in the interpretation of post-mortem findings. With a comprehensive post-mortem examination, underlying causes are usually unequivocal and readily identifiable. However, a conclusion of arrhythmic death is one of exclusion in which no other non-arrhythmic causes of sudden death are found, and in some individuals an autopsy after sudden death can be completely negative or give only non-specific findings, such as myocardial fibrosis. In such findings, past medical history is crucial and might affect conclusions of causes of death.[347] For example, sudden unexpected death in epilepsy can occur in some individuals with high-risk epilepsy who present with unwitnessed sudden death.[348,349] Typically, autopsy findings are negative or only non-specific myocardial fibrosis can be found. With no past medical history and no, or only minor, non-diagnostic findings at autopsy, a genetic analysis of the deceased and clinical assessment of the relatives might reveal disease in primary electrical diseases or cardiomyopathies in up to 40% of individuals.[111,347,350,351]

Despite the importance of autopsy being recognised for many years, autopsy rates in most high-income countries have greatly declined over the past 50 years (figure 14).[353] The decline in autopsy rates has been observed in several studies in all age groups (18–39 years, 40–59 years, and 60–79 years), including the young (ie, aged <50 years).[354,355] Depending on the country, autopsies conducted in cases of sudden death are either clinical or forensic and their aims differ. The clinical autopsy, which typically includes histological analyses, is performed at the request of the physician or the family of the deceased to uncover the underlying cause of death and can often be partial or focused on specific organs. Toxicological analyses are often omitted in these evaluations, leading to uncertainties on the actual cause of sudden death. Conversely, the forensic autopsy is requested by a magistrate, public prosecutor, official death investigator, coroner, or the police to assist in determining the cause and manner of death (ie, attributable to an underlying disease, homicide, or self-inflicted). However, whether the condition causing sudden death might be inherited is of minor legal importance in forensic autopsies. Whatever the legal framework of the autopsy, a systematic, complete autopsy, including histological and toxicological analyses, and a multidisciplinary approach is crucial to establish the cause of death with highest certainty.[22]

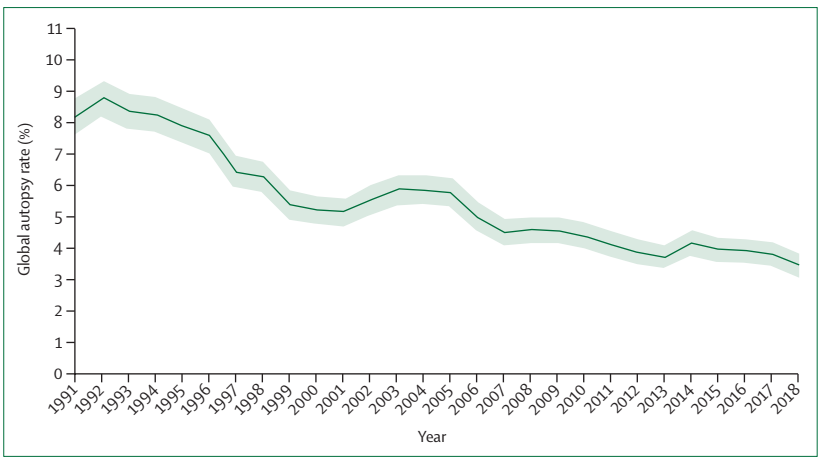


***Figure 14:*** **Yearly global autopsy rate (95% CI) of all deaths in west European countries from 1991 to 2018 according to WHO**

The yearly autopsy rate for all deaths in Austria, Finland, the Netherlands, Portugal, Switzerland, Denmark, Iceland, Luxembourg, Norway, Sweden, and the UK from 1991 to 2018 without distinction between clinical or medicolegal autopsy.[352]

The decline in autopsy rates in high-income countries is principally the consequence of low rates of clinical autopsies,[8,10] whereas forensic autopsy rates have been stable or even increasing in some countries.[356] Multifactorial causes for this decline have been identified and include psychological and religious barriers to autopsy, governmental policies, and law making, and economic restrictions in many cases (table).[357] Understanding the underlying mechanisms behind the declining autopsy rates is crucial to help change our practices in the future.[358] To increase the proportion of both forensic and clinical autopsy in sudden death, care physicians who recommend the medical autopsy or magistrate who request the medicolegal autopsy need to be educated on the diagnostic value of autopsy and when it should be requested.

### *Challenges in autopsy*

The accurate interpretation of gross and histological findings constitutes a real challenge in SCD for two main reasons: the pathologist's experience and autopsy findings of uncertain or borderline significance. Considerable variability in the interpretation of histopathological findings between general and specialist cardiac pathologists has been reported.[359] General pathologists are likely to overestimate the significance of some post-mortem findings, such as fatty infiltration of the right ventricular wall, isolated left ventricular hypertrophy, and focal myocardial disarray without hypertrophy, and to attribute deaths to cardiomyopathy in the presence of a morphologically typical heart.[359] Moreover, even if the histology is performed by an expert cardiac pathologist, some findings, such as left ventricular hypertrophy, myocardial fatty infiltration, myocardial fibrosis or inflammation, and minor coronary artery disease, could have uncertain significance.[360,361] Given the worldwide shortage of cardiac pathologists, there is an urgent need to educate additional experts and investigate ways that technology could be used to assist and support this work. For example, developing an AI system with expert-level grading performance could contribute a second opinion and provide pathology expertise in parts of the world where it does not exist.[362] Another approach could be the introduction of core laboratories and telepathology for highly specialised expert assessment and knowledge dissemination in cardiac pathology. The availability of heart specimens for second opinion or, as an alternative, extensive photographic documentation is essential, and at least one transverse section of the heart including the left and right ventricle beside all other relevant lesions should be sampled. Comprehensive toxicological screening is crucial to reveal occult overdose as the cause of presumed SCD, requiring access to appropriate laboratories and good quality samples. To overcome these challenges, new methods must be developed.

The storage and testing of DNA samples also remain challenging, even when a medical examiner applies a rigorous conventional autopsy protocol for unexplained sudden death. Forensic departments often do not have adequate facilities for long-term storage, such as ultra-low temperature freezer or liquid nitrogen. At the conclusion of an inquest or final certification of death, the coroner's office might request the destruction of the samples, although communication and protocols developed with expertise from medical examiners, genetic counsellors, and cardiologists allow DNA samples or other biological samples to be stored in repositories with appropriate consent.[363] Guidelines and legislation regarding consenting parties and reimbursement vary between countries and are common barriers to adequate genetic testing of individuals who have sudden death and their relatives.

Improving the yield of genetic testing by resolving uncertain or apparently negative genetic results is a priority. Collection of quality samples allowing genetic testing, with options for future functional studies of identified genetic variants, is important.[364] For example, when a genetic variant with potential effect on splicing is identified, evaluation of the RNA and expression analysis has shown to be helpful provided RNA is not degraded. To enable this process, the banking of cardiac tissue for possible future RNA tissue-specific expression analysis would be necessary.

### *Alternatives to autopsy*

Acknowledging the difficulty and inconsistency in obtaining gold-standard autopsy in cases of sudden death, other alternatives will have to be considered whenever comprehensive autopsy is not possible. Although not meant to replace the conventional autopsy, post-mortem, non-invasive imaging, including whole-body CT and MRI, could be more acceptable to populations that have philosophical or religious objections.[365] In addition,

| | For autopsy | For cardiac screening of family members | For genetic testing |
|---|---|---|---|
| Patient and family | Perceived to be little or no benefit; not enough information provided about why an autopsy is needed; fear of disfigurement; concerns about funeral delays; religious or cultural objections | Perceived to be little or no benefit; not enough information provided about why cardiac screening is needed; wish to move on; fear of having disease | Perceived to be little or no benefit; not enough information provided about why genetic testing is needed; wish to move on; fear of having variant |
| Physician and health-care system | Challenges with access; insufficient knowledge of importance; logistical issues; financial issues | Challenges with access; insufficient knowledge of importance | Challenges with access; insufficient knowledge of importance; fear of results that are difficult to interpret |
| Public health policies | Little or no reimbursement; not mandatory; inconsistency in forensic policies | Little or no reimbursement; limited and unequal access | Little or no reimbursement; limited and unequal access |

*Table:* **Potential barriers to autopsy, cardiac screening, and genetic testing**

minimally invasive methods (eg, imaging-guided biopsy) could be used to obtain tissue for histological examination and molecular analyses. In practice, each technique has strengths and weaknesses and is adapted to specific circumstances. CT, most frequently used in forensic investigations, is relatively inexpensive, widely available, and can often reveal non-cardiac causes of sudden death (eg, cerebral haemorrhages, pulmonary embolism, and dissections). CT can also visualise calcified plaques, valves, and haemopericardium, but cannot characterise the myocardial structure.[366,367] Post-mortem MRI, used essentially as a research tool, has sufficient soft-tissue contrast necessary for the diagnosis of acute myocardial infarction, but is more expensive, has longer scanning time, and less availability than CT.[368] In MRI, images might also be substantially affected by changes in body temperature, particularly cooling.[369]

Large-scale studies with uniform post-mortem imaging and reporting protocols compared with a gold-standard complete autopsy are necessary to further elucidate the diagnostic performance of post-mortem imaging in sudden-death investigations.[370] The large amount of data from non-autopsy investigations, such as digital images, histology from biopsies, immunohistochemistry, genetic data, electron microscopy analyses, and biomolecular analyses, could be used to develop advanced technologies to improve the accessibility of post-mortem analysis and AI algorithms, allowing a better understanding of the pathophysiology of SCD.

Another approach to further understand the cause of death when an autopsy has not been performed might be to use available characteristics before death (eg, demographics, family history, cardiac rhythm, and circumstances of cardiac arrest). Using these data, perhaps in combination with imaging, building prediction models to better specify the actual cause of death is conceivable.[23] The overall goal is to identify people with possible inherited cardiac disease to prevent future SCD in the family.

## Management of sudden cardiac arrest survivors

### *In-hospital investigations*

Upon post-mortem evaluation more than a third of sudden deaths are because of non-cardiac causes and two-thirds of SCAs surviving to hospital admission have underlying cardiac causes. This proportion increases to 92% in SCAs surviving to hospital discharge, suggesting that the proportion of cardiac or arrhythmic causes progressively increases as we move along the survival chain.[15] This distribution of underlying causes probably represents a degree of selection bias because SCA due to cardiac arrhythmias is more likely to have successful resuscitation. Early identification of non-cardiac sudden deaths, such as neurologic causes, will help modify management strategies or allow early triage to appropriate specialty centres to improve survival rates.

Attempts to establish a diagnosis after SCA begin in the field before the patient arrives in the hospital. In every SCA, trying to document the primary or presenting arrhythmia (ie, bradycardia, asystole, pulseless electric activity, ventricular tachycardia, or ventricular fibrillation) is important. Documentation can come from multiple sources, such as ambulance emergency equipment, public AEDs, wearable monitors (eg, smartwatch), and data from cardiac implantable electronic devices. With increasing use of AEDs, the data stored in their memory assumes greater importance in subsequent management, especially when only AED shocks suffice to restore circulation. Unfortunately, rhythm data from AEDs are unavailable in most cases. The first presenting rhythm during cardiac arrest is insufficient to implicate an underlying cardiac or arrhythmic cause, because ostensibly lethal arrhythmias can be secondary to non-cardiac causes and the natural outcome of ventricular fibrillation with time is asystole. Documentation of the details of the actual event is important (ie, circumstances, the presence and testimony of eyewitnesses, the patient's medical history, and family history[39,82,371,372]) with the goal to identify a probable explanation and influencing factors for the SCA, including the potential trigger, that can allow optimal treatment and preventive strategies for the future.

As already mentioned, most SCAs are caused by either acute or chronic coronary artery disease. The difficulty in clearly differentiating between these two scenarios and the role of acute ischaemia represents an important area of research in the future. Other causes, such as non-ischaemic cardiomyopathies and primary electrical diseases, can be uncovered after a structured assessment programme as proposed in figure 15. Even so,

comprehensive examinations cannot provide an explanation in all cases. The sensitivity, specificity, and interpretation (ie, causality) of some cardiac investigations are also debatable. For instance, deciding whether ventricular ectopy during an epinephrine stress test is suggestive of catecholaminergic polymorphic ventricular tachycardia, or whether a positive ergonovine or acetylcholine test for coronary spasm explains an SCA, remains challenging.

In an estimated 10–20% of survivors of SCA, no clear cause is identified after the initial evaluation, including ECG, echocardiogram, and invasive or non-invasive coronary imaging.[82,373] In this context, initiating causal investigations as soon as possible within the ICU once the patient is admitted is important because about half of patients die during admission. Although early investigations within the first 24 h can be difficult to interpret (ie, QT prolongation or left ventricular function), they should still be performed because they can allow for targeted intervention and, in the unfortunate event of the patient dying, potentially allow for appropriate screening and intervention for family members who are at risk when a definitive diagnosis is available. Obtaining and storing blood or tissue samples for future analysis is also crucial when possible.

In patients for whom diagnosis remains unclear after initial evaluation, further tests, such as exercise stress testing, cardiac MRI, signal-averaged ECG, and sodium

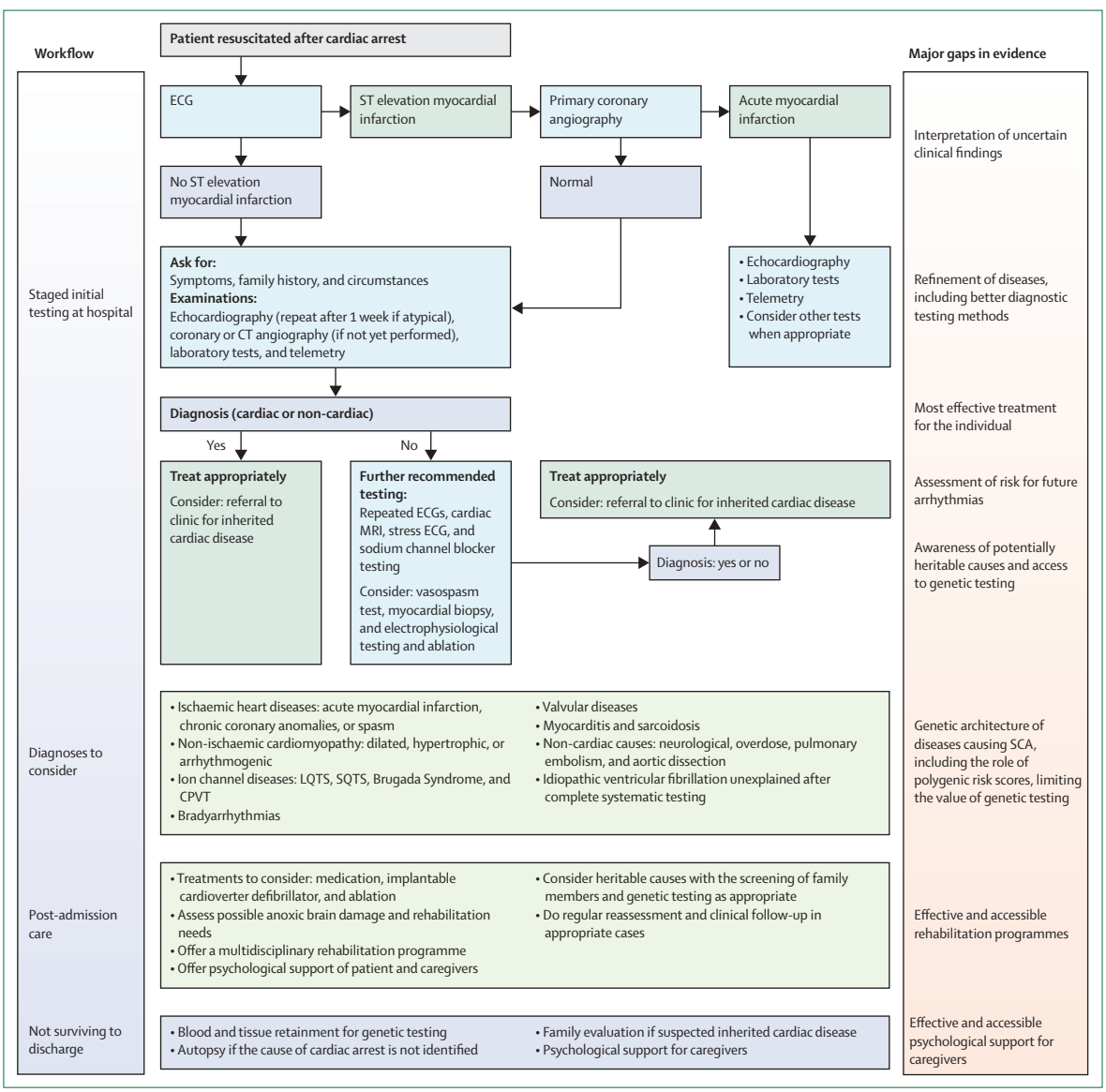


***Figure 15:*** **Management of the patient initially resuscitated after cardiac arrest**
CPVT=catecholaminergic polymorphic ventricular tachycardia. ECG=electrocardiogram. LQTS=long QT syndrome. SCA=sudden cardiac arrest. SQTS=short QT syndrome.

channel blocker provocation, can provide further diagnostic information in nearly half of patients and should be systematically considered.[111,373,374] Overall, around 5–10% will remain unexplained after thorough evaluation and are termed idiopathic ventricular fibrillation (figure 5).[45,82,375]

*Unexplained SCA, or just not yet explained?*

The fact that some idiopathic ventricular fibrillation are caused by new or currently unrecognised diseases is probable, potentially explaining a proportion of idiopathic ventricular fibrillation, as has been the case with Brugada syndrome, short QT syndrome, and more recently the widespread ST-segment depression syndrome, and the identification of microstructural epicardial abnormalities.[100,376–378] Some patients might develop phenotypic traits later in life pointing towards a specific diagnosis, whereas some might only be explained if cardiac screening of family members is initiated because occasionally the phenotype might be more evident among asymptomatic relatives.[379] This area requires further research.

*Treatment considerations in survivors of SCA*

Survivors of SCA with a good neurological outcome and no reversible cause of arrhythmia, such as acute ischaemia, should receive an ICD.[380] The notion of a reversible cause of SCA is sometimes difficult to interpret and implement in clinical practice. In this regard, the new European guidelines indicate a more aggressive approach, considering severe ventricular arrhythmias related to coronary vasospasm (ie, with a reported high risk of recurrence and issues because of non-adherence to pharmacological therapy in the long term) and acute myocarditis as being reasonable candidates for ICD.[111] The guidelines also mentioned that despite a possible correctable cause for ventricular arrhythmias, the need for an ICD should be carefully considered on the basis of an individual evaluation of the risk of subsequent ventricular arrhythmias and SCD. Although the ICD is potentially lifesaving, adverse events and other implications should also be considered and weighed, albeit in the scenario of secondary prevention, risk–benefit ratio is mostly favourable.

*Understanding disease mechanisms for better treatment options*

The utility of catheter ablation with secondary-prevention ICDs and a recurrence of ventricular arrhythmias has been established. By contrast, pharmacotherapy in SCA survivors is an emerging area in which few data currently exist, given the disappointing progress in antiarrhythmics over the past 4 decades. For instance, although it is known that β-blocker therapy is effective in patients with long QT syndrome, different β blockers vary in their degree of effectiveness. In Brugada syndrome, quinidine might be a useful drug to consider for some patients, but is unavailable in many countries and is well known for its potential side-effects, especially gastrointestinal. No pharmacological treatments are proven for patients with idiopathic ventricular fibrillation, despite approximately 30% receiving appropriate therapy from their ICD within 3 years.[375] A more in-depth understanding of the disease mechanisms and causes will allow new therapies that directly target specific pathways. Although large clinical trials might not be feasible in this setting, especially in rare diseases causing SCA, ascertaining whether genotype can influence medical therapy could allow better tailoring of effective treatments. This area requires work because current recommendations are based on very small and often outdated case series.

*Rehabilitation*

Survival rates after SCA are increasing.[47,381] SCA causes a period of cerebral hypoperfusion consequently resulting in varying degrees of anoxic brain injury.[382] The cerebral hypoperfusion and the concomitant brain injury after cardiac arrest remains the primary cause of death in the ICU among patients with SCA who survive to hospital admission. The extent of the anoxic brain injury depends on the severity and duration of the reduction of blood supply to the brain, which is determined by the quality of resuscitation.[383,384] Moreover, after partial or complete restoration of blood flow, persistent or recurrent inadequate delivery of oxygen to the brain can cause secondary brain injury.[385] Remission of the brain injury is expected, to some extent, within the first 3 months after SCA.

Follow-up assessment, as recommended by the ERC guidelines,[384] several months after hospital discharge has revealed persisting mild to moderate neurocognitive impairment in 30–50% of survivors of SCA.[386] Memory for novel information and delayed recall, attention, executive functioning (ie, planning and organisation), and visual–spatial abilities are mostly affected.[387] Whether these effects are because of anoxic brain damage, post-traumatic stress symptoms, or both is more difficult to assess. High rates of psychological issues, including anxiety, depression, post-traumatic stress disorder, and long-term fatigue, have also been reported among survivors of SCA.[82] These factors will negatively affect quality of life, mental and behavioural function, and the ability to return to work.[387,388]

It has been shown that the outcome after SCA, measured as quality of life and societal participation, can be improved by an early intervention providing various support in case of identified cognitive disruption.[389] Current observational literature suggests that effective return-to-work interventions for patients with acquired brain injury are a combination of work-directed interventions, coaching and education, and skills training, orchestrated by a multidisciplinary team consisting of relevant medical specialties, physiotherapists, occupational therapists, social workers, psychologists, and others that collectively work closely together around the patient. These

interventions have been found to facilitate sustained return to work in patients with brain-related effects.[390] Findings in 2022 have stressed the importance of screening for health problems in all SCA survivors to identify those in need of professional support and rehabilitation, independent of neurological outcome.[391]

*Rehabilitation of survivors of SCA*

The SCA recovery journey is different from survivor to survivor, and a holistic approach is needed to create personalised rehabilitation care plans that are iterative, consider the complex needs for the survivor and caregivers, and ensure equitable access for all (figure 16). SCA survivorship is increasingly recognised as an important research field, yet investment in and the acknowledgment of the need for an evidence-based, comprehensive, coordinated rehabilitation pathway for survivors of SCA has been scarce. This paucity is particularly evident when compared with other critical conditions, such as stroke and injury to the spinal cord. However, the gaps in current knowledge of rehabilitation of SCA survivors are extensive and cover almost all spectra from the understanding of the pathophysiology, how and when to intervene, duration of support, and the outcomes that should be measured. Quantifying the problem is another challenge because there are no patient-reported outcome measures specific to survivors of SCA and generic quality-of-life measures are unlikely to address the aspects of life most important to them.[392] Hence, future research should focus not only on developing specific indices for measuring the effect of different rehabilitation programmes, but also on better understanding the biological, neurological, and psychological foundation of the challenges survivors of SCA experience, including in the long term.

## The role of genetics

*Genetic testing the proband and family*

Genetic testing can be a powerful tool in the investigation of SCD and survivors of SCA when an inherited condition is suspected.[77,393] Therefore, all efforts towards a complete clinical investigation focused on identifying a specific cause for SCA should be made.[363] With the decedents, a comprehensive autopsy is essential if a potential inherited cause is identified or suspected (ie, cardiomyopathies or channelopathies in the case of a negative autopsy), and genetic testing should be performed in the appropriate set of genes.[363]

Post-mortem genetic testing (ie, proband genetic testing that is performed on a DNA sample collected after death—either a blood or tissue sample suitable for DNA extraction) relies on the retention and storage of an appropriate sample.[394] Regulations and protocols for collecting samples when a heritable cause of SCD is suspected vary widely, and access to DNA of sufficient quality to perform genetic testing is one of the biggest challenges in this setting.[363,395] Another difficult challenge is the absence of funding support to perform a post-mortem genetic investigation in most countries: a gap that should be filled through the recognition that the deceased individual is the proband of a family wherein future events could be preventable.

Genetic testing for monogenic conditions is a two-step process. The first involves proband genetic testing to identify the underlying genetic cause of disease. If a causative variant is identified, the second step can start with cascade genetic testing (in parallel with the usual phenotypic screening) to first-degree relatives, evaluating the specific variant. Relatives found to have the variant will continue clinical surveillance and, importantly, their own first-degree relatives, including children, should undergo genetic and clinical screening. Conversely, relatives who test negative can be released from lifelong, periodic clinical surveillance and their children are no longer at risk.

The likelihood of a causative variant being identified in those with an established clinical diagnosis is disease dependent, ranging from around 20% for Brugada syndrome, around 40% for hypertrophic cardiomyopathy, and around 75% for long QT syndrome. By contrast,

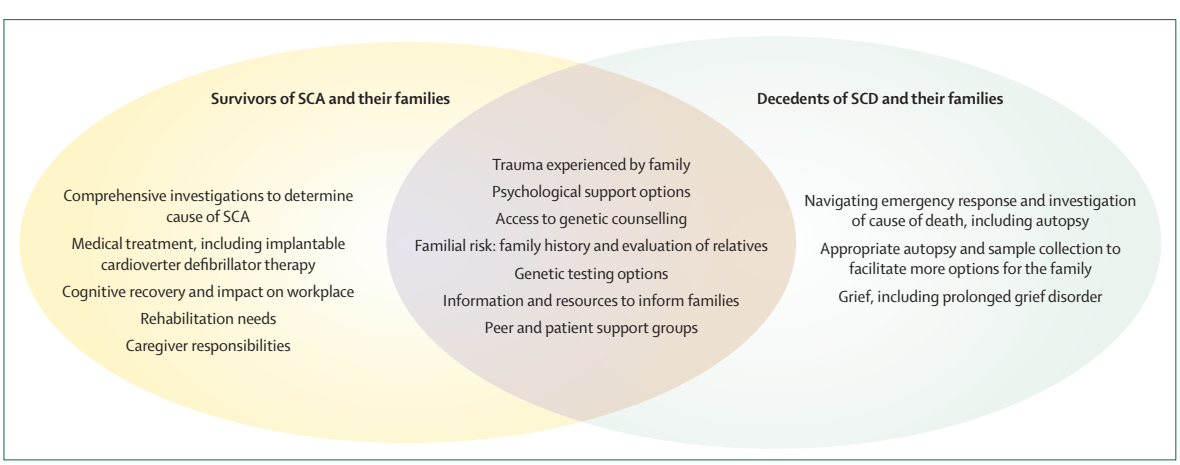


***Figure 16:*** **Holistic overview of key aspects after SCA or SCD**
SCA=sudden cardiac arrest. SCD=sudden cardiac death.

when a clinical cause of death is not established after autopsy and toxicological testing (eg, sudden arrhythmic death syndrome), the current yield of genetic testing in adult survivors is much lower, around 10–15% at best, although might be higher in children.[77,393,396,397] Although this yield is low, the value of identifying a causative variant in a given index patient is immense, providing a cause of death and answers for the family and allowing cascade genetic testing for relatives at risk (figure 17).

*Challenges with variant classification*

Rare variants are often encountered and distinguishing between causative and circumstantial variants is a challenge.[398] Classification of variants is guided by the American College of Medical Genetics and Genomics standards for variant interpretation.[399] If sufficient supportive evidence for causation exists then a variant will be considered pathogenic or likely pathogenic and can be used for family screening. When the evidence is conflicting or insufficient, it will be considered a variant of uncertain significance. Poor representation of diverse ancestral groups among both SCA research cohorts and genomic reference databases makes interpreting genetic variants more challenging, especially for individuals with diverse ancestries. Hence, interpreting genetic variants can be challenging in ancestry groups without population-specific reference datasets.[400] There can be many inherent challenges with achieving more inclusive representation in research, but strong community engagement and partnership are key.

Misclassification of variants has potential for substantial harm and psychological distress to families already dealing with trauma and grief; therefore, efforts to ensure balanced and careful interpretation of variants in experienced centres[400] and the correct communication of the genetic result and its implications through genetic counselling are essential.

*The future of genetic testing*

For patients with inherited heart diseases, variants of uncertain significance have no utility for the family. When clinical genetic testing has been unable to identify a causative genetic variant, in patients for whom a monogenic cause is strongly suspected, genomic research with a focus on novel gene discovery should be prioritised. Public sharing of candidate variants and robust phenotype information has potential to inform identification of new disease mechanisms and genetic causes of disease. The number of variants classified as variants of uncertain significance could be vastly reduced by a greater use of worldwide, publicly available databases merging genetic and phenotypic data, with opportunity for machine-learning approaches to improve variant classification.[401] However, access to genetic testing is scarce in many countries and partnerships should be developed to support health systems with more limited resources, which would also ensure that diverse ancestry groups could be represented. Many studies have shown the potential application of dried blood spots for molecular epidemiology studies, drug monitoring, diagnostic screening, and genetic analysis studies in low-income or remote areas.[396,402,403] The method of dried blood spots has offered several advantages in areas without the appropriate infrastructure for sample storage, processing, and cold-chain transportation, substantially reducing the costs and improving sample accessibility for future molecular analysis, such as whole-genome amplification.

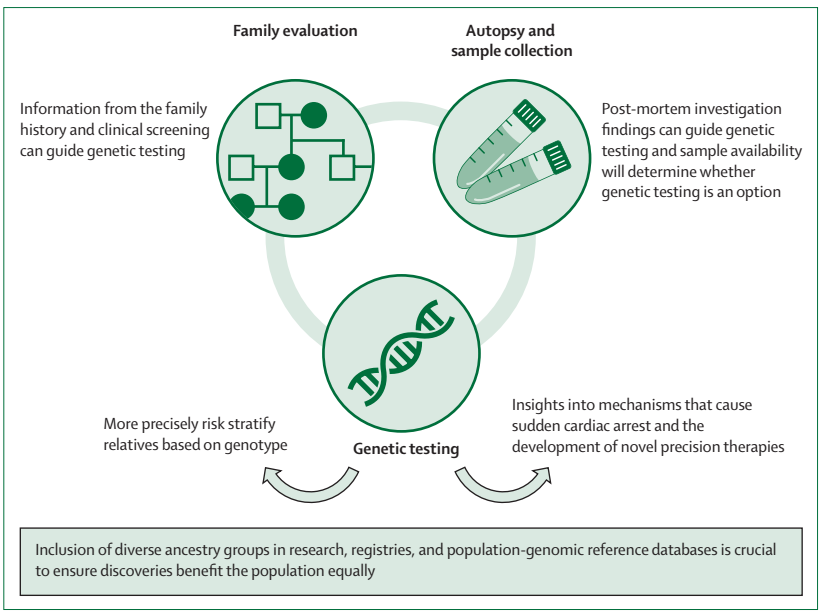


***Figure 17:*** **Challenges and opportunities in genetic testing**

## Family screening and support

SCD is a condition with a particularly profound, two-fold impact on the patients' family, namely the psychological trauma engendered by the event and the possibility that they could also be at risk due to a heritable condition. In management after SCD, a specific focus on the immediate family is essential. Broad goals of family screening include identification of relatives with the similar cardiac pathology as the index patient or, conversely, to aim to identify the cause when unknown through systematic assessment of first-degree relatives. Ongoing surveillance and psychological support and rehabilitation are the other main aspects of helping families afflicted by SCD and SCA.

Overall, family members of young people (ie, aged <50 years) who have SCD have a higher incidence of cardiovascular conditions than the general population.[29,140,141,404] This fact highlights the importance of performing systematic evaluation of first-degree family members of a young SCD patient and in the case of a documented or suspected inherited cardiac disease.

When a probable or definite inherited cardiac disease in a patient who had SCD is diagnosed by post-mortem

evaluation, family screening should be initiated to identify first-degree relatives at risk.[21] If a genetic variant is identified in the person who had SCD, family screening can include targeted genetic testing; otherwise, phenotype-guided cardiac evaluation alone, which can include genetic testing based on the diagnosed phenotype, is indicated to identify affected family members (figure 17). In the absence of genetic testing, or when the genetic variant is not considered as causative, family members should undergo periodic clinical investigation.

When an autopsy is not performed, family screening remains challenging. A wide variability in the yield of family screening (10–50%) in identifying an inherited cardiac disease (mostly primary arrhythmia syndromes) has been reported. This variability might be explained by the relatively small sample sizes of studies, differences in age ranges and characteristics of the decedents and relatives included, the extent of referral bias, the cardiac evaluation protocol, and the diagnostic criteria that were applied.[378,393,405–407] Hence, whenever an inherited condition is considered probable, especially in unexplained SCD of a young person, family screening should be strongly considered.

In survivors of SCA, family screening is much more straightforward and its value usually high when there is an established phenotype of an inherited cardiac disease in the proband.[408] In monogenic diseases with a high penetrance, half of the relatives are likely to be affected. In survivors of unexplained SCA with only limited diagnostic testing, detection yield is only 30–60% in the proband and consequently lower in the relatives.[409,410] In patients with idiopathic ventricular fibrillation, for whom a full diagnostic test has been completed, the diagnostic yield of family screening is reported to be much lower (approximately 4%).[379] Family members of patients with idiopathic ventricular fibrillation generally have a favourable prognosis with a low rate of events at follow-up.[411] Hence family screening can serve to reasonably assuage family members' fears regarding the future. However, some patients of idiopathic ventricular fibrillation might harbour cardiomyopathy-related genetic variants, in which the incident cardiac arrest might in fact be the first manifestation of a later cardiomyopathy. For these patients, reassessing the family would be important.[351]

### *Screening protocol*

Family members of SCD of a young person should be screened in dedicated outpatient clinics by cardiologists who are experienced in recognising and managing patients with inherited cardiac diseases. However, this need might not always be possible because of the non-existence or insufficient capacity of such dedicated outpatient clinics in some areas. Although some general cardiologists might be able to get expert advice through existing networks, in the future this ability might become more broadly scalable to many more parts of the world via online networks of experts in specific disease settings. The differences seen in quality and yield of family screening by specialised versus non-specialised clinics and physicians and the benefit of online expert consulting has not been studied.

Various family-screening protocols have been applied and at least partly explain the differences in detection yield that have been observed.[412] First-line evaluation includes a detailed personal and family history, resting ECG, echocardiography, and an exercise stress test.[21] Additional clinical diagnostic tools, particularly ambulatory Holter monitoring, cardiac MRI, and pharmacological challenge, are also frequently considered. Active family screening to identify disease carriers leads to guideline-based care in affected relatives, which then results in low adverse event-rates.[413] However, knowledge on the optimal screening protocol, ages at which family screening should be initiated and discontinued, and in whom and at what intervals follow-up is indicated, is absent. Sensitivity and specificity of pharmacological challenges in carriers of concealed disease (ie, individuals in whom the resting ECG and exercise stress test do not show clear signs of these conditions and genetic testing is negative) are unclear. Interpreting a positive pharmacological challenge in an asymptomatic and previously healthy family member of a young patient who had SCD can be difficult, especially when the post-mortem evaluation of the patient was insufficient and genetic testing is negative.

Different studies have shown a low percentage of cardiac screening initiated in family members of a young patient who had SCD in whom an inherited cardiac disease could have been present.[414] This infrequent family screening might be explained by the unfamiliarity of the value of family screening among both medical professionals and the family involved, logistical barriers, and emotional barriers.[415] Systematic performance of family screening is not easy to organise and requires detailed counselling and a willingness of the family member to acknowledge risk and proactively take ownership of their future course.

### *Psychological support of relatives and caregivers after SCD or SCA*

An SCD or SCA event has major implications for the family of the patient because of the suddenness of the event and its often inexplicable nature. The grief experienced by family members following the unexpected death of their otherwise healthy relative can be profound. In the largest study to date, up to half of first-degree relatives reported post-traumatic stress or prolonged grief on average 6 years after the death.[29] For relatives who witnessed the death or discovered the decedent's body, there was a four to five times greater likelihood of poor psychological outcomes, illustrating the substantial

trauma associated with unexpected SCD in a family member. Other studies have shown high rates of anxiety and depression, and unique to those families in which a heritable cause was known or suspected, key concerns were understanding the cause of death and ensuring that no other family members were at risk of the same outcome. For parents who have experienced SCD or SCA of a child, there can be marked feelings of guilt, parental anxiety, and fear of recurrence in their other children.[416]

Access to psychological support after SCD is often not provided.[412,417] Relatives of a young patient who had SCD consistently report a need to understand the cause of the death and request psychological support.[418–420] Providing access to community and peer support, offering a safe space with understanding, and normalisation and enabling sense-making might be a powerful approach to supporting relatives.[419] The impact on relatives of a SCA survivor can also be marked, because not only must they navigate the trauma of the event, but there can also be prognostic uncertainty for the survivor. Caregivers have poor psychological wellbeing on follow-up, including post-traumatic stress in up to 40%.[421,422]

Current gaps in knowledge relate to the development and availability of interventions to support family members, facilitate grieving, and enhance psychological wellbeing. When no cause of the SCA is identified, ongoing research efforts to elucidate the clinical and genetic diagnoses will ultimately provide answers for families, reduce uncertainty, and allow some degree of closure. Evidence-based resources for the psychological needs of survivors of SCA and their relatives should be widely available and offered systematically. Addressing the trauma experienced and managing the uncertainty in prognosis and ongoing care needs of the survivor of SCA pose specific support requirements. Likewise, among family members after SCD in the young, emerging evidence supports a role for normalising grief responses, providing information, recognising trauma symptoms, and facilitating meaning-making. For individuals requiring more specialised support, seamless referral pathways to clinical psychologists or other qualified health-care professionals with experience in SCD and trauma are necessary. Resources permitting, a multidisciplinary team comprising all relevant health-care professionals can be helpful to address all needs of survivors of SCA and family of patients who have SCA or SCD.

### Summary and future direction to improve management of decedents, survivors, and relatives

We still have major gaps in evidence, challenges, and unresolved questions in the management after SCD and for survivors of SCA. A full post-mortem investigation is crucial to identify the cause of SCD, yet autopsy rates have been declining and the autopsy protocol often does not follow the minimum standard as recommended by international guidelines. On one hand, all efforts to improve rates of guideline-indicated autopsies worldwide should be made; on the other, acknowledging the difficulty and inconsistency in obtaining the gold standard of autopsy, evidence-based alternatives should be developed.

The cause for SCA remains unexplained in some survivors, either due to incomplete investigations or gaps in our current understanding of SCA pathophysiology. We need to refine existing methods and develop new methods of investigating the underlying cause of SCA to eventually discover new disease entities and allow for targeted treatments for individual patients.

Genetic testing has a key role in the investigation of SCD and SCA to understand the cause of disease in the proband and as a tool for clarifying risk in family members. The importance of the related phenotype is crucial to appreciate the likelihood of a causative association with a potential genetic variant. However, there are limitations in our understanding of the genetic architecture of conditions causing SCD, especially in diverse populations, leading to uncertainty for clinicians and families.

Family screening is also crucial to identify risk and as a diagnostic tool, given that asymptomatic relatives might sometimes present a clear phenotype. However, timelines and optimal methods of screening need further clarification.

The profound neurological and psychological challenges survivors of SCA face need elucidation and recognition. Trials that incorporate multidisciplinary expertise should be performed to optimise support and rehabilitation protocols.

Although there is need for high-level multidisciplinary expertise across all areas of management after SCA, many patients across the globe will not have access. Balancing the accepted gold standard with scalable and broadly accessible options remains a challenge. The implementation of regional networks that can escalate the review of patients requiring expertise in cardiac pathology, clinical investigations, and genetic testing, but also training to build capacity of local services is needed to have a marked global impact. Recommendations for management of decedents, survivors, and relatives are summarised (panel 9).

## Specific considerations

### SCD in LMICs

LMICs are faced with a unique double burden of communicable and non-communicable diseases because of ongoing epidemiological transition. Non-communicable diseases are rapidly overtaking communicable and infectious diseases in prevalence, driven by expanding urbanisation, changes in lifestyle, and dietary patterns.[423] Cardiovascular disease is the main cause of death in many LMICs, with SCD probably contributing to a major proportion of that mortality. The effect of SCD is also probably more

***Panel* 9: Recommendations for management of decedents, survivors, and relatives**

- Establish a minimal standard of protocol and tissue and fluid sampling to ensure the quality of the autopsy investigation (ie, gold-standard autopsy). To ensure fluidity, core laboratories should be promoted for the pathological diagnosis of heart diseases in people who have sudden cardiac death (SCD), including the implementation of digital pathology for second opinion.
- Train and deploy additional experts who can perform high quality cardiac autopsy and investigate ways that technology could be used to assist and support this work, including application of new artificial intelligence-based tools.
- Increase focus on understanding rehabilitation needs to improve outcomes, quality of life, and psychological support to be offered to both patients and caregivers.
- Draw on existing facilities for storage and future analysis of DNA and other biological samples, relying on government agencies to facilitate legislation.
- Elucidate monogenic and polygenic risk of sudden cardiac arrest (SCA), with a focus on bringing together large and diverse international cohorts to provide sufficient statistical power, allowing greater certainty about the cause of SCA and familial risk to relatives.
- With recognition to the issues regarding access in some places, digital tools to support elements of genetic counselling, such as educational content, decision support, and chat bots, could replace some aspects of genetic counselling.
- Perform systematic evaluation of family members at risk, preferably in dedicated outpatient clinics by cardiologists who are experienced in recognising and managing patients with inherited cardiac diseases. Alternatives should also be developed due to insufficient capacity of dedicated outpatient clinics managing patients with inherited cardiac diseases.
- Increase understanding of causes of cardiac arrest and the arrhythmic mechanism, to effective treat the patient and prevent them from having new arrythmias in the future.

profound compared with HICs, given that cardiovascular disease affects, on average, younger individuals.[424] Yet, active engagement of the global community to reduce the burgeoning mortality from cardiovascular disease and SCD in LMICs is relatively less compared with the interest in infectious diseases, such as tuberculosis, malaria, and HIV.

SCD in LMICs poses unique challenges with respect to all its facets (ie, before, during, and after the event). The burden of SCD is difficult to assess accurately because of scarce epidemiologic data, which in turn is related to the relative paucity of organised EMS systems and systematic registries for reliable data collection compared with HICs.[425] A few studies from China and India have suggested out-of-hospital cardiac arrest incidence of about 40–42 per 100 000, with male predominance and coronary artery disease as the main cause.[31,33,82] Not only is the incidence of treated out-of-hospital cardiac arrest reported to be lower overall in Asia compared with North America and Europe, but also the proportion of ventricular fibrillation and survival rates are significantly lower. In the Middle East and Africa, findings from limited autopsy studies support coronary artery disease as the main cause.[426–428] Information from sub-Saharan Africa is even more sparse; a few autopsy-based studies have suggested low overall SCD incidence, again with male preponderance and coronary artery disease as the most frequent cause. However, SCD rates are likely to be substantially underestimated.[429–432] Most studies have involved retrospective reviews of records and death certificates as opposed to prospective, real-time ascertainment, and therefore outcomes are heterogeneous and likely to be subject to bias and error.[433] Additionally, variations in local language, education levels, and understanding can all affect the ability of lay people to recognise SCD, resulting in delays or even non-reporting.[434]

In trying to implement the ten-step approach advocated by the Global Resuscitation Alliance,[435] several barriers can be encountered in LMICs. In addition to a relative deficiency of organised EMS compared with HICs, other logistical problems exist, such as poor roads and traffic systems that can result in substantially prolonged response times. In some remote areas, for any ambulance or emergency response to arrive at all might be simply impossible. Public access defibrillation and AED availability is scarce in many LMICs, being restricted to high-value locations, such as airports, large malls, or recreational facilities, out of reach to most of the public. In addition, little training and awareness, absence of appropriate legislation, fearfulness, and cultural barriers pose substantial obstacles for meaningful public response, with studies showing low rates of lay CPR and public AED use.[428]

SCD prevention also poses unique problems in the context of LMICs. Lower awareness of cardiovascular health and fitness at a population-wide level compared with HICs renders primordial prevention of SCD more difficult. Furthermore, SCD risk markers in Asian and African populations might be different from European ancestries and there is a need for ethnicity-specific SCD research, including genetic studies. In a context in which even basic health-care access might be difficult for a considerable section of the population, advanced techniques, such as post-resuscitation care, electrophysiology services, catheter ablation, and ICDs, will be available only to a select minority.[428] In North America and Europe, pacemakers or cardioverter defibrillator implants average 300 per million population; by contrast, in India there are 25 implants per million population. In some African countries, the implant rates

have been reported to be up to 500 times lower compared with HICs,[436] with an extremely small proportion of ICDs among all cardiac implantable devices.[437] Reimbursement issues, poor access, limited understanding, and cultural outlook might all have a role, with SCD being more acceptable compared with an ICD in some societies.[438]

Keeping these realities in mind, sustained efforts and innovative solutions are needed to address the SCD burden in LMICs. There is a need to support large, prospective epidemiologic studies of SCD in areas such as sub-Saharan Africa.[439] Public–private partnership models, especially with philanthropic organisations, can be useful to drive coordination of EMS systems and promote systematic data collection and quality improvement.[436,440] Public-awareness campaigns and education are essential to improve the public's perception of SCD and how they can contribute to tackle the problem. For instance, the non-governmental initiative, the Revive Heart Foundation (iCARE) in India, has been involved in conducting large-scale training programmes on CPR and AED use for targeted groups, such as police, railway personnel, and various residential societies. iCARE also conducts public-awareness and educational programmes regarding SCD, including using messages from celebrities. Political will and governmental legislation can help by mandating CPR training in schools or as a requirement for issuing a driving licence, for instance.[441] Steps have to be taken to strengthen the chain of survival at all levels, starting from forming nation-wide or region-wide EMS systems with universal access through a single telephone number, the presence of EMS dispatch 24 h a day, 7 days a week with rapid response, and the development of systematic referral to centres capable of providing care and rehabilitation after SCA.

Given widespread poverty and limited health-care budgets in LMICs, workarounds, such as the use of explanted, resterilised cardiac implantable electronic devices, and the reuse of cardiac catheters with appropriate safeguards in place, have to be seriously considered to ensure that therapies reach even the least affluent sections of the population.[442] Appropriate-use criteria specifically tailored to resource-limited settings also need to be developed to optimise therapies for those who would benefit maximally. The concept of 1.5 prevention (representing an intermediate stage between primary and secondary prevention) for ICDs has been suggested as a model for use in resource-constrained systems. In this model, patients satisfying primary-prevention criteria plus an additional risk factor (syncope, non-sustained ventricular tachycardia on Holter, etc) can be prioritised for the primary-prevention ICD because the putative benefit would be expected to be greater than that of the usual primary-prevention approach.[443] Ventricular tachycardia ablation and sympathetic denervation have been proposed as lower-cost alternatives to ICD placement, but need further study to support the concept.[444,445] There is an urgent need to develop indigenous, novel, cost-effective alternative solutions to high-end technology to tackle SCD in LMICs. Such innovation has been shown in other arenas, such as heatstroke management.[446]

Lastly, to successfully implement the ten-step approach or to deliver therapies related to SCD prevention in LMICs, international collaborations that bring together groups with diverse expertise, such as the Pan-Asian Resuscitation Outcomes Study consortium,[447] are needed to identify barriers and evolve effective strategies to solve region-specific problems. The integration of medical, political, and industrial sectors is necessary to find workable solutions. Establishment of national and regional medical advocacy groups and societies can then galvanise efforts to ultimately have a meaningful effect on SCD in LMICs (panel 10).

## SCD during sports activity: a unique model

### *The paradox of exercise*

Physical activity is at the forefront of cardiovascular disease prevention and participation in regular exercise is associated with a multitude of health benefits. The sudden collapse of an ostensibly healthy individual on the playing field contradicts this notion and brings to the fore concerns about potential adverse effects of exercise, referred to as the paradox of exercise (figure 18).[448] Vigorous exercise might transiently increase the risk of dying suddenly, especially in untrained individuals with underlying heart disease.[449] However, in the long term, regular exercise is associated with a dose-dependent reduction in overall and cardiovascular mortality, including SCD.[450–452] Although there is often concern in the general public about the potentially detrimental effects of too much exercise,[453] in most cases exercise is merely the trigger of malignant arrhythmias in an

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***Panel 10*: Recommendations to address the burden of sudden cardiac death (SCD) in low-income and middle-income countries (LMICs)**

- Prospective, epidemiological studies for accurate assessment of SCD burden and outcomes should be initiated and promoted in LMICs to be able to better understand the magnitude of the problem and propose tailored solutions.
- Widespread public education and awareness campaigns on sudden cardiac arrest (SCA), early cardiopulmonary resuscitation (CPR), and defibrillation, backed by legislation, are necessary in LMICs to improve the low rates of bystander CPR and use of automated external defibrillation.
- SCD prevention strategies in LMICs should be cognisant of economic realities and explore low-cost alternatives to high-end, expensive technology. Solutions, such as reusing explanted implantable cardioverter defibrillators, require rigorous testing and well regulated implementation.

individual with quiescent heart disease. Thus, efforts should focus on identifying those individuals with unrecognised heart disease and provide safe exercise recommendations, rather than the restriction or prohibition of exercise.

The relative prevalence of various underlying pathologies in SCD during sports differs in reported series, but coronary artery disease dominates in individuals older than 30–35 years.[33,454–456] Conversely, cardiomyopathies, congenital coronary anomalies, and primary electrical conditions (eg, ion channelopathies) and myocarditis are more frequent in younger patients having SCD during sports.[457,458]

Data published in 2021 suggest that premature coronary artery disease might be more common than previously thought in young, non-competitive athletes, underlining that the causes of sports-related SCD in the general population cannot be extrapolated from the specific competitive-sports setting.[459]

### *Screening for preventing sports-related SCD*

SCD in young, competitive athletes (aged <35 years) accounts for only a minority of overall sports-related SCD, with older (>35 years) individuals engaging in recreational sports activities representing the greater majority of such cases.[455,460–462] The risk of SCD in male athletes appears to be higher (up to 30-fold) than in female athletes, even after consideration of exposure (eg, participation rates) and differences in sports practices.[463–465] The reasons for the striking disparity between sexes are not clear, but could include the higher prevalence of coronary artery disease in young and middle-aged men compared with women, sex-based differences in nutrition and adherence to healthy lifestyles, differences in trigger or autonomic modulators, and susceptibility to arrhythmias.[463,464,466] The reasons underlying the lower risk in women than in men should be assessed further to help improve preventive approaches. A higher risk has also been documented for start-stop sports, such as football and basketball, and in Black compared with White athletes.[466,467]

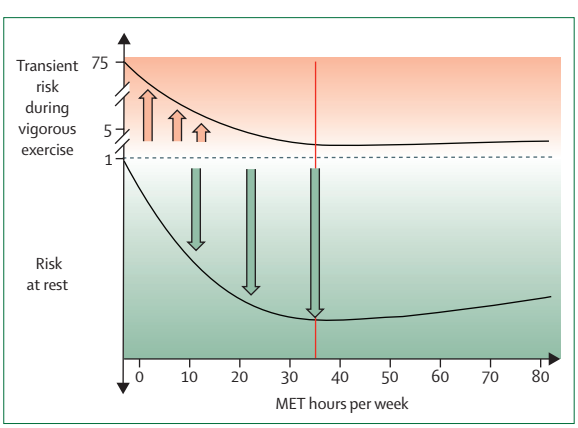


***Figure 18:*** **Benefits and potential harms of sports activity**
Relative risk of SCD at rest and during vigorous exercise (transiently elevated SCD risk) in any patient according to their exposure to regular exercise. Green indicates long-term reduction of SCD. Red indicates an acute increase of SCD during physical activities. For example, a person who walks 30 min vigorously to work and back 5 days a week, runs for 45 min twice a week, and takes a weekly 1-h aerobic class will get the best reduction of SCD risk (red line). MET=metabolic equivalent of task. SCD=sudden cardiac death.

On the premise that for most athletes, SCD is the first presentation of a pre-existing cardiac condition and that participation in high-level competitive sport increases the likelihood of arrhythmias with such predisposition, many scientific and sporting organisations advocate cardiac screening of all athletes before participation, in the hope that risk stratification, appropriate lifestyle measures, pharmacotherapy, enhanced emergency response planning. and cascade family screening could prevent SCD.[468–470] However, screening young competitive athletes and recreational sports participants presents multiple challenges, including identifying the underlying malignant substrates; selecting the target population and the screening method; the availability of resources, expertise, and associated costs; and the ethical, psychological, and medicolegal implications of asking athletes to cease competitive sports.[471,472] Although a targeted approach also has ethical challenges, the striking male predominance among sports-related SCD questions the need for routine screening among female athletes.[465]

Once the target population is defined, common methods for screening and prevention should be identified and universally implemented. Accessibility, affordability, and accuracy are required to ensure global implementation and consistency in practice. The AHA proposes a 14-element cardiovascular checklist as a pragmatic approach for the screening of congenital and genetic heart disease in young athletes.[473] The physician could use this tool to determine whether further cardiovascular examination is required. Due to the poor sensitivity of symptoms in detecting heart disease in the context of pre-participation screening, the European Society of Cardiology advocates the addition of a 12-lead ECG.[474] Additional prospective studies are needed to assess the effect of cardiac screening before participation. There is also a need for prospective, national registries for the documentation and investigation of SCD in young athletes and for recreational sports participants with cardiac conditions predisposing to SCD. Such registries could help inform the best preventive strategies and screening methods for a particular population.

The physician's role and medicolegal frameworks on athlete screening and disqualification vary from country to country, adding further layers of complexity that hamper a unified approach. Some countries adopt a paternalistic approach in which the physician holds the final say and is required to sign a document certifying that the athlete can safely participate in competitive or

even recreational sports. In other countries, the physician has a more advisory role; it is the physician's responsibility to explain the evidence base, knowledge gaps, and current recommendations from scientific organisations to help the patient-athlete come to a guided decision based on the perceived risk–benefit balance. Screening should be viewed as an opportunity to identify athletes with increased risk and manage that risk on the basis of established protocols. The ultimate goal should be a shared decision-making process that allows for an individualised exercise prescription, respects an individual's self-determination, and offers athletes the necessary protection at the same time.[468] Finally, it should be considered that even the most meticulous screening protocols cannot prevent all sports-related SCA;[471] hence, an equal or greater focus is needed on improving on-field and community preparedness and resuscitation to reduce mortality from sports-related SCA. The approach to screening should be individualised depending on different countries, health systems, and societies.

There is also a need to highlight the downsides of screening before sports participation, particularly the risk of overtreatment of potentially clinically unimportant disease and the potential for inappropriate disqualification of individuals from competitive sport, which could be for the rest of their lives.

*Improving outcomes in sports-related SCD*

Sports-related SCD provides a unique setting for maximising survival because most events occur in public places and are witnessed, with survival reported to be up to 70% in the general population.[3,468,475] This finding is mainly driven by higher rates of lay-responder CPR and AED use compared with non-exercise-related SCA.[460,462] Nevertheless, prompt recognition of SCA in a setting of extreme low probability could be a challenge.[476] The stark contrast in survival rates between events occurring in organised sports facilities, which enable early lay-responder CPR and AED use, versus sports-related SCD in the general population in which lay-responder intervention rates are low underscores the potential benefits of improving public-health initiatives in the community setting. There should at least be one AED available in every sport facility. Achieving high rates of survival to hospital discharge is possible with a multipronged approach. Public education in basic life support and use of AEDs, increased AED accessibility, improved emergency response systems, and improved symptom awareness are obvious targets.[2,3,477] Media coverage of sports-related SCD has to be channelled in the proper manner to help improve public awareness and education in basic life support, AED use, and healthier lifestyles, rather than creating a milieu of fear about exercise in general (panel 11).

Emergency-response planning during major sporting events should also take into consideration that road closures and diversion of medical resources to the event could have an adverse effect on transport time to hospital and emergency care for the general public in the vicinity. SCA is a rare occurrence among marathon and half-marathon runners with an incidence of 5 per million participants;[478] however, the 30-day mortality in marathon areas and routes on marathon dates is up to 13·3% higher compared with non-marathon dates.[479] Thus, a city-wide strategy for emergency preparedness for major sports events should consider the risks not only to participants, but also to non-participants. For instance, relocation of marathon routes away from busy areas or to cities' outskirts could be beneficial.

## Ethical considerations

Clinicians are faced with ethical challenges every day when providing health care to individuals with diverse backgrounds, cultures, values, and societal acceptances. SCD prevention and management carries its own share of ethical dilemmas. When evaluating the merits of medical procedures and treatments, there are four main principles of bioethics: autonomy, justice, non-maleficence, and beneficence. Strategies for SCD prevention and management should respect all four of these principles. However, the sudden, unpredictable nature of SCD paired with the need for an immediate response, and the often devastating consequences, pose unique challenges that could lead to potential conflicts between principles.

Starting with justice, health inequities exist across all aspects of SCA prevention, resuscitation, and care after SCA, and in research and innovation efforts. Most research has traditionally focused on more privileged population groups: to date there is more reliable data on

***Panel 11*: Recommendations to decrease the burden of sports-related sudden cardiac death (SCD)**

- Ensure accurate messaging on the rare cases of sports-related SCD to prevent an unwarranted emotional stigma of sports participation posing danger, but rather provide emphasis on the well known benefits from sports participation, decreasing the risk of SCD in the long term.
- Given the great improvement in survival rates of sudden cardiac arrest (SCA) occurring during sports, contrasting with the relatively stable incidence rate over the past half a century, policy makers should harness the momentum, but using the sports environment as an example on the efficacy of immediate cardiopulmonary resuscitation and public automated external defibrillation use.
- Align screening practices based on consistent data in relation to men versus women in sports. With women presenting a largely lower risk of SCA during sports compared with men, an improvement in targeted screening efforts can maximise resources and produce higher success rates.

predominantly White, male populations than other population groups. Although recognised as problematic when translating findings to other population groups, health inequities could become further exacerbated in the advent of AI. Data-rich environments will profit from innovations in this field, whereas translating findings to data-poor settings could be problematic and incorrect. Careful attention is necessary to ensure artificial-intelligence solutions are not inadvertently only tailored to those with easy access to data. Expert clinical input and increased awareness of these inequities remain crucial.

*Ethics of screening and prevention*

Large-scale continuous evaluation of patient records, possibly by means of AI, could help to define high-risk groups that can be approached for further individual evaluation and intensive monitoring. The advent of wearable sensors, smartphone technology, big data, and AI gives rise to novel opportunities in this regard, but also raises ethical questions regarding data security, patient privacy, and autonomy. Technology is progressing at a rapid rate and aspects, such as appropriate use and ethical guidelines, are struggling to keep pace. Data from personal health monitoring devices will increasingly find their way to health-care professionals. Can these heterogeneous data be used as a repository for SCD research? Obtaining informed consent at an individual level would be highly challenging. Therefore, the right balance must be found in the use of large-scale data to gain scientific insights while having a strong respect for autonomy and privacy of the individual. Carefully weighing the resources spent on the use of these data for large-scale monitoring against the number of lives that can potentially be saved is important to ensure a fair, equitable, and appropriate distribution of health-care resources (ie, justice). Furthermore, the harms of profiling on the basis of large-scale data use, whether concerning genetics, behaviour, or anthropometrics, should be consistently considered and avoided (ie, non-maleficence).

In genetic screening for risk prediction, identifying which findings should be reported and acted upon can be challenging. Especially in the general population, the risk of false-positive results is substantial. Considerable uncertainty exists with respect to the relevance of genetic variants, their penetrance, the yield of ensuing clinical surveillance, and cost-effectiveness. Receiving an unexpected genetic result could cause considerable distress, lead to adverse consequences with respect to health insurance and employment, and create difficult decisions involving family planning. Sensitive clinicians and genetic counsellors have a crucial role to play in ensuring optimal use of available genetic tools (ie, non-maleficence).

*Ethics of resuscitation*

Some people might view SCA as a humane way to die, without a long, possibly painful sickbed, and defend the individual's right to die in a society in which advanced medical techniques can prolong life at the cost of quality of life. The sudden nature of SCA makes it difficult to assess a person's end-of-life wishes at the time of the event. Nonetheless, greater efforts are needed to establish patients' desires and hence safeguard their autonomy, even in an emergency situation. Shared decision making for planning advanced care could help, but the health-care system needs to have mechanisms to make patients' preferences available to emergency health-care providers.

Decisions of when to start, stop, or refrain from resuscitation efforts might depend on cultural norms and beliefs, but also on the context of the health-care system. Out-of-hospital resuscitation in a low-resource setting has lower odds of survival than in high-resource settings, and treatment options for comatose survivors admitted to hospital might be limited. Lengthy and complex resuscitations could yield survivors with substantial short-term and long-term health-care needs, and the absence of advanced intensive care and rehabilitation could influence decision making. The question of futility and risk of providing care that is not beneficial to the patient is complex and dependent on context, especially when considering withdrawing care in survivors with a very low likelihood of meaningful neurological recovery. Thus, a careful balance is needed between potentially missed chances of survival and refraining from or discontinuing the resuscitation effort for futile or unfavourable resuscitations However, defining an unfavourable outcome is not easy. Many of the scoring systems used to determine functional outcome are developed by health-care providers and might not reflect patient or family views. Furthermore, there are important variations in how different people perceive quality of life. Determinations of which outcomes make a resuscitation attempt futile, and thus defining when quality of life is too greatly affected, should be treated with the greatest prudence, especially when balanced against cost. Viewed in that light, the rules around the termination of resuscitation are dependent on the same contextual factors and have the danger of becoming a self-fulfilling prophecy.

Finally, in patients with out-of-hospital cardiac arrest, care requirements can conflict with the need to promptly focus efforts on organ preservation and retrieval for donation in patients who are pronounced brain dead. Standardised pathways necessitating multiple opinions for the early identification of patients with essentially no chance of survival might help in decision making about the organ donation process.[480]

*Dignity after death (or near death)*

If a patient has unexplained SCD, an autopsy is crucial to determine the cause of death and assess future risk for family members. However, in many societies across the world, performance of an autopsy is fraught with ethical challenges because of cultural and religious barriers and

personal beliefs. In the absence of clear directives, knowing how the patient would have felt about an autopsy is difficult. In countries where family consent is mandatory to perform an autopsy, the decision often rests with the immediate relative who should be helped through the decision with sensitivity for the personal and cultural context, carefully weighing the benefits of an autopsy (ie, beneficence) against the possible distress experienced by bereaved relatives (ie, non-maleficence). To avoid conflict within the family and provide opportunity for useful data, discussing autopsy after unexplained death as part of the patient's advance directive for care, similar to discussions around organ donation, might be a useful recommendation for institutions.

Organ donation presents a difficult ethical conundrum in a scenario of SCD after an unsuccessful resuscitation attempt, raising a different set of challenges. Although criteria for brain death might have been established, acceptance from families while coping with shock remains a challenging and sensitive area when respecting the options and timing around organ donation. This situation can be particularly overwhelming for a sudden event such as SCD. Is the prolonging of resuscitation or maintaining circulation with supports (ie, extracorporeal CPR) for the sole purpose of maintaining the possibility of organ donation ethical? On the one hand, the abruptness of SCA gives very little time for proper assessment of the patient's wishes and relatives' consent. On the other hand, not performing organ-preserving CPR or ignoring a patient's wish to donate organs after death might also be considered unethical. Excellent health-system organisation is required to have access to patient directives regarding organ donation in an emergency. Public societal-awareness campaigns to improve and increase advance directives can help ease the ethical dilemmas faced in this context.

### Funding considerations

From a public health perspective, tackling SCD requires great political perseverance and commitment. All too often, SCD receives major media and financial attention when an athlete or celebrity dies suddenly; however, the broader issue is soon forgotten or loses priority in the general population. There is a stark contrast between the mortality burden imposed by SCD and the investment made by governments towards it. Cardiovascular disease is the leading cause of death ahead of cancer, with SCD estimated to account for more than a quarter of those deaths, posing a mortality burden more than any individual cancer. However, public funding for SCD projects in the EU is less than an eighth of the funding support earmarked for cancer research. Similarly, the NIH investment per death is among the lowest for SCD compared with diabetes, kidney disease, and cancer. Cardiovascular, specifically SCD research, remains a low priority of European Union Mission 2030, the NIH, and the NHS England top ten priorities for 2022–23. There is much work ahead for researchers and clinicians to push for innovation and streamline systems in order to move the needle to reduce SCD. Finding funding for such progress should not be the biggest challenge of this fight. We call to our sectors of government who determine the appropriation and allocations of budgets and spending, as well as the NIH, NHS, European Union, and all other organisations that allocate research grants around the world, to join the fight in reducing the burden of SCD. The time is now to work collectively to shift priorities, update policy, and use a forward-thinking perspective to create a more consistent and equal process of the allocation of research funds while maximising population impact.

## Tackling SCD: the need for a multidisciplinary approach

When one considers the multiple broad-ranging issues that are involved in the optimal prediction, prevention, and management during and after the SCD event, the need for a multidisciplinary team effort to achieve the best outcomes is self-evident (figure 19). This effort includes not only the varied medical specialties, such as cardiology, critical care, emergency medicine, epidemiology, genetics, neurology, pathology, primary care, and public health, but also the important role of disciplines including dietetics, nursing, occupational therapy, paramedics, physiotherapy, and health-care policy and decision making personnel. A multidisciplinary team must work together seamlessly with strong communication between themselves so that their collective effort is channelled in the best possible way to maximally draw on individual expertise in a complementary way without undue overlap or waste of resources.

In the field of SCD prediction and prevention, the role of the individual treating physicians, whether the primary-care physician or the cardiologist, is complimentary to the public-health expert or epidemiologist who has a broad perspective. Primordial prevention begins at the primary-care level with emphasis

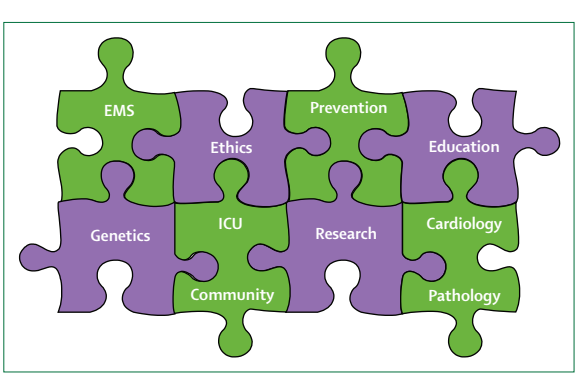


*Figure 19:* **The sudden cardiac death puzzle—a multidisciplinary approach**
EMS=emergency medical services. ICU=intensive care unit.

on heart-healthy lifestyle, diet, and nutrition, in which not only primary physicians, but also dietitians and nurses have an important role in patient education and management. During SCA, paramedics and other first responders, such as firefighters, form the backbone of a fluid emergency medical system, without whom the crucial first parts of the chain of survival will not be effective. A survivor of SCA in the ICU and beyond needs to be managed by a multidisciplinary team, not only including critical care specialists and cardiologists, but also neurologists, expert critical care nurses, and rehabilitation specialists.

After SCD, the involvement of pathologists and medical examiners in establishing a cause of death and thereby prognosticating for immediate family members cannot be overemphasised. For SCA survivors and their families, comprehensive care is required through rehabilitation therapists (ie, physiotherapists and occupational therapists), psychological support as needed through psychologists and clinical psychiatrists, and ongoing overall care from their primary care or family physicians. Genetic counsellors have an important role in counselling patients and relatives and guiding them through what can be a complex, bewildering process in terms of understanding a diagnosis of a potentially lethal inherited or genetic condition.

Finally, experts in public-health policy and legislation have a key role in issues of screening, public AED programmes, organisation of EMS systems, autopsy-related legislation, and many issues that can all directly affect long-term outcomes of SCA in any given community or population.

As such, the need for a multidisciplinary approach (figure 19) to SCD argues for the establishment of sudden death expertise centres that can function as coordinating hubs and bring together different experts with functions beyond patient care, such as research, teaching, advisory, and advocacy roles.

## Conclusion

SCD is an event at a single point in time, but constitutes the perfect culmination of a multitude of factors. Therefore, multiple avenues of intervention must be sought and used to reduce the SCD burden. The international scientific community should identify the most impactful, cost-effective approaches that can yield maximum reductions in SCD incidence and show improvements in survival for the investments made. Through the prism of the circle of SCD, which views SCD in a systematic, temporal way, we have provided an in-depth appraisal of the current state of SCD research and presented key measures for consideration to move towards the goal of minimising SCD burden in the next decade. Accurately identifying the individual who is likely to have an SCA is a major priority. The current approach to SCD prediction requires overhauling through the use of improved SCD phenotyping; the development of newer clinical, genetic markers; multiparametric risk scores; the intelligent application of evolving technologies, such as AI; and the expansion of international collaborative efforts. Likewise, increasing global awareness around coronary artery disease and adopting progressively healthy lifestyles at both the individual and population level (eg, concrete measures to improve environmental and socioeconomic aspects of living) can help weaken the platforms upon which SCD thrives. There is a clear need for innovations in drug development and devices, which will not only treat arrhythmias, but also translate into actual reductions in SCD. Strengthening and standardising EMS and emergency care systems across varied geographical regions is a major task requiring joint efforts from health-care, governmental, and other organisational structures so that, ideally, the same consistent response can be achieved whether a person collapses with an SCA in the USA or sub-Saharan Africa. Continued efforts are needed to make communities an active partner in emergency responses towards SCA with appropriate legislations and protections in place. The expansion of population-level awareness will hopefully provide the required impetus to increase autopsy rates across the world, reducing diagnostic uncertainty while uncovering new SCD mechanisms. Now is the time to widely disseminate accurate information regarding SCD, its root causes, and preventive and therapeutic options to the general public and policy makers, rather than just to the medical community, so that all stakeholders can work together to provide a solid foundation to fight this cause of death. Using a multidisciplinary approach and organised collaboration to maximise outcomes, we need to perform high-yield research, implement life-changing EMS, and create innovation to drastically reduce fatality from SCA in the near future.

**Contributors**

EM (chair) and KN (deputy chair) led the work. CMA coordinated the Commission captains and reviewed the overall manuscript. BGW, FF, and KS led and reviewed respective sections as Commission captains. EM and KG conducted the fundraising. KG organised the Commission events and conferences. All authors contributed to the key messages, conclusions, recommendations, and writing and editing of the Commission.

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