UNIVERSITÀ DI PARMA

UNIVERSITA' DEGLI STUDI DI PARMA

DOTTORATO DI RICERCA IN
MEDICINA MOLECOLARE

CICLO XXXVIII

Causative predictors of sudden cardiac death after myocardial infarction

Coordinatore:
Chiar.mo Prof. Prisco Mirandola

Tutore:
Chiar.mo Prof. Diego Ardissino

Dottorando: Luca Bearzot

Anni Accademici 2022/2023 – 2024/2025

Funder: Project funded under the National Recovery and Resilience Plan (NRRP), Mission 4 Component 2 Investment 3.3 – Call for tender No. 352 of 09/04/2022 of Italian Ministry of University and Research funded by the European Union - NextGenerationEU

Index

1. Introduction

1.1. Definition

Sudden cardiac death (SCD) is defined as a sudden natural death presumed to be of cardiac cause that occurs within 1 h of onset of symptoms in witnessed cases, and within 24 h of last being seen alive when it is unwitnessed.[1]

Typically, the leading electrical events are ventricular arrhythmias (VA):[1]

- Ventricular tachycardia (VT): ≥ 3 consecutive beats with a rate > 100 bpm originating from the ventricles, independent from atrioventricular (AV) nodal conduction;
- Ventricular fibrillation (VF): a chaotic rhythm with undulations that are irregular in timing and morphology, without discrete QRS complexes on the surface ECG.

1.2. Epidemiology

It is estimated that approximately 10-20% of all deaths in Western countries are SCDs, accounting for 50% of all cardiovascular deaths.[1,2] Every year about 300000 people in Europe have an out-of-hospital cardiac arrest (OHCA).[3] A major nationwide study in Denmark found that SCD accounted for up to 13% of all deaths, and almost half of all cases occurred without a history of cardiovascular disease (CVD).[4]

The incidence and epidemiology of SCD changes widely with age.

In the young (1-35 years old), the incidence of SCD is low (1-3 per 100000 person-year)[5–7] and the leading causes are mainly primary electric diseases, cardiomyopathies, myocarditis and coronary anomalies.

In older patients, the incidence of SCD arises from 50 per 100000 person-year in middle-aged individuals (fifth to sixth decades of life) to 200 per 100000 person-year in the eighth decade of life.[2,4,7,8] Although primary electric diseases and cardiomyopathies may account for about 50% of SCD in patients under the age of 50 years old, chronic structural heart diseases are the leading causes, especially coronary artery disease (CAD, including acute coronary events and chronic coronary stenoses), accounting for approximately 80% of all SCD cases.[9]

1.3. Pathophysiology

The mechanisms responsible for cardiac arrhythmias are generally divided into disorders of impulse formation (automaticity or triggered activity), disorders of impulse conduction (re-entry), or a combination of both.[10]

Re-entry is the likely mechanism of most clinical ventricular arrhythmias. It occurs when a propagating action potential wave fails to extinguish after initial tissue activation; instead, it blocks in circumscribed areas, circulates around the zoned of block, and re-enters and reactivates the site of original excitation after it recovers excitability.[10]

Three key factors (the so-called Coumel's triangle of arrhythmogenesis) are considered prerequisite for re-entry:[11]

- Vulnerable heart: the presence of anatomical or electrical substrate is a critical condition for induction and sustainability of VT/VF.

  The initiation and maintenance of re-entrant arrhythmias require the presence of myocardial tissue with adjacent joinable structures with different conduction and refractoriness properties.

  Depending on the underlying disease, substrate may be different:

  - Structural heart disease (SHD, e.g. CAD): in this case, VA substrate is related to areas of heterogeneous fibrosis that leads to anatomically determined circuits with a discrete unexcitable obstacle surrounded and/or crossed by excitable tissue.
  - Primary electrical disease (e.g. long QT syndrome (LQTS), Brugada syndrome (BrS)): inherited channelopathies determine intrinsic heterogeneity of electrophysiologic (EP) properties of the myocardium, leading to dispersion of excitability or refractoriness and functional re-entry circuits.
- External precipitation factors (triggers): several conditions (e.g. acute myocardial ischemia, electrolyte imbalance, sepsis, …) may elicit or bring to a critical state a susceptible substrate, anatomical or functional.

  Although important, triggers may be found only in a minority of SCD/VA cases.[12]
- Autonomic nervous system (ANS): the effect of the ANS on cardiomyocytes is related to changes in ion channel functioning and consequent potentially critical EP properties modification (e.g. heterogeneity of depolarization, dispersion of repolarization, early/late afterdepolarizations (EAD/LAD), …).

1.4. SCD in CAD

CAD is the leading cause of the majority of SCD cases (approximately 80%).[9]

The most common cascade is VT initially degenerating into VF and later into asystole. In these patients, there is a combination of vulnerable myocardium (i.e. infarcted areas with heterogeneous fibrosis, corresponding typically to non-transmural scar with viable subepicardial myocardium and areas of functional conduction delay or block) and ANS disfunction (i.e. sympathetic denervation of scar areas ad subsequent nerve sprouting in the nearby regions with super-sensitivity to catecholamines). In this condition, several triggers may precipitate the equilibrium and lead to VAs.

Clinical presentation of CAD relates to different risk of SCD.

1.4.1 Acute coronary syndrome (ACS)

Myocardial infarction (MI) with (STEMI) or without (NSTEMI) ST-segment elevation is a major cause of SCD, mostly caused by VF. In the first 48h after the onset of symptoms related to MI, 4-12% of patients develop a sustained VA.[15,16]

In the era of primary percutaneous coronary intervention (PPCI), the majority of VAs related to MI occur before the end of reperfusion procedure and 90% within 48h.[16] Recurrence of sustained VAs typically relates to incomplete reperfusion or new acute ischemia and needs immediate coronary angiography.

Although early VAs (< 48h) are related to 6-fold increase in in-hospital mortality, long-term prognosis seems not to be effected.[17–19] Several studies found that haemodynamic instability, cardiogenic shock, a poor left ventricle ejection fraction (LVEF), early repolarization (ER) pattern and the sum of ST-segment deviations in all leads are independent predictors of VAs in MI.[15,16,20]

The risk of SCD is highest in the weeks after MI, particularly in patients with reduced LVEF.[21] In this setting, any non-invasive test has proven to be useful for risk stratification.[22] In addition, two randomized studies (DINAMIT and IRIS)[23,24] failed in demonstrating a benefit in early (< 40 days after MI) routine prophylactic implantable cardiac defibrillator (ICD) strategy in patients with reduced LVEF.

1.4.2. Chronic coronary artery disease (cCAD)

After the early post-MI phase (≥ 40 days), a poorer LVEF correlates to higher risk of VAs, although reduced with modern early revascularization strategies and heart failure (HF) therapies. Typical VA in cCAD is monomorphic sustained VT (MSVT).

Approximately 5% of patients will have an LVEF ≤ 35% 40 days after a STEMI.[25] In this population, a prophylactic ICD strategy demonstrated a survival benefit in four RCTs,[26–29] with a cumulative relative reduction in mortality of 27%.[30,31]

The vast majority of post-MI have a mildly reduced (= 40-49%) or preserved (≥ 50%) LVEF. In this setting, the annual incidence of SCD is relatively small (0.6%)[32] but it becomes significant considering the overall population. In fact, the majority of OHCA occurs in patients with LVEF ≥ 35%,[33] in which substrate heterogeneity plays an important role.

1.5. Prevention of SCD in CAD

Considering the risk of VAs in patients with CAD, the only strategy to prevent SCD in this population is ICD implantation.

In survivors of cardiac arrest, recurrence has a particularly high incidence. Three pivotal randomized controlled trials (RCT)[34–36] and a subsequent metanalysis[37] demonstrated a significant mortality reduction in patients with documented VF or haemodynamically not-tolerated VT, almost entirely guided by a reduction of arrhythmic death.

In light of these data, current guidelines recommend ICD implantation in SCD survivors with a high grade of recommendation (COR I, LOE A). Because of the exclusion of MSVT patients from ICD trials, there is a lesser grade of recommendation in this setting (COR IIa, LOE C), considering that catheter ablation has become a valid alternative.[1]

As opposed to secondary prevention strategies, data for prophylactic ICD implant in patients without previous VAs are limited to specific settings.

It is important to remark that implantation of ICD in primary prevention is not a zero-risk choice: technological advances have made ICDs easier and safer to implant but early (e.g. bleeding, pneumothorax, tamponade, infection) and late complications (e.g. lead fracture/dislodgment necessitating extraction, infections due to ICD generator changes) have to be considered.

In a cost/effectiveness evaluation it is also important to consider that ICD shocks, both appropriate and inappropriate, reduce quality of life and can worsen prognosis.[38] Furthermore, an appropriate shock may be delivered on a self-limiting arrhythmia, narrowing his real utility.

Four RCTs demonstrated a benefit in survival in patients with symptomatic HF (NYHA II-III) and LVEF ≤ 35% (COR I, LOE A) and in asymptomatic patients with LVEF ≤ 30% (COR IIa, LOE B) after 40 days from MI.[26–29] In patients with LVEF = 36-40% and unexplained syncope or non-sustained VTs (NSVT), programmed electrical stimulation (PES) may be useful in selecting patients with the highest risk of SCD.[39]

In patients with preserved or mildly reduced LVEF there are no data supporting ICD implantation in a primary prevention setting, although they may have a heterogeneous arrhythmogenic substrate. In fact, the majority of OHCAs happened in these patients, comprising 70-80% of total SCD.[40] On the other hand, absolute SCD rates are declining in conjunction with comprehensive HF medical and device therapies

It has been shown that LVEF is an insensitive and non-specific marker predicting SCD,[41] and risk stratification based only on this parameter is burdened with a great number of false negatives. This is due to the fact that LVEF alone is an inadequate surrogate for the underlying substrate and is burdened by inter-individual and inter-operator assessment variability.

The current lack of health efficiency in the ICD allocation process, whereby some patients are misjudged as low-risk and subsequently experience SCD, and some are misjudged as high-risk and undergo an unnecessary procedure, calls for improved risk identification.

Several markers have been studied in order to seek subgroups at high risk of events.

1.5.1. ECG

The 12-lead ECG represents a wide-available, low cost and non-invasive tool that can be used to improve SCD risk stratification.

Several ECG markers were associated to higher risk of VAs (i.e. higher heart rate (HR) at rest, slow HR increase during exercise, slow HR decrease during recovery, prolonged corrected QT (QTc) interval, prolonged interval between the peak and the end of the T wave (Tpeak to Tend [TpTe]), depolarization abnormalities, late potentials (LPs), Q-waves, bundle-branch blocks, ST-T elevation or depression, atrial fibrillation or flutter),[42–47] although individually not enough discriminative.

Aro et al.[48] analysed the ECGs of Oregon Sudden Unexpected Death Study (SUDS),[49] a population-based case-control study investigating OHCAs in the North-western USA. Interestingly, in the Oregon SUDS controls mostly had established CAD. Investigators found that combining multiple ECG variables (i.e. resting HR > 75 bpm, left ventricle hypertrophy (LVH), QRS transition > V4, QTc interval > 450 ms, frontal QRS-T angle > 90°, and TpTe interval > 89 ms) into a cumulative risk score resulted in significant additive improvement in SCD risk estimation, with ORs of over 20 for SCD in the presence of ≥ 4 abnormal ECG markers. The risk was independent of LVEF and multiple clinical characteristics.

Risk scores may improve discrimination of individual ECG parameters. Although promising, these data had to be validated with ongoing trials.

1.5.2. Plasma biomarkers

Several mechanisms play a role in disease progression and HF after MI, including neurohormonal activation, inflammation, myocardial stretch, matrix remodelling, and myocyte injury.[50]

Although several inflammation (e.g. CRP, IL-6, IL-18) and neuro-hormonal biomarkers (e.g. renin, aldosterone, NT-proBNP) have been associated with an increased risk of SCD, they have not been found to be clinically useful because of the lack of verification in extended cohorts and their inconsistent causality.

1.5.3. Echocardiographic parameters

Beyond LVEF assessment, echocardiography may provide several useful tools and parameters to better stratify patients' risk of SCD.

Myocardial strain is a quantitative echocardiographic parameter that measures myocardial deformation as a percentage change in length, assessed primarily with speckle-tracking imaging. Longitudinal strain (i.e. shortening along the long axis of the heart) is commonly reported as global longitudinal strain (GLS) and represent a more reproducible and sensitive method than LVEF to quantify systolic function and detect subclinical systolic dysfunction.[51,52]

In a sub-study of the MADIT-CRT trial,[53] authors analysed speckle-tracking images of the enrolled patients (i.e. ischemic and non-ischemic patients with HF, LVEF ≤ 30% and QRS duration ≥ 130 ms, randomized to CRT-D or ICD alone) and found that the risk of VAs increased with decreasing GLS and impaired isolated inferior wall longitudinal deformation.

In addition to longitudinal strain, radial strain (i.e. measure of the timing differences in radial (thickening) contraction of different heart segments) may be used for assessing LV dyssynchrony, typically defined as a time difference in peak radial strain between the septum and the posterior wall ≥ 130 ms. Persistent or new radial dyssynchrony after CRT implantation is found associated with an increased rate of VAs, defining the long-term success of this therapy.[54]

An additional potentially useful parameter is relative wall thickness (RWT), defined as 2 times posterior wall thickness divided by the LV diastolic diameter. High RWT is related to higher levels of concentric hypertrophy and is a marker of increased mortality in hypertrophic cardiomyopathies. A sub-study of the MADIT-CRT trial analysed the relationship between VAs and eccentric remodelling (i.e. low RWT) and found a significant increased risk of VAs in patients with RWT < 0.24.[55]

Although promising, these parameters can't be used alone to assess SCD risk but can be useful in addition to LVEF for a better stratification.

1.5.4. Programmed electrical stimulation (PES)

PES protocols typically involve the coupling of up to 3 premature extrastimuli to a short train (six to eight paced beats) at 2 different cycle lengths (typically 600 and 400 ms) from right ventricle (RV) apex and RV outflow tract. The coupling intervals are decreased progressively by 10-ms decrements until an arrhythmia is induced or the first extrastimulus loses capture (i.e. the effective refractory period (ERP) of the tissue is reached).

As stated before, PES may be useful in selecting patients at highest risk of SCD with borderline LVEF (i.e. 36-40%) and unexplained syncope or NSVT, because of the potential identification of those who have a vulnerable substrate for monomorphic VAs (i.e. scar). However, inducibility of polymorphic VT or VF is suggested to be non-specific, being more probably related to myocardial irritability or global electrical instability, especially for more aggressive PES protocols.

This is particularly important to consider for patients with preserved or mildly reduced LVEF (≥ 40%), considering their heterogeneity with regard to their potential arrhythmic substrate.

In the PRESERVE EF study,[56] authors analysed a two-step risk stratification algorithm for post-MI patients with LVEF ≥ 40%. The first step was the identification of a group of non-invasive risk factors (NIRFs, i.e. > 30 premature ventricular complexes (PVC)/hour on 24h Holter ECG, presence of NSVT on 24h Holter ECG, presence of late potentials (LPs), QTc derived > 440 ms

(men) or > 450 ms (women) on 24h Holter ECG, presence of T wave alternans on Holter ECG, presence of autonomic dysregulation as defined by the ISAR-risk study,[57] SD of normal RR intervals ≤ 75ms on Holter ECG). In the presence of at least one NIRF, patients underwent PES and were classified inducible if sustained monomorphic or polymorphic VTs were induced. If inducible, patients underwent ICD implantation.

In this observational study, 41 of 575 patients were inducible during PES and received an ICD. During the 32-month follow-up period, no SCD occurred and 9 of 37 ICD patients received an appropriate ICD therapy. However, the role of appropriate ICD treatment as surrogate for SCD in patients with preserved LVEF is unknown. In fact, the major utility of PES in this setting was the identification of patients at low risk (i.e. non-inducible).

Randomized trials are needed to confirm the utility of PES in identifying patients with higher risk of SCD.

1.5.5. Cardiac magnetic resonance imaging (CMRI)

Myocardial scars create regions of slowed electrical conduction that favour macro re-entrant VT, although their role in VF is less clear.[58] CMR with LGE may be used to identify and quantify areas of replacement fibrosis, that is a marker strongly related to infarct size and subsequent risk of remodelling and arrhythmogenic substrate.[59]

It is now well established that both the presence and extent of myocardial scar visualized by LGE on CMR are independent prognostic markers of SCD or ventricular arrhythmias (VA) in ICM, regardless of LVEF.[60–65] However, beyond LVEF assessment, in ICM setting CMR is recommended only for diagnostic and follow-up purpose in currently available guidelines.[1,66] The main limitation in clinical applicability of fibrosis quantification is the lack of consensus over which scar metrics and thresholds are the best predictors of VA.

Electrical instability leading to VA is not the consequence of a single abnormality and can't be predicted by a single variable. New methods incorporating different parameters are needed to better characterize arrhythmogenic substrate and develop a more efficient risk profiling. In this context, grey zone fibrosis (GZF) is emerging as an additional tool.

GZF is defined as tissue with intermediate signal intensity enhancement between normal and fibrotic myocardium.[59] GZF identifies an area of tissue heterogeneity within the infarct periphery that may contain slow conductivity channels connecting healthy tissue areas,

corresponding with the arrhythmogenic substrate of the scar. Quantification of GZF on CMR has been shown to be superior to the LGE burden alone in predicting VA.[65,67–69]

Although their ability to better evaluate arrhythmic substrate, non-LGE CMR parameters can't be used alone for risk stratification. Further studies are needed to evaluate their role in the context of a multiparametric CMR risk stratification.

1.5.6. Genetic biomarkers

Genetic studies have been made possible a great number of discoveries concerning genetic causes of rare inherited cardiac disorders associated to SCD, but very little progress has been made in identifying the genetic risk factors associated with more complex arrhythmogenic substrates (e.g. after MI) because of the complexity of the substrate involved.

In the 90s, studies revealed that a family history of SCD was an independent risk factor for SCD, distinct from a family history of CAD.[70] This was further supported by studies on patients with VF during first MI.[71,72]

In the context of CAD, genetic influences can act through multiple mechanisms (e.g. absolute risk of atherosclerosis, type and characteristics of plaque burden, myocardial response to ischemia) and represent an important field of research.

The conventional approaches used to study genetic risk of SCD in CAD are two: candidate genes studies and genome-wide association studies (GWAS).

The candidate gene approach hypothesizes an association between SCD and genes linked to inherited arrhythmia syndromes starting from common pathophysiological characteristics (e.g. long QT in LQTS and as a risk factor in CAD).

Several studies suggested common and rare variants of ionic cardiac channels as potentially useful markers for genetic risk profiling.[73–76] Other promising variants include those involved in lipid metabolism (APOE), inflammation (IL6R), and myocardial remodelling (MMP9).[77,78] However, for complex pathologies as CAD, it is unlikely that a single or small group of genetic variants significantly impact SCD risk, reducing their power in this context.

In order to identify other associations that suggest pathways for further investigations, GWAS approach has been developed.

A GWAS is an observational study that scans the genomes of many individuals, typically using hundreds of thousands to millions of single nucleotide polymorphisms (SNPs), to determine whether any genetic variants are statistically associated with a particular phenotype. Large

sample sizes are needed because most variants have small effect sizes, considering that most significant SNPs lie in non-coding regions and point to regulatory elements.

Several GWAS found interesting associations,[79–81] although these results require further replication. Clinical applications are limited by the fact that these studies found only associations but, in the absence of large effects sizes and considering relevant confounding factors (e.g. mode of expression, interactions with other genes and environment), they are usually insufficient to define causation.[82]

Nonetheless, individual risk may be related to a cumulative effect of multiple genetic variants.[83,84] In this context, GWAS approach may be used in order to find new unexpected associations in order to develop polygenic risk scores (PRSs).

In recent years, PRSs have been shown to improve prediction of incident cardiovascular events above and beyond traditional risk factors.[85–89] This underscores the potential of genetic profiling in refining risk assessment strategies for this patient population.

In a similar fashion, the PREDETERMINE study found that a validated genome-wide polygenic score (GPS_{CAD}) outperformed traditional clinical risk factors in predicting SCD in CAD patients with preserved LVEF.[90] However, it is important to consider that GPS_{CAD} was previously validated for predicting incident CAD,[91] and the discovery of specific variants associated with SCD was beyond the scope of the study.

It is otherwise essential to differentiate between arrhythmic and non-arrhythmic origins of SCD in ischemic heart disease. This explains the genetic complexity of SCD in ischemic heart disease and the need for further replication.

1.6. Mendelian randomization studies

None of the markers described above has demonstrated its usefulness in clinical practise because of the lack of consistency in subsequent validation studies. It is of pivotal importance to understand the causal role of biomarkers in SCD in order to be able to find effective predictive approaches.

Randomized controlled trials (RTCs) are considered the gold standard design to infer causality because of the randomization process: participants are randomly assigned to treatment or control and, because assignment is random, the two groups are similar in all observed (e.g. age, sex, disease severity) and unobserved variables (genetics, behaviour); therefore, any

difference in outcomes cannot be explained by confounders, but it must be due to the treatment. However, RCTs are often unfeasible due to the need for great sample size, high costs and long follow-up.

Considering feasibility limitations of RCTs, observational studies have been used to find relationships between risk factors and/or markers (or treatment) and outcomes. In this setting, researchers must reconstruct the causal effect using statistical and conceptual tools in order to reduce the risk of confounding (e.g. regression adjustment, propensity score matching, stratification) and make treated/exposed and untreated/unexposed subjects as similar as possible with respect to variables that influence both treatment and outcome.

As compared to RCTs, the major limitation of observational studies is the risk of exaggerate or mask underlying truly causal relationships because of the risk of confounding and reverse causation bias (i.e. marker may be consequence and not cause of studied outcome).

Confounding of can be minimised by using mendelian randomization (MR), a causal inference method that uses genetic variants as instrumental variables to estimate the causal effect of an exposure (risk factor or biomarker) on an outcome.[92]

MR relies on the principle of Mendel's laws of independent assortment and segregation, which ensure that genetic variants are randomly distributed with respect to most confounding factors. In this context, people with a genetic variant associated to a specific exposure can be compared to those without the variant, as if they were randomized at conception.

The three core assumptions that must hold for valid results in an MR study are:

- Relevance: the genetic variant must be associated with the biomarker;
- Independence: the genetic variant must not be associated with any known or unknown confounders;
- Exclusion restriction: the genetic variant influences the outcome only through the biomarker and not through alternative pathways (i.e. no horizontal pleiotropy).

This type of analysis offers a strategy to eliminate, or anyway reduce, the typical residual confounding of observational studies, thus making it possible to obtain generalizable results. An MR study also diminishes the risk of reverse causation bias, as genetic variants are unchangeable and cannot be influenced by disease status.

Furthermore, MR studies are often faster and cheaper to conduct than RCTs, as they can be conducted using existing large-scale GWAS data.

If correctly conducted and carefully interpreted, MR studies can provide useful scientific evidence to support or reject causal hypotheses that verify the association between environmental exposures and diseases.

Depending on the population analysed, MR studies are classified in one-sample or two-sample.

In one-sample MR studies, genetic variant associations with biomarker/risk factor and outcome are obtained from the same individuals. Instead, in two-samples MR studies these associations come from two independent populations with similar characteristics: this design can provide a greater statistical power because of the possibility of using large scale GWAS populations.

Although promising, MR analysis is still subject to active research and is vulnerable to several risks.

First of all, statistical power may be low due to the fact that for complex phenotypes genetic variants typically have a small effect (i.e. violated relevance assumption). This limit can be theoretically overcome using multiple variants associated with the same biomarker, although detection of weak effects requires large sample sizes.

Secondly, confounders may be associated to identified genetic variants due to suboptimal population stratification or unidentified correlations (i.e. violated independence assumption).

Lastly, identified genetic variants may influence the outcome not only via studied biomarkers but also via other pathways (i.e. violated exclusion restriction assumption). This may be due for example to horizontal pleiotropy (i.e. genetic variant can influence other biomarkers that in turn influence the outcome) or linkage disequilibrium (i.e. identified genetic variant is correlated with nearby variants that affect the outcome through other pathways).

2. Objectives

The aim of this project is to explore the potential predictive value of multiple phenotypic and genetic variables in an attempt to advance our understanding of the etiological factors underlying SCD and improve our ability to estimate SCD risk in MI patients.

The results of this project could be broadly used to improve the individualised targeting of ICD therapy, identifying specific high-risk phenotypes in order to improve the dichotomous and non-specific classification based on LVEF, and may eventually lead to the identification of new and potentially important therapeutic targets.

3. Methods

3.1. Population

The base study data (Dataset 1) comes from the Italian Genetic Study on Early-onset Myocardial Infarction (IGSEMI), originally designed to investigate the genetics of susceptibility to MI in Italy by means of a case-control study.[93] The IGSEMI enrolled patients under the age of 45 admitted to 125 Italian Coronary Care Units between 1998 and 2002 after a first MI with a median follow-up of 19.9 years. The primary composite endpoint was the occurrence of cardiovascular death, non-fatal myocardial re-infarction, or non-fatal ischemic stroke.

The early age of the index MI in this cohort suggests greater genetic involvement, which may increase the probability of finding specific genetic variants associated with high-risk pre-MI phenotypes.

A second dataset (Dataset 2) will be collected from a cohort of 1000 post-MI patients prospectively recruited by 25 Italian centres. Blood samples and pre-MI data will be collected and patients will undergo a series of exams: whole-genome sequencing (WGS), baseline post-MI ECG, autonomic examination, PES, and CMRI within 3 months from discharge.

3.2. Study protocol

The study protocol of IGSEMI study was approved by the Ethics Committee of the coordinating centre (Ospedale Niguarda, Ca' Granda), and all of the study patients gave their written informed consent to enrolment.

After identifying patients suitable for enrolment, investigators completed a standardized case report form collecting detailed cardiovascular history of the individual patients and all first- and second-degree relatives, cardiovascular risk factors, lifestyle, and medications. This was carried out at the time of admission for the index event.

The patients were followed up from the date of recruitment for any subsequent cardiovascular events for a median of 19.9 years from study enrolment. Follow-up was done by means of scheduled outpatient examinations and standardized telephone calls. Follow-up by means of visits was attempted in all patients but, when this was not possible, their primary care physicians were contacted. If this was unsuccessful or not possible, a member of the family was contacted.

The reported deaths were verified on the basis of death certificates specifying the cause(s) of death, and each reported event was investigated by means of source data verification.

3.3. Outcomes

The primary endpoint of the study was the occurrence of either SCD, clinical ventricular tachycardia/fibrillation and/or appropriate ICD activation.

SCD was defined in accordance with the ESC definition as any sudden natural death presumed to be of cardiac cause that occurs within one hour of symptom onset in witnessed cases or within 24 hours of the patient last being seen alive in unwitnessed cases.[1]

ICD activation was defined as the moment in which the device detects an arrhythmia that meets its programmed criteria and delivers therapy (i.e. anti-tachycardia pacing (ATP) or shock).

3.4. Statistical analysis

Causal assumptions underlying subsequent analysis are represented in Figure 1.

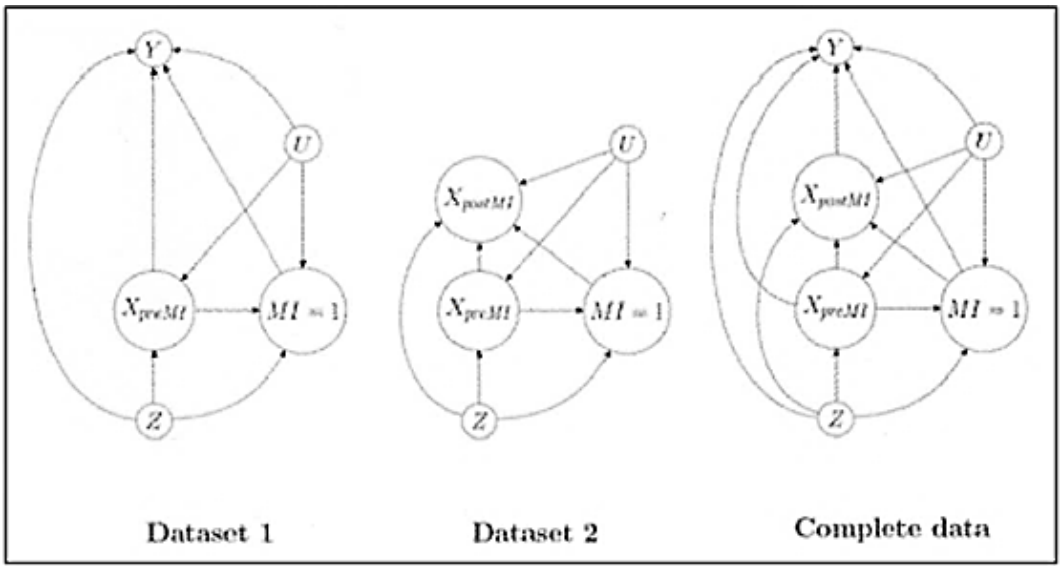

Figure 1 Causal assumptions of the analysis. MI: binary indicator of a MI, always = 1 because of the main focus on MI patients. XpreMI: pre-MI phenotype (e.g. sex, age, hypertension). XpostMI: variables observed after MI. Z: set of genetic variants. Y: binary indicator of a favourable (Y=0) or unfavourable (Y=1) SCD/VAs outcome. U: unobserved confounders.

The analysis plan involves a series of sequences.

The first step consists in the identification of genetic variants associated with high-risk phenotype for post-MI SCD or sustained VAs. Dataset 1 will be used with this purpose, considering the early age of the index MI and the high likelihood of genetic involvement in subsequent outcomes.

The second step consists in the construction of a polygenic risk score (PRS) for post-MI SCD with the identified and selected genetic variants.

A polygenic risk score (PRS) is a quantitative measure that estimates an individual's genetic predisposition to a disease or trait by aggregating the effects of many genetic variants across the genome. Each variant contributes a small effect, but cumulatively they can explain substantial variation in risk.

The third step consists in the validation of PRS in an independent sample, specifically UK Biobank MI patients.

UK Biobank is a large, prospective, population-based research resource that includes about 500000 participants aged 40–69 recruited across the UK between 2006 and 2010.[94] It links genome-wide genotyping with extensive baseline phenotypic data, biological samples, and long-term health follow-up to enable large-scale biomedical research.

The fourth step consists in the development of a predicting model of SCD based on patient's pre-MI history and validated PRS.

The final step will be the assessment of predictive and causal effects of post-MI variables on the occurrence of SCD. Joint analysis of Dataset 1 and 2 using two-sample MR will allow to assess the causal effects of post-MI risk factors on the occurrence of SCD.

3.5. Limitations

MR analysis is still subject to active research and is vulnerable to several risks.

First, statistical power is a potential concern, especially because the number and magnitude of relevant genetic effects on post-MI measurements are currently unknown. IGSEMI population (Dataset 1) size and characteristics increase the chances of identifying useful genetic variants.

Second, it's possible that the project fails to find any direct associations between SNPs and SCD/VAs.

Third, restricting attention to only MI patients may induce index event bias (IEB): when multiple risk factors contribute to the risk of an outcome (in this case MI), conditioning on the outcome induces dependence between the risk factors, even when they are independently distributed in the general population. This can negatively affect the generalisability of the identified predictive exposures (i.e. failing in validating constructed PRS) or bias MR assessment of causality.

4. Results

Preliminary data on clinical characteristics of Dataset 1 patients that experienced SCD were already published.[95]

Over the course of follow-up, 195 individuals died suddenly, underscoring that SCD remains a significant long-term threat even decades after early-onset MI.

Patients who eventually experienced SCD differed meaningfully from those who did not (Table 1).

At their initial presentation, they showed a more adverse clinical profile: hypertension, diabetes, and prior thrombo-embolic events were all more common, and angiographic evaluation revealed more severe and widespread coronary atherosclerosis (reflected in higher SYNTAX scores). Left ventricular ejection fraction (LVEF) measured after the index event was also lower in the SCD group, indicating early impairment of ventricular function.

Multivariable modelling confirmed these factors (diabetes, hypertension, history of thromboembolism, increased coronary atherosclerotic burden, and reduced LVEF) as independent predictors of SCD during follow-up (Figure 2).

These findings point toward a unifying mechanism: progressive atherosclerotic disease and its consequences, rather than isolated arrhythmic substrate, may underpin the long-term risk of fatal sudden events in this young MI population.

The sequence of clinical events preceding SCD varied.

In 101 patients, SCD was the first manifestation after the initial MI, occurring without intermediate cardiovascular events. The remaining 94 patients experienced further non-fatal ischemic episodes (i.e. recurrent MI, stroke, coronary revascularization) before SCD.

This pattern reinforces the idea that SCD often arises in the setting of ongoing or destabilized coronary disease rather than as a purely electrical phenomenon.

Interestingly, the timing of SCD events showed no evidence of clustering, contrasting with earlier pre-reperfusion era studies that observed a peak risk within the first year post-MI. In this contemporary cohort, risk appeared distributed relatively evenly over the two-decade follow-up (Figure 3). These evidences suggest that improvements in acute care, including rapid reperfusion strategies, and a survivorship effect may explain the absence of early clustering commonly seen in older cohorts.

	All ($n = 2000$)	SCD ($n = 195$)	Non-SCD ($n = 1805$)	*P*-value
Median age, years (IQR)	41 (37–43)	41 (38–44)	41 (37–43)	0.27
Median weight, kg (IQR)	78 (70–88)	80 (71–93)	78 (70–87)	0.005
Median BMI, kg/cm^2 (IQR)	26.3 (24.1–29.1)	27.1(24.1–30.2)	26.2 (24–29)	0.03
Females, *n*, %	222 (11.1)	12 (6.2)	210 (11.6)	0.03
Index event				
STEMI	1708 (85.4)	161(82.6)	1547 (85.7)	0.28
NSTEMI	292 (14.6)	34 (17.4)	258 (14.3)	
Family history of CVD	1629 (81.5)	157 (80.5)	1472 (81.6)	0.79
Hypertension	536 (26.8)	75 (38.5)	461 (25.5)	<0.001
Dyslipidaemia	1184/1936 (61.2)	108/180 (60)	1076/1756 (61.3)	0.8
Diabetes	154 (8)	25 (12.8)	129 (0.07)	0.007
Alcohol consumption	1225/1994 (61.4)	116 (59.5)	1109/1801 (61.6)	0.75
Current smokers (no ex-smokers)	922 (46.1)	94 (48.2)	828 (45.9)	0.6
Cocaine use	57 (2.9)	4 (2.1)	53 (2.9)	0.63
Previous thromboembolism	317 (15.9)	46 (23.6)	271 (15)	0.003
Median LVEF (%)	55 (49–58)	50 (40–55)	55 (50–59)	<0.001
Beta-blocker	1629 (81.4)	170 (87.2)	1459 (80.8)	0.18
Aspirin	1860 (93.0)	190 (97.4)	1670 (92.5)	0.22
P2Y12 inhibitor	1009 (50.5)	92 (47.2)	917 (50.1)	0.35
ACE inhibitor or ARB	865/1581 (54.7)	59/97 (60.1)	806/1484 (54.3)	0.25
Statin	1949 (97.5)	195 (100)	1754 (97.2)	0.4
SYNTAX score (IQR)	9 (4–15)	13 (7–20.5)	9 (4–14.5)	<0.001
Duke's score (IQR)	48 (23–56)	48 (37–56)	48 (23–56)	<0.001
Normal	264 (13.2%)	15 (7.7)	249 (13.8)	<0.001
Non-significant stenosis	90 (4.5%)	4 (2.1)	86 (4.8)	
Single-vessel disease	896 (44.8%)	77 (39.5)	819 (45.4)	
Multi-vessel disease	750(37.5%)	99 (50.8)	651 (36.1)	

Table 1 Baseline demographic, clinical, angiographic, and treatment characteristics of the study population in the sudden cardiac death and non-sudden cardiac death groups. SCD, sudden cardiac death; BMI, body mass index; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; CVD, cardiovascular disease; LVEF, left ventricular ejection fraction; ARB, angiotensin 2 receptor blockers; ACE, angiotensin-converting enzyme.
(Reproduced from: Bricoli S et al, Sudden cardiac death after early-onset myocardial infarction: a multicentre longitudinal cohort study with a 20-year follow-up, European Heart Journal: Acute Cardiovascular Care, 2024;13(10):726–730, doi:10.1093/ehjacc/zuae089.[95]

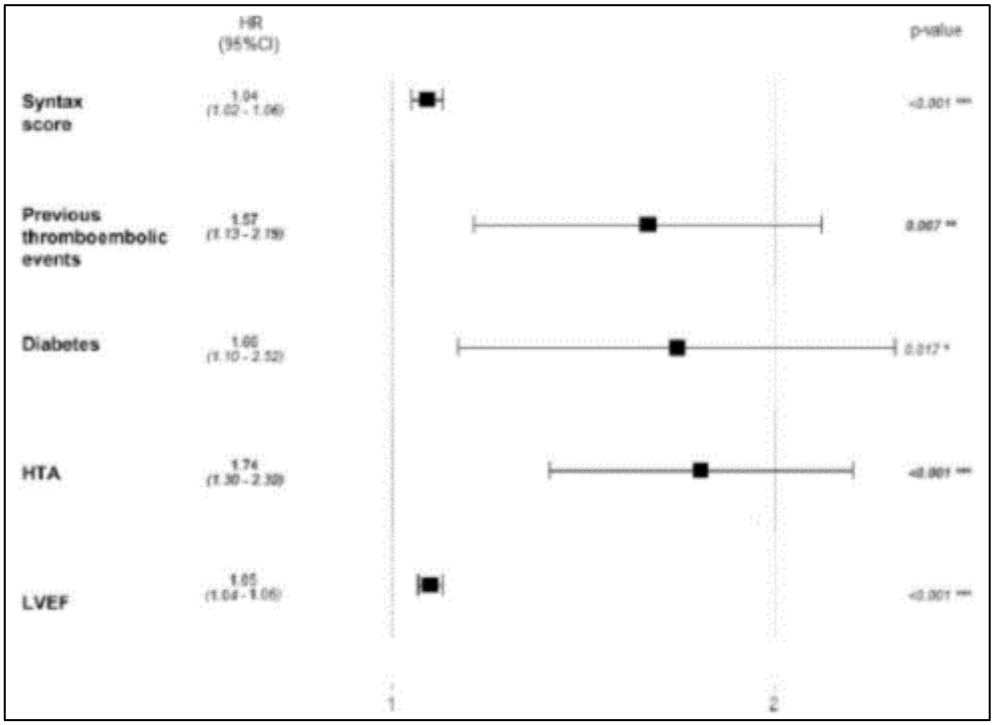

Figure 2 A forest plot of the independent factors associated with sudden cardiac death during the follow-up in the most parsimonious Fine–Gray multivariable model adjusted for reperfusion therapy, ST-segment elevation myocardial infarction at the time of the index event, beta-blocker therapy, and recurrent ischaemic events. SHR, sub-hazard ratio.
(Reproduced from: Bricoli S et al, Sudden cardiac death after early-onset myocardial infarction: a multicentre longitudinal cohort study with a 20-year follow-up, European Heart Journal: Acute Cardiovascular Care, 2024;13(10):726–730, doi:10.1093/ehjacc/zuae089.[95]

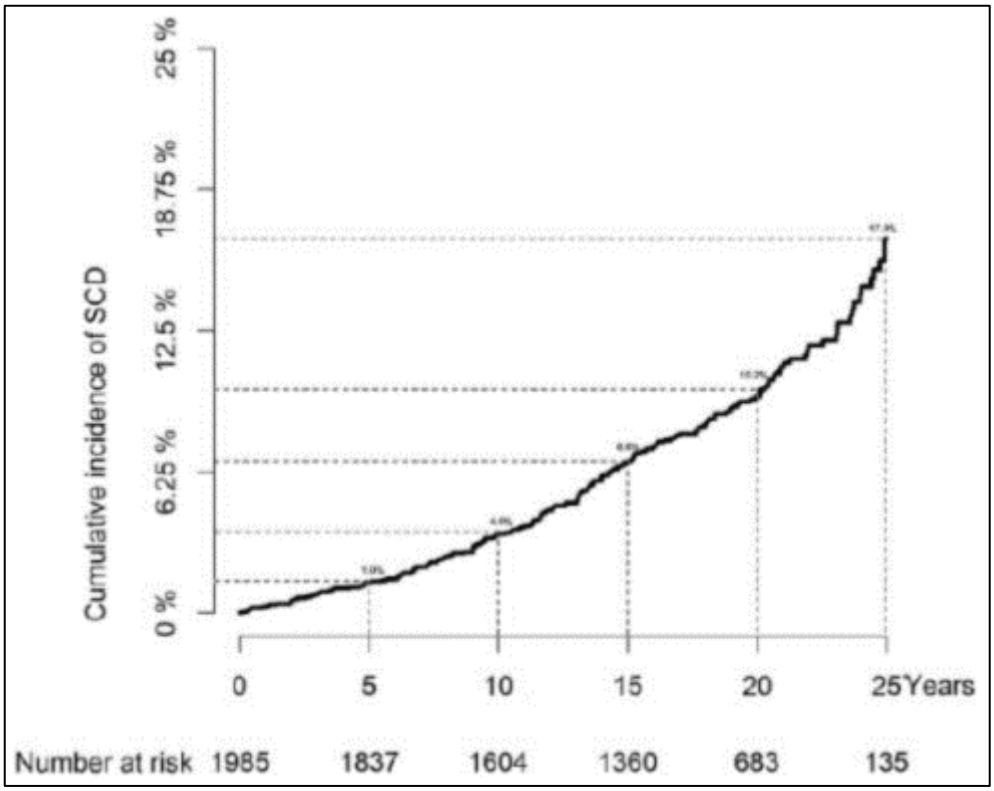

Figure 3 An Aalen–Johansen cumulative incidence plot of the cumulative incidence of sudden cardiac death.
(Reproduced from: Bricoli S et al, Sudden cardiac death after early-onset myocardial infarction: a multicentre longitudinal cohort study with a 20-year follow-up, European Heart Journal: Acute Cardiovascular Care, 2024;13(10):726–730, doi:10.1093/ehjacc/zuae089.[95]

5. Discussion

Preliminary data on clinical characteristics of MI survivors from IGSEMI study highlight a meaningful risk of SCD for decades after the initial event. The predictors identified (i.e. classic cardiovascular risk factors, reduced LVEF, and a high burden of coronary atherosclerosis) point toward progressive coronary disease as the central driver of late SCD rather than isolated electrical instability.

Clinically, this underscores several priorities.

Firstly, aggressive long-term intensive risk-factor management and lifestyle changes remains essential even in young patients, whose prolonged lifespan amplifies the cumulative impact of atherosclerotic progression.

Secondly, angiographic markers of coronary disease severity (e.g. SYNTAX score) may help refine long-term risk stratification and identify individuals who might benefit from closer follow-up or earlier revascularization strategies.

Thirdly, periodic imaging for LVEF assessment may be warranted, especially in patients with recurrent ischemia or high-risk profiles.

Overall, the results emphasize the need for sustained, contemporary secondary prevention and individualized long-term surveillance to reduce the burden of SCD in this distinct and relatively understudied patient population.

6. Subsequent analysis

Based only on patients considered for preliminary data (i.e. only patients that experienced SCD), monogenic variants with a significant discrimination ability for SCD/VAs could not be extracted.

The analysis is currently underway, including patients with clinical VAs and/or appropriate ICD activation with the purpose of enhancing statistical power.

7. Bibliography

1. Zeppenfeld K, Tfelt-Hansen J, Riva M de, Winkel BG, Behr ER, Blom NA, Charron P, Corrado D, Dagres N, Chillou C de, Eckardt L, Friede T, Haugaa KH, Hocini M, Lambiase PD, Marijon E, Merino JL, Peichl P, Priori SG, Reichlin T, Schulz-Menger J, Sticherling C, Tzeis S, Verstrael A, Volterrani M, ESC Scientific Document Group. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Developed by the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC) Endorsed by the Association for European Paediatric and Congenital Cardiology (AEPC). *European Heart Journal* 2022;**43**:3997–4126.

2. Stecker EC, Reinier K, Marijon E, Narayanan K, Teodorescu C, Uy-Evanado A, Gunson K, Jui J, Chugh SS. Public health burden of sudden cardiac death in the United States. *Circ Arrhythm Electrophysiol* 2014;**7**:212–217.

3. Atwood C, Eisenberg MS, Herlitz J, Rea TD. Incidence of EMS-treated out-of-hospital cardiac arrest in Europe. *Resuscitation* 2005;**67**:75–80.

4. Lynge TH, Risgaard B, Banner J, Nielsen JL, Jespersen T, Stampe NK, Albert CM, Winkel BG, Tfelt-Hansen J. Nationwide burden of sudden cardiac death: A study of 54,028 deaths in Denmark. *Heart Rhythm* 2021;**18**:1657–1665.

5. Pilmer CM, Kirsh JA, Hildebrandt D, Krahn AD, Gow RM. Sudden cardiac death in children and adolescents between 1 and 19 years of age. *Heart Rhythm* 2014;**11**:239–245.

6. Winkel BG, Holst AG, Theilade J, Kristensen IB, Thomsen JL, Ottesen GL, Bundgaard H, Svendsen JH, Haunsø S, Tfelt-Hansen J. Nationwide study of sudden cardiac death in persons aged 1-35 years. *Eur Heart J* 2011;**32**:983–990.

7. Risgaard B, Winkel BG, Jabbari R, Behr ER, Ingemann-Hansen O, Thomsen JL, Ottesen GL, Gislason GH, Bundgaard H, Haunsø S, Holst AG, Tfelt-Hansen J. Burden of sudden cardiac death in persons aged 1 to 49 years: nationwide study in Denmark. *Circ Arrhythm Electrophysiol* 2014;**7**:205–211.

8. Bougouin W, Lamhaut L, Marijon E, Jost D, Dumas F, Deye N, Beganton F, Empana J-P, Chazelle E, Cariou A, Jouven X, SDEC Co-Investigators. Characteristics and prognosis of sudden cardiac death in Greater Paris: population-based approach from the Paris Sudden Death Expertise Center (Paris-SDEC). *Intensive Care Med* 2014;**40**:846–854.

9. Chugh SS, Reinier K, Teodorescu C, Evanado A, Kehr E, Al Samara M, Mariani R, Gunson K, Jui J. Epidemiology of sudden cardiac death: clinical and research implications. *Prog Cardiovasc Dis* 2008;**51**:213–228.

10. Issa ZF, Miller JM, Zipes DP. 3 - Electrophysiological Mechanisms of Cardiac Arrhythmias. In: Issa ZF, Miller JM, Zipes DP, eds. *Clinical Arrhythmology and Electrophysiology (Third Edition)*. Philadelphia: Elsevier; 2019. p51–80.

11. Lenarczyk R, Zeppenfeld K, Tfelt-Hansen J, Heinzel FR, Deneke T, Ene E, Meyer C, Wilde A, Arbelo E, Jędrzejczyk-Patej E, Sabbag A, Stühlinger M, Biase L di, Vaseghi M, Ziv O, Bautista-Vargas W-F, Kumar S, Namboodiri N, Henz BD, Montero-Cabezas J, Dagres N, Peichl P, Frontera A, Tzeis S, Merino JL, Soejima K, Chillou C de, Tung R, Eckardt L, Maury P, Hlivak P, Tereshchenko LG, Kojodjojo P, Atié J. Management of patients with an electrical storm or clustered ventricular arrhythmias: a clinical consensus statement of the European Heart Rhythm Association of the ESC—endorsed by the Asia-Pacific Heart Rhythm Society, Heart Rhythm Society, and Latin-American Heart Rhythm Society. *Europace* 2024;**26**:euae049.

12. Hohnloser SH, Al-Khalidi HR, Pratt CM, Brum JM, Tatla DS, Tchou P, Dorian P, SHock Inhibition Evaluation with AzimiLiDe (SHIELD) Investigators. Electrical storm in patients with an implantable defibrillator: incidence, features, and preventive therapy: insights from a randomized trial. *Eur Heart J* 2006;**27**:3027–3032.

13. Stevenson WG, Khan H, Sager P, Saxon LA, Middlekauff HR, Natterson PD, Wiener I. Identification of reentry circuit sites during catheter mapping and radiofrequency ablation of ventricular tachycardia late after myocardial infarction. *Circulation* 1993;**88**:1647–1670.

14. Zecchin M, Muser D, Vitali-Serdoz L, Buiatti A, Morgera T. Arrhythmias in Dilated Cardiomyopathy: Diagnosis and Treatment. In: Sinagra G, Merlo M, Pinamonti B, eds. *Dilated Cardiomyopathy: From Genetics to Clinical Management*. Cham (CH): Springer; 2019.

15. Jabbari R, Engstrøm T, Glinge C, Risgaard B, Jabbari J, Winkel BG, Terkelsen CJ, Tilsted H-H, Jensen LO, Hougaard M, Chiuve SE, Pedersen F, Svendsen JH, Haunsø S, Albert CM, Tfelt-Hansen J. Incidence and risk factors of ventricular fibrillation before primary angioplasty in patients with first ST-elevation myocardial infarction: a nationwide study in Denmark. *J Am Heart Assoc* 2015;**4**:e001399.

16. Mehta RH, Starr AZ, Lopes RD, Hochman JS, Widimsky P, Pieper KS, Armstrong PW, Granger CB, APEX AMI Investigators for the. Incidence of and Outcomes Associated With Ventricular Tachycardia or Fibrillation in Patients Undergoing Primary Percutaneous Coronary Intervention. *JAMA* 2009;**301**:1779–1789.

17. Orvin K, Eisen A, Goldenberg I, Gottlieb S, Kornowski R, Matetzky S, Golovchiner G, Kuznietz J, Gavrielov-Yusim N, Segev A, Strasberg B, Haim M. Outcome of contemporary acute coronary syndrome complicated by ventricular tachyarrhythmias. *Europace* 2016;**18**:219–226.

18. Bougouin W, Marijon E, Puymirat E, Defaye P, Celermajer DS, Le Heuzey J-Y, Boveda S, Kacet S, Mabo P, Barnay C, Da Costa A, Deharo J-C, Daubert J-C, Ferrières J, Simon T, Danchin N, FAST-MI Registry Investigators. Incidence of sudden cardiac death after ventricular fibrillation complicating acute myocardial infarction: a 5-year cause-of-death analysis of the FAST-MI 2005 registry. *Eur Heart J* 2014;**35**:116–122.

19. Podolecki T, Lenarczyk R, Kowalczyk J, Jedrzejczyk-Patej E, Chodor P, Mazurek M, Francuz P, Streb W, Mitrega K, Kalarus Z. Prognostic Significance of Complex Ventricular Arrhythmias Complicating ST-Segment Elevation Myocardial Infarction. *Am J Cardiol* 2018;**121**:805–809.

20. Demidova MM, Carlson J, Erlinge D, Platonov PG. Predictors of ventricular fibrillation at reperfusion in patients with acute ST-elevation myocardial infarction treated by primary percutaneous coronary intervention. *Am J Cardiol* 2015;**115**:417–422.

21. Solomon SD, Zelenkofske S, McMurray JJV, Finn PV, Velazquez E, Ertl G, Harsanyi A, Rouleau JL, Maggioni A, Kober L, White H, Van de Werf F, Pieper K, Califf RM, Pfeffer MA, Valsartan in Acute Myocardial Infarction Trial (VALIANT) Investigators. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *N Engl J Med* 2005;**352**:2581–2588.

22. Exner DV, Kavanagh KM, Slawnych MP, Mitchell LB, Ramadan D, Aggarwal SG, Noullett C, Van Schaik A, Mitchell RT, Shibata MA, Gulamhussein S, McMeekin J, Tymchak W, Schnell G, Gillis AM, Sheldon RS, Fick GH, Duff HJ, REFINE Investigators. Noninvasive risk assessment early after a myocardial infarction the REFINE study. *J Am Coll Cardiol* 2007;**50**:2275–2284.

23. Steinbeck G, Andresen D, Seidl K, Brachmann J, Hoffmann E, Wojciechowski D, Kornacewicz-Jach Z, Sredniawa B, Lupkovics G, Hofgärtner F, Lubinski A, Rosenqvist M, Habets A, Wegscheider K, Senges J, IRIS Investigators. Defibrillator implantation early after myocardial infarction. *N Engl J Med* 2009;**361**:1427–1436.

24. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, Fain E, Gent M, Connolly SJ, DINAMIT Investigators. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 2004;**351**:2481–2488.

25. Altmann DR, Mutschelknauss M, Ehl N, Koller M, Schaer B, Jörg L, Ammann P, Kühne M, Rickli H, Osswald S, Sticherling C. Prevalence of severely impaired left ventricular ejection fraction after reperfused ST-elevation myocardial infarction. *Swiss Med Wkly* 2013;**143**:w13869.

26. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996;**335**:1933–1940.

27. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML, Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;**346**:877–883.

28. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999;**341**:1882–1890.

29. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH, Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;**352**:225–237.

30. Zabel M, Willems R, Lubinski A, Bauer A, Brugada J, Conen D, Flevari P, Hasenfuß G, Svetlosak M, Huikuri HV, Malik M, Pavlović N, Schmidt G, Sritharan R, Schlögl S, Szavits-Nossan J, Traykov V, Tuinenburg AE, Willich SN, Harden M, Friede T, Svendsen JH, Sticherling C, Merkely B, EU-CERT-ICD Study Investigators. Clinical effectiveness of primary prevention implantable cardioverter-defibrillators: results of the EU-CERT-ICD controlled multicentre cohort study. *Eur Heart J* 2020;**41**:3437–3447.

31. Schrage B, Uijl A, Benson L, Westermann D, Ståhlberg M, Stolfo D, Dahlström U, Linde C, Braunschweig F, Savarese G. Association Between Use of Primary-Prevention Implantable Cardioverter-Defibrillators and Mortality in Patients With Heart Failure: A Prospective Propensity Score-Matched Analysis From the Swedish Heart Failure Registry. *Circulation* 2019;**140**:1530–1539.

32. Ikeda T, Yoshino H, Sugi K, Tanno K, Shimizu H, Watanabe J, Kasamaki Y, Yoshida A, Kato T. Predictive value of microvolt T-wave alternans for sudden cardiac death in patients with preserved cardiac function after acute myocardial infarction: results of a collaborative cohort study. *J Am Coll Cardiol* 2006;**48**:2268–2274.

33. Gorgels APM, Gijsbers C, Vreede-Swagemakers J de, Lousberg A, Wellens HJJ. Out-of-hospital cardiac arrest--the relevance of heart failure. The Maastricht Circulatory Arrest Registry. *Eur Heart J* 2003;**24**:1204–1209.

34. Kuck K-H, Cappato R, Siebels J, Rüppel R. Randomized Comparison of Antiarrhythmic Drug Therapy With Implantable Defibrillators in Patients Resuscitated From Cardiac Arrest. *Circulation* 2000;**102**:748–754.

35. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, Mitchell LB, Green MS, Klein GJ, O'Brien B. Canadian implantable defibrillator study (CIDS) : a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000;**101**:1297–1302.

36. Hallstrom AP, Greene HL, Wyse DG, Zipes D, Epstein AE, Domanski MJ, Schron EB, AVID Investigators. Antiarrhythmics Versus Implantable Defibrillators (AVID)--rationale, design, and methods. *Am J Cardiol* 1995;**75**:470–475.

37. Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, Greene HL, Boczor S, Domanski M, Follmann D, Gent M, Roberts RS. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg . Canadian Implantable Defibrillator Study. *Eur Heart J* 2000;**21**:2071–2078.

38. Healey J, Connolly S. Life and Death after ICD Implantation. *New England Journal of Medicine* 2008;**359**:1058–1059.

39. Gatzoulis KA, Tsiachris D, Arsenos P, Archontakis S, Dilaveris P, Vouliotis A, Sideris S, Skiadas I, Kallikazaros I, Stefanadis C. Prognostic value of programmed ventricular stimulation for sudden death in selected high risk patients with structural heart disease and preserved systolic function. *Int J Cardiol* 2014;**176**:1449–1451.

40. Wellens HJJ, Schwartz PJ, Lindemans FW, Buxton AE, Goldberger JJ, Hohnloser SH, Huikuri HV, Kääb S, La Rovere MT, Malik M, Myerburg RJ, Simoons ML, Swedberg K, Tijssen J, Voors AA, Wilde AA. Risk stratification for sudden cardiac death: current status and challenges for the future. *Eur Heart J* 2014;**35**:1642–1651.

41. Wu KC, Calkins H. The Powerlessness of a Number: Why Left Ventricular Ejection Fraction Matters Less for Sudden Cardiac Death Risk Assessment. *Circulation Cardiovascular imaging* 2016;**9**:e005519.

42. Jouven X, Empana J-P, Schwartz PJ, Desnos M, Courbon D, Ducimetière P. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med* 2005;**352**:1951–1958.

43. Schwartz PJ, Wolf S. QT interval prolongation as predictor of sudden death in patients with myocardial infarction. *Circulation* 1978;**57**:1074–1077.

44. Panikkath R, Reinier K, Uy-Evanado A, Teodorescu C, Hattenhauer J, Mariani R, Gunson K, Jui J, Chugh SS. Prolonged Tpeak-to-tend interval on the resting ECG is associated with increased risk of sudden cardiac death. *Circ Arrhythm Electrophysiol* 2011;**4**:441–447.

45. Couderc JP, Chevalier P, Fayn J, Rubel P, Touboul P. Identification of post-myocardial infarction patients prone to ventricular tachycardia using time-frequency analysis of QRS and ST segments. *Europace* 2000;**2**:141–153.

46. Auer R, Bauer DC, Marques-Vidal P, Butler J, Min LJ, Cornuz J, Satterfield S, Newman AB, Vittinghoff E, Rodondi N, Health ABC Study. Association of major and minor ECG abnormalities with coronary heart disease events. *JAMA* 2012;**307**:1497–1505.

47. Jørgensen PG, Jensen JS, Marott JL, Jensen GB, Appleyard M, Mogelvang R. Electrocardiographic changes improve risk prediction in asymptomatic persons age 65 years or above without cardiovascular disease. *J Am Coll Cardiol* 2014;**64**:898–906.

48. Aro AL, Reinier K, Rusinaru C, Uy-Evanado A, Darouian N, Phan D, Mack WJ, Jui J, Soliman EZ, Tereshchenko LG, Chugh SS. Electrical risk score beyond the left ventricular ejection fraction: prediction of sudden cardiac death in the Oregon Sudden Unexpected Death Study and the Atherosclerosis Risk in Communities Study. *Eur Heart J* 2017;**38**:3017–3025.

49. Stecker EC, Vickers C, Waltz J, Socoteanu C, John BT, Mariani R, McAnulty JH, Gunson K, Jui J, Chugh SS. Population-Based Analysis of Sudden Cardiac Death With and Without Left Ventricular Systolic Dysfunction. *JACC* 2006;**47**:1161–1166.

50. Ibrahim NE, Januzzi JL. Established and Emerging Roles of Biomarkers in Heart Failure. *Circulation Research* 2018;**123**:614–629.

51. Hasselberg NE, Haugaa KH, Sarvari SI, Gullestad L, Andreassen AK, Smiseth OA, Edvardsen T. Left ventricular global longitudinal strain is associated with exercise capacity in failing hearts with preserved and reduced ejection fraction. *Eur Heart J Cardiovasc Imaging* 2015;**16**:217–224.

52. Haugaa KH, Grenne BL, Eek CH, Ersbøll M, Valeur N, Svendsen JH, Florian A, Sjøli B, Brunvand H, Køber L, Voigt J-U, Desmet W, Smiseth OA, Edvardsen T. Strain echocardiography

improves risk prediction of ventricular arrhythmias after myocardial infarction. *JACC Cardiovasc Imaging* 2013;**6**:841–850.

53. Biering-Sørensen T, Knappe D, Pouleur A-C, Claggett B, Wang PJ, Moss AJ, Solomon SD, Kutyifa V. Regional Longitudinal Deformation Improves Prediction of Ventricular Tachyarrhythmias in Patients With Heart Failure With Reduced Ejection Fraction. *Circulation: Cardiovascular Imaging* 2017;**10**:e005096.

54. Haugaa KH, Marek JJ, Ahmed M, Ryo K, Adelstein EC, Schwartzman D, Saba S, Gorcsan J. Mechanical dyssynchrony after cardiac resynchronization therapy for severely symptomatic heart failure is associated with risk for ventricular arrhythmias. *J Am Soc Echocardiogr* 2014;**27**:872–879.

55. Biton Y, Goldenberg I, Kutyifa V, Baman JR, Solomon S, Moss AJ, Szepietowska B, McNitt S, Polonsky B, Zareba W, Barsheshet A. Relative Wall Thickness and the Risk for Ventricular Tachyarrhythmias in Patients With Left Ventricular Dysfunction. *JACC* 2016;**67**:303–312.

56. Gatzoulis KA, Tsiachris D, Arsenos P, Antoniou C-K, Dilaveris P, Sideris S, Kanoupakis E, Simantirakis E, Korantzopoulos P, Goudevenos I, Flevari P, Iliodromitis E, Sideris A, Vassilikos V, Fragakis N, Trachanas K, Vernardos M, Konstantinou I, Tsimos K, Xenogiannis I, Vlachos K, Saplaouras A, Triantafyllou K, Kallikazaros I, Tousoulis D. Arrhythmic risk stratification in post-myocardial infarction patients with preserved ejection fraction: the PRESERVE EF study. *Eur Heart J* 2019;**40**:2940–2949.

57. Bauer A, Barthel P, Schneider R, Ulm K, Müller A, Joeinig A, Stich R, Kiviniemi A, Hnatkova K, Huikuri H, Schömig A, Malik M, Schmidt G. Improved Stratification of Autonomic Regulation for risk prediction in post-infarction patients with preserved left ventricular function (ISAR-Risk). *Eur Heart J* 2009;**30**:576–583.

58. Desjardins B, Crawford T, Good E, Oral H, Chugh A, Pelosi F, Morady F, Bogun F. Infarct architecture and characteristics on delayed enhanced magnetic resonance imaging and electroanatomic mapping in patients with postinfarction ventricular arrhythmia. *Heart Rhythm* 2009;**6**:644–651.

59. Mewton N, Liu CY, Croisille P, Bluemke D, Lima JAC. Assessment of Myocardial Fibrosis With Cardiovascular Magnetic Resonance. *Journal of the American College of Cardiology* 2011;**57**:891–903.

60. Izquierdo M, Ruiz-Granell R, Bonanad C, Chaustre F, Gomez C, Ferrero A, Lopez-Lereu P, Monmeneu JV, Nuñez J, Chorro FJ, Bodi V. Value of Early Cardiovascular Magnetic Resonance for the Prediction of Adverse Arrhythmic Cardiac Events After a First Noncomplicated ST-Segment–Elevation Myocardial Infarction. *Circulation: Cardiovascular Imaging* 2013;**6**:755–761.

61. Wu E, Ortiz JT, Tejedor P, Lee DC, Bucciarelli-Ducci C, Kansal P, Carr JC, Holly TA, Lloyd-Jones D, Klocke FJ, Bonow RO. Infarct size by contrast enhanced cardiac magnetic resonance is a stronger predictor of outcomes than left ventricular ejection fraction or end-systolic volume index: prospective cohort study. *Heart* 2008;**94**:730–736.

62. Klem I, Weinsaft JW, Bahnson TD, Hegland D, Kim HW, Hayes B, Parker MA, Judd RM, Kim RJ. Assessment of Myocardial Scarring Improves Risk Stratification in Patients Evaluated for Cardiac Defibrillator Implantation. *Journal of the American College of Cardiology* 2012;**60**:408–420.

63. Bello D, Fieno DS, Kim RJ, Pereles FS, Passman R, Song G, Kadish AH, Goldberger JJ. Infarct morphology identifies patients with substrate for sustained ventricular tachycardia. *Journal of the American College of Cardiology* 2005;**45**:1104–1108.

64. Bello D, Einhorn A, Kaushal R, Kenchaiah S, Raney A, Fieno D, Narula J, Goldberger J, Shivkumar K, Subacius H, Kadish A. Cardiac magnetic resonance imaging: infarct size is an independent predictor of mortality in patients with coronary artery disease. *Magnetic Resonance Imaging* 2011;**29**:50–56.

65. Zegard A, Okafor O, Bono J de, Kalla M, Lencioni M, Marshall H, Hudsmith L, Qiu T, Steeds R, Stegemann B, Leyva F. Myocardial Fibrosis as a Predictor of Sudden Death in Patients With Coronary Artery Disease. *Journal of the American College of Cardiology* 2021;**77**:29–41.

66. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Granger CB, Hammill SC, Hlatky MA, Joglar JA, Kay GN, Matlock DD, Myerburg RJ, Page RL. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. *Circulation* 2018;**138**:e272–e391.

67. Thomsen AF, Bertelsen L, Jøns C, Jabbari R, Lønborg J, Kyhl K, Göransson C, Nepper-Christensen L, Atharovski K, Ekström K, Tilsted H-H, Pedersen F, Køber L, Engstrøm T, Vejlstrup N, Jacobsen PK. Scar border zone mass and presence of border zone channels assessed with cardiac magnetic resonance imaging are associated with ventricular arrhythmia in patients with ST-segment elevation myocardial infarction. *Europace* 2022;**25**:978–988.

68. Roes SD, Borleffs CJW, Geest RJ van der, Westenberg JJM, Marsan NA, Kaandorp TAM, Reiber JHC, Zeppenfeld K, Lamb HJ, Roos A de, Schalij MJ, Bax JJ. Infarct Tissue Heterogeneity Assessed With Contrast-Enhanced MRI Predicts Spontaneous Ventricular Arrhythmia in Patients With Ischemic Cardiomyopathy and Implantable Cardioverter-Defibrillator. *Circulation: Cardiovascular Imaging* 2009;**2**:183–190.

69. Haghbayan H, Lougheed N, Deva DP, Chan KKW, Lima JAC, Yan AT. Peri-Infarct Quantification by Cardiac Magnetic Resonance to Predict Outcomes in Ischemic Cardiomyopathy. *Circulation: Cardiovascular Imaging* 2019.

70. Friedlander Y, Siscovick DS, Weinmann S, Austin MA, Psaty BM, Lemaitre RN, Arbogast P, Raghunathan TE, Cobb LA. Family history as a risk factor for primary cardiac arrest. *Circulation* 1998;**97**:155–160.

71. Dekker LRC, Bezzina CR, Henriques JPS, Tanck MW, Koch KT, Alings MW, Arnold AER, Boer M-J de, Gorgels APM, Michels HR, Verkerk A, Verheugt FWA, Zijlstra F, Wilde AAM. Familial sudden death is an important risk factor for primary ventricular fibrillation: a case-control study in acute myocardial infarction patients. *Circulation* 2006;**114**:1140–1145.

72. Kaikkonen KS, Kortelainen M-L, Linna E, Huikuri HV. Family history and the risk of sudden cardiac death as a manifestation of an acute coronary event. *Circulation* 2006;**114**:1462–1467.

73. Noseworthy PA, Havulinna AS, Porthan K, Lahtinen AM, Jula A, Karhunen PJ, Perola M, Oikarinen L, Kontula KK, Salomaa V, Newton-Cheh C. Common genetic variants, QT interval, and sudden cardiac death in a Finnish population-based study. *Circ Cardiovasc Genet* 2011;**4**:305–311.

74. Albert CM, Nam EG, Rimm EB, Jin HW, Hajjar RJ, Hunter DJ, MacRae CA, Ellinor PT. Cardiac sodium channel gene variants and sudden cardiac death in women. *Circulation* 2008;**117**:16–23.

75. Pfeufer A, Sanna S, Arking DE, Müller M, Gateva V, Fuchsberger C, Ehret GB, Orrú M, Pattaro C, Köttgen A, Perz S, Usala G, Barbalic M, Li M, Pütz B, Scuteri A, Prineas RJ, Sinner MF, Gieger C, Najjar SS, Kao WHL, Mühleisen TW, Dei M, Happle C, Möhlenkamp S, Crisponi L, Erbel R, Jöckel K-H, Naitza S, Steinbeck G, Marroni F, Hicks AA, Lakatta E, Müller-Myhsok B, Pramstaller PP, Wichmann H-E, Schlessinger D, Boerwinkle E, Meitinger T, Uda M, Coresh J, Kääb S, Abecasis GR, Chakravarti A. Common variants at ten loci modulate the QT interval duration in the QTSCD Study. *Nat Genet* 2009;**41**:407–414.

76. Newton-Cheh C, Eijgelsheim M, Rice KM, Bakker PIW de, Yin X, Estrada K, Bis JC, Marciante K, Rivadeneira F, Noseworthy PA, Sotoodehnia N, Smith NL, Rotter JI, Kors JA, Witteman JCM, Hofman A, Heckbert SR, O'Donnell CJ, Uitterlinden AG, Psaty BM, Lumley T, Larson MG, Stricker BHC. Common variants at ten loci influence QT interval duration in the QTGEN Study. *Nat Genet* 2009;**41**:399–406.

77. Zeng L, Talukdar HA, Koplev S, Giannarelli C, Ivert T, Gan L-M, Ruusalepp A, Schadt EE, Kovacic JC, Lusis AJ, Michoel T, Schunkert H, Björkegren JLM. Contribution of Gene Regulatory Networks to Heritability of Coronary Artery Disease. *J Am Coll Cardiol* 2019;**73**:2946–2957.

78. Hindy G, Aragam KG, Ng K, Chaffin M, Lotta LA, Baras A, Regeneron Genetics Center, Drake I, Orho-Melander M, Melander O, Kathiresan S, Khera AV. Genome-Wide Polygenic Score, Clinical Risk Factors, and Long-Term Trajectories of Coronary Artery Disease. *Arterioscler Thromb Vasc Biol* 2020;**40**:2738–2746.

79. Bezzina CR, Pazoki R, Bardai A, Marsman RF, Jong JSSG de, Blom MT, Scicluna BP, Jukema JW, Bindraban NR, Lichtner P, Pfeufer A, Bishopric NH, Roden DM, Meitinger T, Chugh SS, Myerburg RJ, Jouven X, Kääb S, Dekker LRC, Tan HL, Tanck MWT, Wilde AAM. Genome-wide association study identifies a susceptibility locus at 21q21 for ventricular fibrillation in acute myocardial infarction. *Nat Genet* 2010;**42**:688–691.

80. Hernesniemi JA, Karhunen PJ, Oksala N, Kähönen M, Levula M, Rontu R, Ilveskoski E, Kajander O, Goebeler S, Viiri LE, Hurme M, Lehtimäki T. Interleukin 18 gene promoter polymorphism: a link between hypertension and pre-hospital sudden cardiac death: the Helsinki Sudden Death Study. *Eur Heart J* 2009;**30**:2939–2946.

81. Kao WHL, Arking DE, Post W, Rea TD, Sotoodehnia N, Prineas RJ, Bishe B, Doan BQ, Boerwinkle E, Psaty BM, Tomaselli GF, Coresh J, Siscovick DS, Marbán E, Spooner PM, Burke GL, Chakravarti A. Genetic variations in nitric oxide synthase 1 adaptor protein are associated with sudden cardiac death in US white community-based populations. *Circulation* 2009;**119**:940–951.

82. Hill AB. The Environment and Disease: Association or Causation? *Proc R Soc Med* 1965;**58**:295–300.

83. Noseworthy PA, Newton-Cheh C. Genetic determinants of sudden cardiac death. *Circulation* 2008;**118**:1854–1863.

84. Arking DE, Chugh SS, Chakravarti A, Spooner PM. Genomics in sudden cardiac death. *Circ Res* 2004;**94**:712–723.

85. Sun L, Pennells L, Kaptoge S, Nelson CP, Ritchie SC, Abraham G, Arnold M, Bell S, Bolton T, Burgess S, Dudbridge F, Guo Q, Sofianopoulou E, Stevens D, Thompson JR, Butterworth AS, Wood A, Danesh J, Samani NJ, Inouye M, Di Angelantonio E. Polygenic risk scores in cardiovascular risk prediction: A cohort study and modelling analyses. *PLoS Med* 2021;**18**:e1003498.

86. Marston NA, Pirruccello JP, Melloni GEM, Koyama S, Kamanu FK, Weng L-C, Roselli C, Kamatani Y, Komuro I, Aragam KG, Butterworth AS, Ito K, Lubitz SA, Ellinor PT, Sabatine MS, Ruff CT. Predictive Utility of a Coronary Artery Disease Polygenic Risk Score in Primary Prevention. *JAMA Cardiol* 2023;**8**:130–137.

87. Inouye M, Abraham G, Nelson CP, Wood AM, Sweeting MJ, Dudbridge F, Lai FY, Kaptoge S, Brozynska M, Wang T, Ye S, Webb TR, Rutter MK, Tzoulaki I, Patel RS, Loos RJF, Keavney B, Hemingway H, Thompson J, Watkins H, Deloukas P, Di Angelantonio E, Butterworth AS, Danesh J, Samani NJ, UK Biobank CardioMetabolic Consortium CHD Working Group. Genomic Risk Prediction of Coronary Artery Disease in 480,000 Adults: Implications for Primary Prevention. *J Am Coll Cardiol* 2018;**72**:1883–1893.

88. Guarischi-Sousa R, Salfati E, Kho PF, Iyer KR, Hilliard AT, Herrington DM, Tsao PS, Clarke SL, Assimes TL. Contemporary Polygenic Scores of Low-Density Lipoprotein Cholesterol and Coronary Artery Disease Predict Coronary Atherosclerosis in Adolescents and Young Adults. *Circ Genom Precis Med* 2023;**16**:480–482.

89. Khan SS, Page C, Wojdyla DM, Schwartz YY, Greenland P, Pencina MJ. Predictive Utility of a Validated Polygenic Risk Score for Long-Term Risk of Coronary Heart Disease in Young and Middle-Aged Adults. *Circulation* 2022;**146**:587–596.

90. Sandhu RK, Dron JS, Liu Y, Moorthy MV, Chatterjee NA, Ellinor PT, Chasman DI, Cook NR, Khera AV, Albert CM. Polygenic Risk Score Predicts Sudden Death in Patients With Coronary Disease and Preserved Systolic Function. *J Am Coll Cardiol* 2022;**80**:873–883.

91. Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, Natarajan P, Lander ES, Lubitz SA, Ellinor PT, Kathiresan S. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet* 2018;**50**:1219–1224.

92. Larsson SC, Butterworth AS, Burgess S. Mendelian randomization for cardiovascular diseases: principles and applications. *Eur Heart J* 2023;**44**:4913–4924.

93. Maglietta G, Ardissino M, Malagoli Tagliazucchi G, Disisto C, Merlini PA, Crocamo A, Notarangelo MF, Calabrò P, Berzuini C, Ardissino D. Long-Term Outcomes After Early-Onset Myocardial Infarction. *J Am Coll Cardiol* 2019;**74**:2113–2115.

94. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, Motyer A, Vukcevic D, Delaneau O, O'Connell J, Cortes A, Welsh S, Young A, Effingham M, McVean G, Leslie S, Allen N, Donnelly P, Marchini J. The UK Biobank resource with deep phenotyping and genomic data. *Nature* 2018;**562**:203–209.

95. Bricoli S, Magnani G, Ardissino M, Maglietta G, Celli P, Ferrario M, Canosi U, Cernetti C, Negri F, Merlini PA, Tubaro M, Berzuini C, Manzalini C, Moschini L, Ponte E, Pozzi R, Buratti S, Botti A, Barocelli F, Biagi A, Bonura R, Bearzot L, Moccetti T, Crocamo A, Notarangelo MF, Moscarella E, Calabrò P, Niccoli G, Ardissino D. Sudden cardiac death after early-onset myocardial infarction. A multicentre longitudinal cohort study with 20 years' follow-up. *Eur Heart J Acute Cardiovasc Care* 2024:zuae089.