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Sudden death in ischemic heart disease: looking for new predictors: polygenic risk

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The phenomenon of sudden death (SD) occurs, in 70% of cases, in people who do not fall within the indications of the guidelines relating to the implantation of the defibrillator. There is a way of inheriting the risk condition by genetic means, the polygenic one, in which mutations are not found, but an increase in alleles of common variations called polymorphisms. The PRE-DETERMINE cohort study has the primary objective of determining whether biological markers, and electrocardiogram can be used to identify individuals more likely to experience SD. Within the study, we investigated the utility of the genome-wide polygenic score for coronary artery disease (GPSCAD) for SD risk stratification in an intermediate-risk population with stable coronary artery disease without severe systolic dysfunction and/or indication for an implantable cardioverter defibrillator in primary prevention. Over a mean follow-up period of 8.0 years, patients in the top decile of GPSCAD were at higher absolute (8.0% vs. 4.8%; $P < 0.005$) and relative (29% vs. 16%; $P < 0.0003$) risk of SD compared to the rest of the cohort. No association was found between the highest decile of GPSCAD and other forms of death, cardiac, and non-cardiac. The data on the increase in absolute and relative terms of SD can be used, at this stage, only for a theoretical estimate on the possible efficacy of the defibrillator in the population with chronic coronary artery disease and moderately depressed left ventricular function as number needed to treat and possible reduction of mortality in high-risk patients (those included in the top decile of GPSCAD).

Ischemic heart disease is the most common substrate underlying sudden death. The latter constitutes the end-of-life modality in 15–20% of cases.[1] Taking into account the epidemiological impact of coronary artery disease, it is clear that it is of primary importance to identify those subjects most likely to experience sudden death (SD). The common indications for implantable cardioverter defibrillator (ICD) cannot satisfactorily protect the population with coronary artery disease, as the phenomenon of SD occurs, in 70% of cases, in people who do not qualify according to the guidelines.[2]

The methodologies for predicting the development of ischemic heart disease have been enriched, in recent years, with new indicators taken from the genetic study of the individual on the basis of the longitudinal evaluation of subjects enrolled in large biobanks. It is known that up to 30% of heart attack cases do not have the risk factors used in the classic prediction models.[3] Compounding this situation is the finding that ST-elevation myocardial infarction (STEMI) cases that did not have risk factors had higher mortality in the subsequent 30 days after the event.[4] Myocardial infarction is a multifactorial pathology with an important hereditary component, estimated through large-scale studies at ~40–60%.[5] The genetic component of heart attack has been shown to be of two types: monogenic and polygenic. The mutations can be identified thanks to sequencing with next generation sequencing (NGS) technology and bioinformatic analyses, whose pathogenicity is then confirmed by the geneticist. There is a way of inheriting the risk condition by genetic means, the polygenic one, in which mutations are not found (i.e. errors in the genetic code that cause an alteration of the encoded protein) but an increase in alleles of common variations called polymorphisms. Polymorphisms are variations that do not cause

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a gene alteration, each with a small effect on risk: when these variations add up, they confer a significantly increased genetic risk of developing the phenotype. Polymorphisms can identify a larger population than mutations.[6]

The PRE-DETERMINE cohort study[7]

This is a US National Institute of Health-supported prospective multicentre cohort study of patients with a history of coronary artery disease and documentation of a prior myocardial infarction or mild to moderate left ventricular dysfunction [ejection fraction (EF) 35–50%]. The main objective is to determine whether biological markers and electrocardiogram (ECG) can be used to identify individuals more likely to experience MI. Identifying such markers could lead to more efficient use of the implantable defibrillator (automatic ICD) and advance our understanding of the mechanisms underlying SD.

Patients were enrolled at 135 centres, with electronic capture of demographics, clinical characteristics, lifestyle habits, cardiac test results, and medications. ECG and a blood sample were sent to central laboratories and stored for future analysis. Magnetic resonance imaging (MRI) with contrast was performed in a subset of patients. Enrolment closed in November 2013 and patients are being followed up by the coordination centre via mail/telephone to document non-fatal arrhythmic events and cause-specific death. Questionnaires are periodically sent inquiring about ICD implantation, ICD therapies, cardiac arrest, and other pertinent cardiovascular end points. The identification of several predictors has been the subject of many recent publications. Silverman and colleagues have verified that plasma microRNAs (miRNAs) can regulate remodelling processes and can be used to identify patients with chronic coronary syndrome more exposed to the risk of sudden and arrhythmic death.[8] Lee *et al.*[9] demonstrated that in patients with a previous infarction, a simple electrocardiographic score is able to estimate the extension of the infarcted area to a similar extent to that of MRI, thus providing another important predictor of the risk of SD. Chatterjee *et al.*[10] verified how in patients with chronic coronary syndrome simple electrocardiographic parameters are able to significantly improve the relative and absolute risk stratification of MI compared with standard risk factors such as EF. Four ECG markers were independently associated with arrhythmic death: left ventricular hypertrophy, presence of contiguous Q waves, QRS duration, and prolonged JTc interval.

The polygenic score as a predictor of sudden death

Sandhu *et al.*[11] demonstrated that in the cohort of patients without severe left ventricular dysfunction enrolled in the PRE-DETERMINE study, a genome-wide validated polygenic risk score was able to predict a clinically significant absolute risk of sudden arrhythmic death. The study investigated the utility of the genome-wide polygenic score for coronary artery disease (GPSCAD) for risk stratification of SD in an intermediate-risk population with stable coronary artery disease without severe systolic dysfunction and/or indication for an ICD in primary prevention. GPSCAD, which includes >6 million common variants, has previously been shown to predict the occurrence of acute coronary heart disease and account for up to 22% of the heritability of coronary heart disease in populations of European ancestry.[12] The obtained data were then used to verify whether the GPSCAD, in combination with clinical indicators and ECG, could be able to identify a population at higher absolute and relative risk of SD for inclusion in future studies on ICD implantation.

A total of 4698 patients followed for 8 years were enrolled in the study, divided into 2 groups: the highest decile of GPSCAD and the rest of the population, compared with respect to the rate of sudden death and non-sudden death (NSD). Multivariate analysis was adjusted for age and sex, diabetes, hypertension, body mass index, AF, New York Heart Association (NYHA) class, history of smoking, use of anti-dyslipidemic drugs, diuretics, family history of SD, and a validated ECG score previously associated with SD in the same population.[10] Over a mean follow-up period of 8.0 years, patients in the top decile of GPSCAD were at higher absolute (8.0% vs. 4.8%; $P < 0.005$) and relative (29% vs. 16%; $P < 0.0003$) risk of SD compared to the rest of the cohort. On the other hand, no association was found between the highest decile of GPSCAD and other forms of death, cardiac and non-cardiac. The predictive power of SD of GPSCAD in the top decile increased in the group of patients classified at greatest risk according to clinical and electrocardiographic criteria.

To what extent could the polygenic score modify the indications for defibrillator implantation?

Heart disease associated with SD varies according to the age of the individual. In young people, primary electrical diseases and cardiomyopathies predominate, as do myocarditis and coronary artery anomalies. In older populations, chronic structural diseases (ischemic heart disease, valvular heart disease, and heart failure) predominate, while potentially inherited electrical or non-ischaemic structural diseases can cause more than 50% of SD cases in individuals younger than 50 years.

For decades, researchers have imagined a wide range of 'markers' for SD, particularly in the context of coronary heart disease. Several non-invasive risk markers have been proposed (including late potentials, heart rate variability, repolarization phase changes, and baroreflex sensitivity). Despite the promising results of initial studies, however, these 'predictors' have not yet influenced clinical practice. Left ventricular ejection fraction (LVEF) is used alone or in combination with the NYHA class, for the indication for ICD implantation in primary prevention in the context of chronic coronary artery disease and dilated cardiomyopathy. Risk stratification schemes and calculators have been developed for inherited arrhythmogenic diseases, such as hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and lamine A/C cardiomyopathy (LMNA).

The European Society of Cardiology Guidelines of October 2022 relating to the prediction and prevention of SD[13] recommend the practice of genetic testing in those conditions in which there is a probable genetic basis for the development of potentially fatal arrhythmias. When

a potentially pathogenic variant is identified, it is recommended that it be validated in an internationally accepted scientific context and that counselling with its potential consequences be entrusted to a multidisciplinary expert team. It is also recommended that genetic testing not be performed in patients with insufficient demonstration of a genetic basis for the disease. With these assumptions, what value should we give to the data emerging from the study we examined and published almost simultaneously with the guidelines to which we refer?

Bioinformatic technologies have dramatically increased the possibility of performing genetic tests at low cost. Numerous associations between genes have been tested for their possible diagnostic utility. Genome-wide association studies have shown that genetic variations of single nucleotide polymorphisms can produce or modify the phenotype in Brugada syndrome, long QT syndrome, hypertrophic cardiomyopathy, and dilated cardiomyopathy. Polygenic risk scores, measures derived from the cumulative effects of these single nucleotide polymorphisms, could play an important role in the future diagnosis and prognosis of these conditions. Sequencing produces digital data that require a subsequent bioinformatics analysis that allows an accurate examination of most of the DNA alterations that influence the coding possibility of each gene. In order to classify the causal weight of the genetic variants, five possibilities have been formulated: V 'pathogen'; IV 'probably pathogenic'; III 'variant of uncertain meaning'; II 'probably benign'; and I 'benign'.

In this context, how can we interpret and use the data emerging from the study by Sandhu *et al.*?

We have seen that the highest decile of GPSPAD is more likely to be associated with SD in patients with chronic coronary syndrome, but is this sufficient to broaden the use of the implantable defibrillator in primary prevention? The data on the increase in absolute and relative terms of SD can be used, at this stage, only for a theoretical estimate on the possible efficacy of the defibrillator in the population with chronic coronary artery disease and moderately reduced left ventricular function as number needed to treat (NNT) and possible reduction of mortality in high-risk patients (those included in the top decile of GPSCAD).

Assuming that ICD implantation could reduce the risk of sudden death by 60%, it can be calculated that patients in the top decile would have a 17% relative risk reduction in all-cause mortality, with an NNT of 27 implants to save a life. The number of patients to be enrolled in a confirmatory trial would be 3600 to be followed for 8 years. It is estimated that if further risk stratification is added using an ECG risk score,[10] the relative risk reduction of death from all causes in the top decile of GPSCAD would rise to 24% with ICD implantation, with an NNT of 11. The number of patients to be enrolled in a trial, in this case, would be 864 to be followed for 5 years. It remains unclear why GPSCAD is able to predict only SD and no other forms of cardiac mortality. One hypothesis could be the increased propensity to plaque rupture or instability, or pleiotropic effects towards the formation of an unfavourable scar or alteration of ion channels which could increase the predisposition to fatal arrhythmias. In conclusion, at the present state of knowledge, the genetic prediction of SD in patients with ischemic heart disease can be considered an advanced stage demonstration of acquisition. Surely it can be used together with other risk markers, such as electrocardiographic and clinical ones, for greater attention to the categories defined as being at greater risk. The data available to us, however, still do not allow us to broaden the indications for defibrillator implantation in primary prevention. For this reason, we still have an estimate of the research effort needed for the next few years.

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Data availability

No new data were generated or analysed in support of this research.

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