

# Risk Stratification and Prevention of Sudden Cardiac Death: Bridging Structural and Electrical Etiologies

Shrikant Verma<sup>1</sup>, Sushma Verma<sup>1</sup>, Bashir Ahmad Mir<sup>2</sup>, Tabrez Faruqui<sup>1</sup>, Mohammad Abbas<sup>1,3</sup>, Farzana Mahdi<sup>1</sup>

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## ABSTRACT

**Background:** Sudden cardiac events represents a global health concern in developing countries. The term refers to a sudden death from a heart related cause that is usually unexpected and happens within one hour of the first symptom even in people without known heart disease. This paper highlights if Sudden cardiac death (SCD) is mostly due to structural defects of the heart, electrical problems, or a mixture of the two, and how it matters for diagnosis, predicting risks, and prevention.

**Methodology:** A systematic literature search was done with the help of various electronic databases such as PubMed, Scopus, Web of Science and Google Scholar.

**Output:** According to clinical studies imaging autopsy reports, and genetic research, it has been demonstrated that it is the defects in the heart's structure and electrical system that cause deadly arrhythmias. Sudden cardiac events in younger people mainly occur due to inheriting cardiomyopathies and arrhythmogenic channelopathies. Cardiomyopathies lead to risk through their specific structural changes like fibrosis, myocyte disarray, or the presence of adipose tissue. Most electrical disorders are caused by mutations in genes. Besides this, there is growing evidence showing a structural electrical continuum: very small areas of fibrosis or inflammation can cause arrhythmias, and even "pure" electrical diseases may have subtle structural changes. The present study aims to determine if SCD is mainly due to structural heart disease, electrical disorders, or their combination, and this is crucial because a proper mechanistic understanding is the key to better risk stratification, early detection, and effective prevention of fatal cardiac events.

**KEYWORDS:** Sudden cardiac events, Structural heart disease, Electrical disorders, Cardiomyopathies, Arrhythmias, Myocardial infarction, Channelopathies.

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## INTRODUCTION

Sudden cardiac events are one of the major and often unpredictable causes of mortality worldwide. Sudden cardiac death (SCD) is usually caused by cardiac disorders, happening within a short time frame, typically within one hour since the first symptoms in persons with or without already known heart disease.<sup>1</sup> Even though there have been remarkable advancements in cardiovascular diagnostics, risk stratification and treatment measures, sudden cardiac events remain at the core of causes of global mortality and thus, constitute a major public health problem. 15 - 20% global deaths occur due to SCDs in developed countries and responsible for half of mortality associated with cardiovascular diseases.<sup>2,3</sup> SCD occurrence differs greatly between populations as a consequence of variation in study design, case ascertainment and demographic characteristics; thus, annual incidence rate in the general population has been reported to vary from 50 to more than 100/100,000 individuals.<sup>1,3</sup> In adults, especially in elderly ones, coronary artery disease is the main cause of SCD, by far, while in young people and those with no apparent structural abnormalities of the heart, the most common

<sup>1</sup>Department of Personalized and Molecular Medicine, Era University, Lucknow, Uttar Pradesh, India.

<sup>2</sup>Department of Cardiology, Era's Lucknow Medical College and Hospital, Era University, Lucknow, Uttar Pradesh, India.

<sup>3</sup>Department of Biotechnology, Era University, Lucknow, Uttar Pradesh, India.

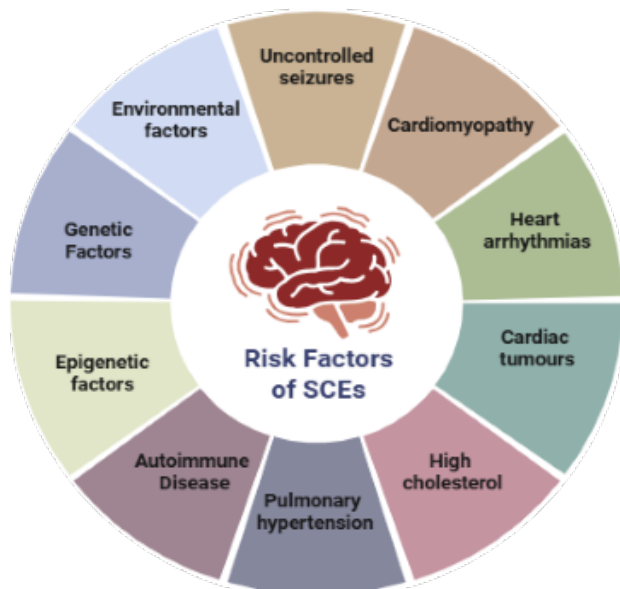
**Corresponding Author:** Shrikant Verma

**Email:** Shri050795@gmail.com

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causes are hereditary cardiomyopathies and primary electrical disorders.<sup>4,5</sup>

The unpredictable nature of sudden cardiac events is one of the most alarming features about them. Most people who suffer from such an event do not have any warning symptoms, and in a number of cases, sudden cardiac arrest is actually the first clinical signal of heart disease.<sup>3</sup> The survival rate for a cardiac arrest that occurs outside of a hospital is still very low, which means that there is a great need to understand better the mechanisms that cause sudden cardiac events. Various researches have shown that,



**Figure 1:** Risk factors of sudden cardiac events.

It is not only the structural defects of the heart muscle but also the primary electrical disorders which lead to the development of fatal ventricular arrhythmias, and these factors often interact in a complex way.<sup>1,5</sup> Undoubtedly, the epidemiology and complex pathophysiology of sudden cardiac events must be fully understood in order to come up with effective preventive measures, to detect individuals at high risk at the earliest stage, and to apply personalized therapeutic interventions.

## METHODOLOGY

A systematic literature search was carried out with the help of a number of electronic databases. Keywords that are relevant to the topic such as sudden cardiac death, risk stratification, structural heart disease, electrical disorders, arrhythmias, cardiomyopathy, and channelopathies were combined to make the retrieved results more specific. Study characteristics, risk factors, diagnostic methods, and preventive measures were systematically recorded. The information was organized and presented in a descriptive manner by separating the results into structural and electrical sides and highlighting their interaction at the same time. To combine these two fields, a thematic framework was designed which covers structural heart diseases, primary electrical disorders, the most common mechanisms, and new multimodal risk stratification methods.

## Structural vs. Electrical Causes

It is important to distinguish structural from electrical causes in sudden cardiac events for several reasons; firstly, identifying the main nature of the event in the heart is crucial for grasping the mechanisms that may trigger such events. Structural heart diseases, for instance, include ischemic heart disease, cardiomyopathies, valvular

abnormalities, and congenital defects. These conditions result in the development of an arrhythmogenic substrate in the myocardium due to myocardial scarring, fibrosis, hypertrophy, or ventricular remodeling, which can make the heart susceptible to malignant ventricular arrhythmias.<sup>1,2</sup> The sudden cardiac event in this type of pathology is typically the final stage of the progressive myocardial disease. Conversely, electrical disorders, also known as channelopathies, are those that happen in the absence of any visible abnormality in the structure of the heart. Such conditions are a result of genetic and environmental factors that work together to cause dysfunction and abnormalities of ion channels in myocardial cell membranes. They predominantly affect younger individuals and may present with sudden cardiac arrest as the first.<sup>5,6</sup>

From a clinical point of view, distinguishing structural from electrical causes of heart conditions leads to the different prognosis, treatment, and family screening. Identifying that a patient has structural heart disease can suggest that they are candidates for treatments like revascularization, heart failure management, and implantable cardioverter defibrillators. Conversely, diagnosing a primary electrical disorder will lead to genotype-guided therapy, personalized pharmacotherapy, and cascade screening of the patient's family members.<sup>1,5</sup> Besides, recent studies reveal that the structural and electrical mechanisms are capable of interfacing, sharing genetic determinants and having a modulating interaction, which is a further argument for a mechanistic, instead of solely phenotypic, classification of SCD events.

## Structural Heart Diseases and SCD

Structural heart diseases are the main substrate of SCD by creating an arrhythmogenic milieu through myocardial scarring, fibrosis, hypertrophy, and ventricular remodeling in adult populations.<sup>7</sup> Moreover, ischemic heart disease continues to be the major cause of SCD around the globe. A past or recent myocardial infarction leads to the formation of scarred and electrically heterogeneous myocardial areas that maintain re-entrant ventricular tachyarrhythmias even in the absence of ischemia.<sup>8,9</sup> Cardiomyopathies are yet another large category of structural abnormalities that have a significant association with SCD.<sup>10</sup> Similarly, dilated cardiomyopathy leads to ventricular dilatation, decreased systolic function, and widespread fibrosis, which trigger electrical instability and, thus, carry the risk of SCD.<sup>11,12</sup> There are also several other structural abnormalities like valvular heart disease, myocarditis, and congenital heart defects, which have been shown to increase SCD risk through alterations in myocardial structure and conduction pathways.<sup>13</sup>

## 1. Ischemic heart disease (IHD) and SCD

IHD is also a major cause of cardiac deaths globally, especially in the middle age and elderly populations. It causes most of

SCD cases in the developed and developing countries and is still a major problem contributing to the deaths of persons with IHD despite the advances in acute coronary care.<sup>2,9</sup> The danger of SCD to the IHD patients is very significant whether the patient suffers from an acute ischemic episode or has old myocardial injury. Acute myocardial ischemia can lead to the death of the patient without the possibility of resuscitation due to the ventricular arrhythmias caused by the metabolic and electrophysiological changes such as dysfunction of the ion channels, overload of intracellular calcium, and autonomic imbalance.<sup>8</sup> The ventricles in patients with the chronic form of ischemic heart disease, especially after a myocardial infarction, will be a mix of different tissue types: scars from previous infarcts which are fibrotic, normal tissues, and the border zones. The scarred and viable (border) zones will make the ventricles become heterogeneous at the microscopic level. This condition can lead to re-entrant circuits, ventricular fibrillation, both major sources of sudden cardiac death. Left ventricular failure, how much heart tissue is scarred, and problems with the autonomic nervous system are strong indicators of risk.<sup>1,7</sup> For now, these factors point to ischemic heart disease as a structural root of dangerous arrhythmias. Early detection matters. Implantable cardioverter-defibrillators could help in people at higher risk.<sup>3</sup>

## 2. Cardiomyopathies and SCD

Cardiomyopathies are a major group of heart diseases that structurally link to sudden cardiac death, notably in the young and middle-aged populations. While coronary artery disease is the major cause of ischemic heart disease, cardiomyopathies can be genetically passed down and cause SCD even in the absence of coronary artery disease. HCM, DCM and ACM/ARVC represent a trio of cardiomyopathies differing in their pathological features, mechanisms of arrhythmogenesis, and epidemiological patterns; however, they ultimately converge on malignant ventricular arrhythmias as a shared final outcome.<sup>10,12</sup>

One of the main reasons for SCD in the youth and among athletes is Hypertrophic cardiomyopathy (HCM). It shows various pathological features including unexplained left ventricular thickening, disorder in myocytes, and interstitial fibrosis, which together cause significant electrical heterogeneity.<sup>10</sup> Major cohort studies have been able to show that the presence of risk factors like extreme hypertrophy, unexplained syncope, and non-sustained ventricular tachycardia are very indicative of SCD.<sup>14</sup> In comparison with IHD SCD in HCM frequently occurs during sleep or with very little effort and may be the first symptom of the disease, thereby underlining the stealthy yet deadly nature of this cardiomyopathy.

Dilated cardiomyopathy (DCM) refers to a condition in which the heart ventricles become enlarged and their ability to pump blood is reduced. Myocardial fibrosis identified

through cardiac imaging has shown to better predict SCD than left ventricular ejection fraction only, thus indicating that changes in the heart's structure, rather than the degree of systolic dysfunction, are the main cause of arrhythmias.<sup>11,15</sup> Unlike in hypertrophic cardiomyopathy (HCM) where lethal arrhythmias could be the first manifestation with preserved systolic function, in DCM ventricular arrhythmias resulting in SCD are usually seen in association with severe remodelling of the ventricles and advanced heart failure. Studies comparing the two conditions suggest that although the absolute risk of SCD might be less in DCM as compared to ischemic cardiomyopathy, a significant number of death cases in DCM are actually sudden and not due to pump failure.<sup>9</sup> Arrhythmogenic cardiomyopathy (ACM), which is most commonly referred to as ARVC, is a disease considered by the substitution of the myocardium by fibro, fatty tissue, mainly affecting the right ventricle, but in the latter stages of the disease, the left ventricle is often involved as well. It is a condition highly associated with the occurrence of ventricular arrhythmias and sudden cardiac death that are the main reasons for the fatalities, especially in young people and athletes.<sup>12</sup>

Exercise has been shown to speed up the development of the disease and greatly raise the risk of arrhythmias, as evidenced by longitudinal studies, although this is a less significant finding in HCM and DCM.<sup>16</sup> When compared to other forms of cardiomyopathy, ARVC has a greater number of cases of SCD at a younger age and that are often associated with minimal structural changes visible on routine imaging, thereby highlighting the significance of genetic and electro-anatomical assessment.

By comparing different research work, we learn that all 3 cardiomyopathies may cause SCD however each one has distinct mechanisms and risk factors. HCM's hallmark features include sarcomeric mutations and myocardial disarray, DCM is marked by diffuse remodelling and fibrosis, and ARVC is based on desmosomal dysfunction and fibro fatty infiltration.<sup>10,12</sup> However, it is noteworthy that recent multi-centre research indicates that these cardiomyopathies share common genetic pathways and may change phenotypically, thus suggesting a structural electrical continuum rather than separate diseases.<sup>17</sup> Cumulatively, cardiomyopathies are a major contributor to the problem of SCD in different age groups.

## 3. Valvular, Congenital Heart Diseases and Sudden Cardiac Death

Both valvular and congenital heart diseases are among the structurally important substrates for SCD; hence they have been implicated in the causation of risk in both paediatric and adult populations. Even though these diseases are less common in comparison to ischemic heart disease or cardiomyopathies, they are clinically significant because sudden death may be the first indicator of an underlying

problem, or in patients with very mild symptoms only.<sup>13</sup> The valvular diseases of the heart have been the predominant ones associated with SCD, with aortic stenosis and mitral valve prolapse being the major ones to feature. The most striking histological features in the hearts of animals and humans with severe aortic stenosis and subsequent sudden death, include the presence of extensive areas of myocardial fibrosis, the atrophied and hypertrophied myocytes as well as severe left ventricular hypertrophy. An experimental animal study indicates that the main electrophysiological substrate for ventricular arrhythmias is related to myocardial fibrosis.<sup>18</sup> Evidence from observational studies suggests that the natural course of severe aortic stenosis with no intervention affords a significant risk of sudden death which is considerably lessened after aortic valve replacement.<sup>18,19</sup> Generally, mitral valve prolapse is considered a very harmless condition. However, recent studies have revealed that a small group of patients with arrhythmic mitral valve prolapse have papillary muscles fibrosis and inferobasal left ventricle which leads to ventricular arrhythmias and sudden death.<sup>13,20</sup> Congenital heart diseases (CHD) represent the main factor of SCD in children and young adults. Advancements in surgical and medical care have so deeply altered survival that we are now witnessing an expanding demographic of adults with repaired or palliated CHD who remain vulnerable to arrhythmias and sudden death for the rest of their lives.<sup>21</sup> Patients with such diagnoses as transposition of the great arteries, ventricle physiology have a remarkably higher risk for SCD due to leftover hemodynamic lesions, ventricular scarring from surgical procedures, and ongoing myocardial remodelling.<sup>21,22</sup>

Comparative studies reveal that the mechanisms behind SCD in valvular and congenital heart diseases are quite different from those in ischemic cardiomyopathy. While ischemic SCD is mainly the result of scar, related re, entry following myocardial infarction, valvular and congenital pathologies are highly likely to be accompanied by a mixture of pressure or volume overload, chamber enlargement, fibrosis, and surgical scars which altogether constitute the complex arrhythmogenic substrates.<sup>13,21</sup> These results are well supported by multicentre registry data illustrating that ventricular arrhythmias are the prevalent immediate causes of death in both severe valvular disease and repaired congenital heart disease.

### Electrical Disorders and SCD

One major non-structural cause of SCD in children, adolescents, and young adults with structurally normal hearts is electrical disorders of the heart (also called primary electrical diseases or channelopathies). The reason behind these diseases is genetically or chemically changed cardiac ion channels or proteins resulting in abnormal cardiac depolarization or repolarization and the formation of malignant ventricular arrhythmias.<sup>5,6</sup>

Long QT Syndrome is a common heart rhythm issue. It affects how the ventricles recover after contraction.<sup>23</sup> Large cohort studies have showed that there is a strong genotype phenotype correlation, with certain ion channel mutations affecting the arrhythmic risk and response to therapy.<sup>5</sup> Brugada syndrome is yet one more prominent cause of the SCD that is beyond the usual scope of consideration, especially in the case of young adult males. The syndrome shows a very unique pattern on an ECG and carries a risk of ventricular fibrillation, which is more likely to happen when the person is at rest or asleep.<sup>24</sup> While the heart appears to be normal in structure on conventional imaging, some studies have even reported subtle structural and inflammatory changes, thus, the findings might be extending from the electrical to structural disorders.<sup>25</sup> The research studies based on the population show that Brugada syndrome is the major cause of sudden unexplained deaths among the people of Southeast Asian ancestry.<sup>24</sup> Abnormalities in calcium-handling proteins are central to its pathogenesis, and untreated individuals carry a markedly elevated risk of SCD at young age.<sup>26</sup> Unlike ischemic or structural cardiomyopathies, CPVT at rest is ECGs are usually completely normal which is one of the reasons why it is so hard to diagnose.

Short QT syndrome and other rare channelopathies add to the range of electrical disorders linked to SCD. These less common conditions still account for a high rate of ventricular arrhythmias and sudden death, frequently as the first clinical symptom.<sup>27</sup> Comparative studies have shown that, in contrast to structural heart diseases where the remodelling and scarring of the myocardium are the main factors behind arrhythmogenesis, electrical disorders are mainly characterized by functional aberrations of the ion channel activity in the absence of any gross anatomical abnormalities.<sup>6</sup> Evidence shows that both electrical and structural diseases are on a continuum with, common genetic factors, and the gradual appearance of the phenotype over time.<sup>5</sup> Therefore, the identification of electrical disorders is of utmost importance because the early detection and treatment, risk assessment, and family screening can greatly reduce the incidence of SCD.

### Overlap Between Structural and Electrical Mechanisms in SCD

SCD has long been categorized into two groups: structural and electrical causes. New research including experimental, clinical, and genetic studies shows that these mechanisms may not be that different after all and that SCD most probably involves both structural and electrical changes rather than being two completely separate categories. This broad idea has deepened our understanding of how arrhythmias develop and match well with results from big cohort and translational studies.<sup>5,6</sup> Myocardial problems such as fibrosis hypertrophy inflammation, and scar formation influence cardiac electrophysiology

in a very significant way both structurally and electrically. Researches with cardiac magnetic resonance imaging have revealed that tiny patches of myocardial fibrosis alone are capable of changing conduction velocity and repolarization, thereby intensifying the vulnerability of the heart to re-entrant ventricular arrhythmias.<sup>15</sup> These results are constant with earlier pathological studies that indicated microscopic structural changes, which are not detectable by standard imaging techniques, can lead to electrical instability.<sup>13</sup> This corroborates the idea that numerous "structural" heart diseases may lead to death mainly via later electrical changes. On the other hand, data from electrical and structural routes indicate that primary electrical irregularities could still be linked to hearts that are not completely normal. To illustrate, Brugada syndrome, which has been considered a "pure" channelopathy, presents the histological features of right ventricular fibrosis, inflammation, and down-regulation of connexin, among others, as shown by a few histopathological and electro-anatomical mapping studies.<sup>25,28</sup> These findings align with genetic studies indicating that mutations in ion channel genes may also impair myocardial development, intercellular coupling, and structural integrity over time.<sup>5</sup> Studies examining the correlation between genotype and phenotype provide further support for the overlap hypothesis. Research indicates that mutations in specific genes, such as SCN5A, may be linked to both electrical disorders like Brugada syndrome and LQT syndrome, as well as structural cardiomyopathies.<sup>29</sup> This dual manifestation aligns with previous population-based studies where family members exhibited overlapping clinical phenotypes, reinforcing the idea that shared molecular pathways can result in both structural remodeling and electrical dysfunction.<sup>17</sup> Comparative analysis of different registries and autopsy-based studies, they found that many SCD cases classified as electrical were actually cardiomyopathies. This was evident only after the use of advanced imaging, molecular autopsy, or family screening.<sup>13,30</sup> These results are in line with previous epidemiological data which indicated that "idiopathic" ventricular fibrillation is frequently a manifestation of an initial or partial stage of a structural or genetically inherited problem, rather than a purely electrical abnormality. The above studies point out the constantly changing and interactive heart muscle-electrical activity relationship. Discerning this cardiac electrical-structural interplay is key in practice because it paves the way for comprehensive phenotyping that is aided through imaging, electrophysiological testing, and genetic examination. With the help of this combined disease approach, researchers can develop a sense of the direction precision medicine might take by moving away from strict disease models towards mechanistic pathways. And those pathways, being capable of predicting arrhythmic risks more accurately, will lead to personalized ways of preventing SCD.

## Prevention & Risk Stratification of SCD

Proper prevention of SCD largely centres on estimating the risk accurately and giving the right treatment accordingly. Pharmacological treatment, implantable cardioverter defibrillators, lifestyle modification, and preventive interventions are all components of the equation besides identifying those at highest risk. The main differentiator of the methods is that they are based on the mechanism (structural, electrical, or mixed) and combine clinical, imaging and genetic data.<sup>15</sup>

### 1. Identifying High Risk Individuals

Risk stratification represents the fundamental step in the prevention of SCD. Predictors like cardiac MRI, detected myocardial fibrosis, history of myocardial infarction, ventricular hypertrophy, and inducible ventricular arrhythmias are useful for pinpointing the most vulnerable patients.<sup>11,15</sup> In hypertrophic cardiomyopathy, a composite risk score incorporating variables such as maximal wall thickness, left atrial size, history of syncope, are used to estimate the 5-year risk of SCD.<sup>14</sup> For primary electrical disorders, arrhythmic risk is based on clinical history (syncope or aborted cardiac arrest), electrocardiographic findings, and genotype phenotype correlations.<sup>5,6</sup>

### 2. Pharmacological Therapy

Many inherited arrhythmic conditions, such as LQT syndrome and CPVT continue to rely on beta-blockers as the first-line therapy.<sup>5</sup> Some structural heart disease patients may have fewer arrhythmic events if they use antiarrhythmic drugs like amiodarone when ICD therapy is contraindicated or they have to wait for it.<sup>1</sup> Drug therapy is typically accompanied by risk factor control, such as the use of drugs for heart failure, adjustment of electrolyte levels, and treatment of ischemia.<sup>9</sup>

### 3. Cardiovascular aids

Implantable cardioverter-defibrillators (ICDs) work as the best treatment option for preventing SCD in people at high risk, whether it is for the first time or a repeat event. Patients who have a weak left ventricle, hypertrophic cardiomyopathy, and individuals with malignant channelopathies are the ones who will most likely benefit from ICD implantation.<sup>1,10</sup> ICD treatment physically stops ventricular arrhythmias that would be lethal, while appropriate patient selection through risk stratification helps reduce the risk and related complications.

### 4. Lifestyle and Preventive Strategies

Lifestyle changes are an essential part of SCD prevention. As example, in cases of ARVC and CPVT, one of the measures to reduce arrhythmias is cutting down on physical activity.<sup>16</sup> On the other hand, raising awareness of symptoms and risks, drug avoidance of those that significantly prolong the QT-interval, frequent checks of electrolytes and

education of patients are measures that lead to better outcomes.<sup>15,5</sup> Moreover, through the identification and genetic counselling of families with inherited arrhythmias or cardiomyopathies, one of the ways to early detection and proper management of SCDs..

### 5. Molecular Diagnostics

Recent advances in molecular diagnostics have significantly transformed the identification and management of peoples at risk for SCD. The use of next-generation sequencing (NGS) gene panels targeting cardiomyopathy- and channelopathy-associated genes enables the detection of pathogenic variants in both symptomatic and asymptomatic individuals.<sup>31</sup> Molecular autopsy has been a great tool for forensic medicine, especially in the case of unexplained sudden deaths, which allows finding arrhythmogenic inherited disorders even in structurally normal hearts.<sup>30</sup> Combining molecular information with clinical and imaging data significantly improves individual risk stratification, helps choose the right medication, determines the necessity of implantable devices and supports family members' genetic screening (cascade screening), thus saving genetically predisposed individuals from sudden death scenarios.<sup>5,6</sup>

### Future Perspectives

The future of preventing sudden cardiac deaths (SCD) heavily depends on the combination of genomics, precision medicine, and translational research. The continuous progress in next, generation sequencing and whole, exome/genome analysis has allowed discovering new pathogenic variants in cardiomyopathies and channelopathies, thus early identification of susceptible individuals and preventive measures in families.<sup>30,31</sup> Moreover, using genetic information along with state-of-the-art imaging, electrocardiographic data, and clinical biomarkers will probably raise the level of prediction of risk models significantly by going beyond traditional methods like left ventricular ejection fraction or QT interval. This will enable customized risk assessment and more effective treatment.<sup>14,15</sup> Also, newly developed machine learning and AI methods improve the ability to predict outcomes by utilizing multi, modal data sets, including structural, electrical, and molecular features, and unveiling the hidden substrates that could be the cause of sudden arrhythmias.<sup>17</sup> Besides, translational research unravels the structural electrical continuum molecular mechanisms, thus explaining how slight changes in the heart muscle, defective ion channels, and genetic variations can suddenly cause a cardiac arrest even in individuals who seem to be at very low risk.<sup>5,6</sup> These developments are indicative of a future in which SCD prevention strategies will be proactive, finely directed, and multi-disciplinary. Besides incorporating molecular diagnostics, personalized pharmacologic therapy, lifestyle modification, and device-based interventions, they aim to significantly reduce the global incidence of sudden

death. To make these technological advances change patient survival for the better, it will be essential that basic science, clinical research, and population-based studies evolve in synergy continuously.

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**Orcid ID:**Shrikant Verma - <https://orcid.org/0000-0002-8356-8448>Sushma Verma - <https://orcid.org/0000-0001-6705-161X>Bashir Ahmad Mir - <https://orcid.org/009-0004-6773-4241>Tabrez Faruqui - <https://orcid.org/0000-002-2894-3014>Mohammad Abbas - <https://orcid.org/0000-0002-9810-8313>Farzana Mahdi - <https://orcid.org/0000-0002-2188-2992>