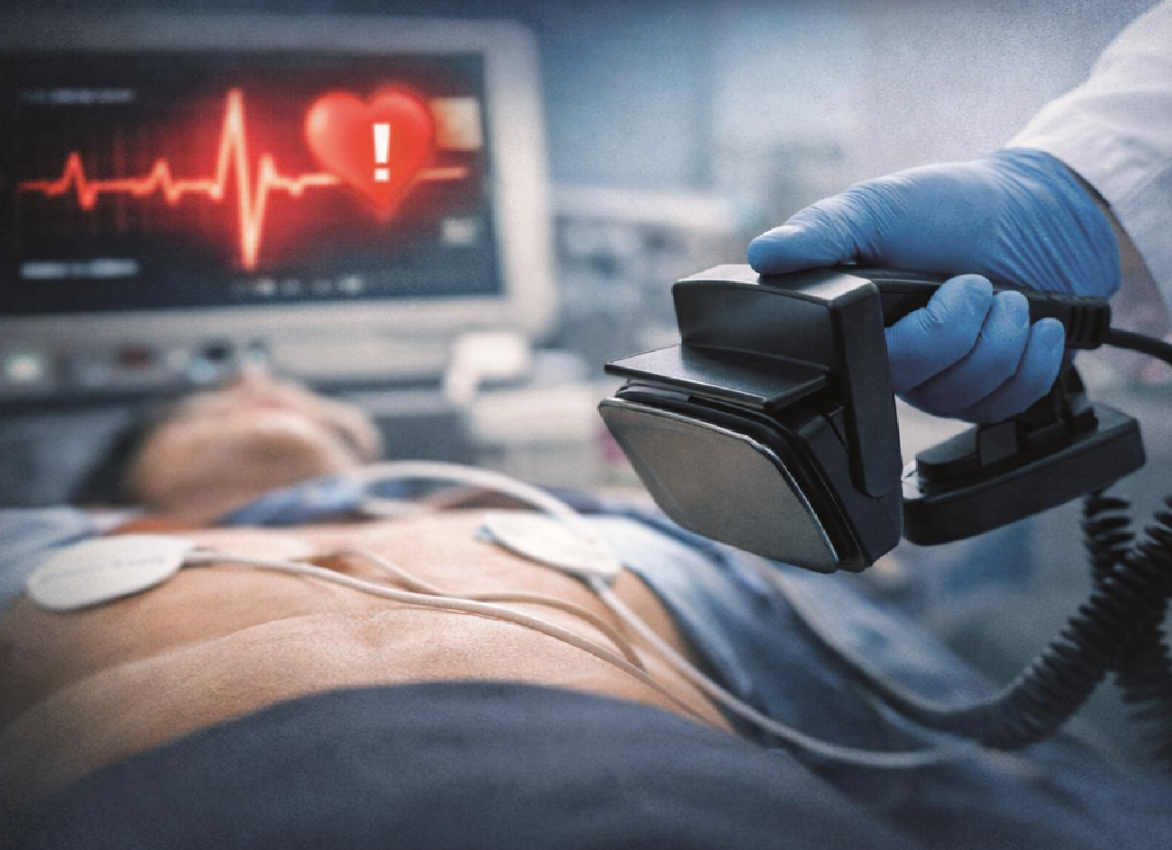
SUDDEN CARDIAC DEATH

FROM PATHOPHYSIOLOGY TO CLINICAL MANAGEMENT



Editor; Prof. Dr. Ataç ÇELİK

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Sudden Cardiac Death: From Pathophysiology to Clinical Management

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Önsöz

“Ani kardiyak ölüm, modern kardiyolojinin en çarpıcı, en sarsıcı ve hâlâ pek çok yönüyle aydınlatılmayı bekleyen klinik olgularından biridir. Bir yandan bilimsel olarak önlenebilir risklerin, patofizyolojik mekanizmaların ve erken tanının sınırlarını zorlayan bu tablo; diğer yandan insan hayatının kırılganlığını, zamanın geri döndürülemezliğini ve hekimliğin insani yönünü bizlere her seferinde yeniden hatırlatmaktadır. Bu kitap, ani kardiyak ölümü yalnızca istatistikler, kılavuzlar ve klinik algoritmalar çerçevesinde ele almak amacıyla değil; aynı zamanda bu kavramın ardında kalan sessiz boşluğu, yarım kalan cümleleri ve dokunulan hayatları unutmamak için kaleme alınmıştır. Bu nedenle eserimizi, değerli meslektaşımız Ahmet Şimşek’in aziz hatırasına ithaf ediyoruz. Bilimsel üretkenliği, mesleki titizliği ve insani duruşuyla çevresine ilham veren Ahmet Şimşek, ironik bir biçimde üzerinde çalıştığımız bu alanın tam merkezinde, ani kardiyak ölüm nedeniyle aramızdan ayrılmıştır. Onun kaybı, bu konunun yalnızca akademik bir başlık olmadığını; bizlerin, ailelerimizin ve hastalarımızın hayatına doğrudan dokunan bir gerçeklik olduğunu derin bir şekilde hissettirmiştir. Bu kitap, başta kıymetli eşi Zeynep Şimşek olmak üzere, sevgili kızları Şeyma ve Asel Şimşek’e, duyulan saygının, paylaşılan acının ve hiç eksilmeyecek vefanın mütevazı bir ifadesi olarak armağan edilmiştir. Bilimsel bilgi kalıcı olabilir; ancak insanın bıraktığı iz, çoğu zaman bilgiden daha derin ve daha uzun ömürlüdür. Ahmet Şimşek’in mesleki duruşunun ve insani değerlerinin, bu çalışmanın her satırında sessiz bir rehber olarak varlığını sürdürmesini diliyoruz. Onu saygı, özlem ve minnetle anıyoruz."

Prof. Dr. Ataç ÇELİK ve çalışma arkadaşları

Preface

“Sudden cardiac death is one of the most striking and unsettling clinical phenomena in modern cardiology, and one that still awaits deeper understanding in many of its aspects. On the one hand, it challenges the limits of science through preventable risk factors, complex pathophysiological mechanisms, and the pursuit of early diagnosis. On the other hand, it reminds us—again and again—of the fragility of human life, the irreversibility of time, and the profoundly human dimension of medical practice. This book was written not only to address sudden cardiac death through statistics, clinical guidelines, and diagnostic or therapeutic algorithms, but also to acknowledge the silent void it leaves behind—the unfinished sentences and the lives it touches. For this reason, we dedicate this work to the cherished memory of our esteemed colleague, Ahmet Şimşek. With his scientific productivity, professional rigor, and exemplary human character, Ahmet Şimşek inspired everyone around him. In a tragic irony, he passed away due to sudden cardiac death—the very condition that lies at the center of the subject we study in this book. His loss reminded us, in the most profound way, that this topic is not merely an academic subject, but a reality that directly touches the lives of ourselves, our families, and our patients. This book is therefore offered as a humble expression of respect, shared grief, and enduring remembrance to his beloved wife Zeynep Şimşek and their dear daughters Şeyma and Asel Şimşek. Scientific knowledge may endure, but the legacy a person leaves behind often runs deeper and lasts longer than knowledge itself. We hope that the professional integrity and human values that defined Ahmet Şimşek will continue to serve as a quiet guide throughout every page of this work. We remember him with respect, longing, and gratitude."

Prof. Dr. Ataç ÇELİK and his colleagues.

SUDDEN CARDIAC DEATH: DEFINITION, EPIDEMIOLOGY, AND RISK FACTORS

KAYIHAN KARAMAN[1]

Sudden Cardiac Death and Sudden Cardiac Arrest: Definitions, Conceptual Distinction, and Clinical Revelance

Sudden cardiac death (SCD) represents one of the most dramatic and clinically challenging manifestations of cardiovascular disease, accounting for a substantial proportion of global mortality. Despite remarkable advances in cardiovascular prevention, diagnostic imaging, electrophysiology, and acute care, SCD continues to strike unexpectedly — frequently in individuals without previously recognized high-risk conditions, and often without preceding warning symptoms (Myerburg & Castellanos, 2008). The unpredictable nature of this entity underscores the critical importance of precise definitions, a rigorous conceptual framework, and a thorough understanding of its pathophysiological and clinical implications. Without standardized terminology, epidemiological surveillance, risk stratification research, and preventive interventions lose their scientific foundation.

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Definitions and Temporal Criteria

Sudden cardiac death is traditionally defined as a natural, unexpected death of presumed cardiac origin that occurs within a short time period — generally within one hour of symptom onset when the event is witnessed, or within 24 hours of the individual being last seen alive and in a stable condition when the event is unwitnessed (Priori, et al., 2015: 2793–2867). This temporal criterion is critical, as it distinguishes SCD from deaths resulting from progressive heart failure, end-stage chronic illness, or non-cardiovascular causes. The World Health Organization (WHO) and major cardiology societies, including the European Society of Cardiology (ESC) and the American Heart Association (AHA), have endorsed broadly similar definitions, though minor variations in the time window exist across guidelines (Al-Khatib, et al., 2018: e210–e271).

The defining feature of SCD is not merely the suddenness of death, but the presumed underlying cardiac mechanism. In the majority of cases, this mechanism is a malignant ventricular arrhythmia — most commonly ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) — arising from a structurally diseased or electrically vulnerable myocardium (Bayes de Luna, Coumel, & Leclercq, 1989: 151–159). Less frequently, bradyarrhythmias, complete heart block, or mechanical causes such as aortic dissection or pulmonary embolism may be responsible; however, by convention, the latter are often excluded from the strict definition of SCD.

Sudden cardiac arrest (SCA), by contrast, refers to the abrupt cessation of effective cardiac mechanical activity resulting in hemodynamic collapse, loss of consciousness, and absence of a palpable pulse. Critically, SCA is a potentially reversible clinical event, provided that prompt and effective resuscitative measures —

including cardiopulmonary resuscitation (CPR) and defibrillation — are initiated in a timely manner (Hasselqvist-Ax, et al., 2015: 2307–2315). The concept of reversibility is fundamental: SCD represents the fatal outcome of an SCA that is either not treated, treated too late, or refractory to all resuscitation efforts.

The relationship between these two entities can be conceptualized as follows: every SCD is preceded by an SCA, but not every SCA results in SCD. The outcome — survival or death — is determined largely by factors external to the cardiac event itself, including the availability of bystanders trained in CPR, the presence of automated external defibrillators (AEDs), and the response time of emergency medical services (EMS) (Rea, et al., 2004: 17–24).

Pathophysiological Basis of Sudden Cardiac Arrest

In the vast majority of cases, SCA is precipitated by abrupt electrical instability of the myocardium. Ventricular tachycardia degenerating into ventricular fibrillation remains the most common initial rhythm documented in witnessed out-of-hospital cardiac arrests, particularly during the early phases (Weisfeldt & Becker, 2002: 3035–3038). As time elapses without treatment, the amplitude and frequency of the fibrillatory waves diminish, eventually giving way to asystole — a terminal rhythm associated with far worse resuscitation outcomes. Less frequently, primary bradyarrhythmias, high-degree atrioventricular block, or pulseless electrical activity (PEA) are observed as the initial rhythm, particularly in the context of advanced structural heart disease, hypoxia, or prolonged arrest.

The electrical derangements leading to SCA typically arise from a pathological interaction between a vulnerable myocardial substrate and a transient triggering factor — a conceptual model sometimes referred to as the "substrate–trigger" paradigm (Huikuri, Castellanos, & Myerburg, 2001: 1473–1482). Structural abnormalities such as myocardial fibrosis secondary to prior

infarction, ischemic or non-ischemic scar tissue, pressure-overload hypertrophy, or fibrofatty ventricular infiltration can profoundly disrupt normal electrical conduction, prolong local refractory periods unevenly, and create the anatomical basis for re-entrant ventricular circuits. In parallel, acute or transient triggers — including myocardial ischemia, heightened sympathetic tone, electrolyte disturbances (hypokalemia, hypomagnesemia), proarrhythmic drug effects, or intense physical or emotional stress — may initiate malignant arrhythmias in susceptible individuals (de Bakker, et al., 1988: 589–606).

Importantly, SCA may also occur in the complete absence of overt structural heart disease. In such cases, inherited primary electrical diseases — often referred to as channelopathies — play a dominant pathological role (Schwartz, et al., 2009: 1761–1767). Conditions such as long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), and short QT syndrome involve mutations in genes encoding cardiac ion channels or their regulatory proteins, resulting in abnormal depolarization or repolarization kinetics. These disorders can render the myocardium susceptible to life-threatening arrhythmias even in the absence of any macroscopic or histological abnormality (Antzelevitch, et al., 2005: 659–670). This subset of SCA reinforces a fundamental principle: a structurally normal heart on imaging does not equate to electrical stability or arrhythmic safety.

Clinical and Epidemiological Implications of the Distinction

The conceptual distinction between SCA and SCD carries profound clinical and epidemiological implications. From a public health perspective, the incidence of SCA is inherently higher than that of SCD, since a meaningful proportion of cardiac arrests are successfully resuscitated — particularly in settings with high-performance emergency response systems (Hasselqvist-Ax, et al.,

2015: 2307–2315). Studies that fail to rigorously differentiate between these entities may consequently overestimate cardiac mortality rates or, conversely, underestimate the effectiveness of community-based emergency interventions.

From a clinical standpoint, recognizing SCA as a potentially survivable event reorients the clinical approach toward early recognition, rapid intervention, and chain-of-survival optimization. Community-based strategies — such as systematic lay rescuer CPR training, strategic placement of public-access AEDs, and dispatcher-assisted CPR protocols — are aimed specifically at interrupting the progression from SCA to SCD in the critical minutes before professional medical help arrives (Rea, et al., 2004: 17–24). The concept of the "chain of survival," originally articulated by the AHA and subsequently adopted globally, reflects this time-sensitive continuum: early recognition and activation, early CPR, early defibrillation, advanced life support, and post-arrest care.

Conversely, strategies directed at SCD prevention necessarily operate on a longer timescale and emphasize identification of high-risk individuals before the arrest occurs. These strategies encompass long-term risk stratification using imaging, electrophysiological testing, biomarkers, and genetic analysis; optimization of pharmacological management for underlying cardiovascular conditions; and the implantation of ICDs in patients meeting established risk criteria (Priori, et al., 2015: 2793–2867).

In the landscape of clinical research, precise and consistent terminology is indispensable for cross-study comparability. Randomized controlled trials assessing ICD efficacy — such as MADIT-II and SCD-HeFT — prospectively defined SCD as an adjudicated endpoint, distinct from non-sudden cardiac death or non-cardiac mortality (Bardy, et al., 2005: 225–237). By contrast, large registry-based studies of out-of-hospital cardiac arrest — such as the

Resuscitation Outcomes Consortium (ROC) trials — focus primarily on SCA incidence and neurologically intact survival to hospital discharge (Rea, et al., 2004: 17–24). The conflation of these endpoints in meta-analyses or systematic reviews can introduce substantial heterogeneity and limit the validity of pooled conclusions.

Relevance to Special Populations

The distinction between SCA and SCD carries particular relevance in certain high-profile populations. In young individuals and competitive athletes, SCA often represents the first and only clinical manifestation of a previously silent cardiac disorder — whether an inherited cardiomyopathy, a channelopathy, or a congenital coronary anomaly (Harmon, et al., 2015: 10–19). When prompt defibrillation is available — as may occur in organized sports environments equipped with AEDs — survival is achievable, and the incident is correctly classified as an SCA rather than SCD. This distinction alters the epidemiological profile without reducing the underlying prevalence of the predisposing cardiac condition, and it has important implications for the design of mandatory pre-participation screening programs (Corrado, et al., 2006: 1593–1601).

In patients with known advanced cardiovascular disease, particularly those carrying ICDs, recurrent SCA episodes may be averted by appropriate device therapy without causing death (Moss, et al., 2002: 877–883). In these individuals, SCA becomes a recurrent, measurable marker of arrhythmic vulnerability — a clinical endpoint that can be monitored, characterized, and targeted therapeutically — rather than an irreversible terminal event.

Summary

Sudden cardiac death and sudden cardiac arrest are intimately related yet conceptually distinct entities that must not be conflated.

SCA represents an abrupt, potentially reversible electrical catastrophe of the myocardium, while SCD denotes its fatal outcome when effective resuscitation fails or is unavailable. The substrate–trigger interaction model provides the mechanistic basis for understanding both entities. Precise differentiation between SCA and SCD is essential for accurate epidemiological surveillance, rigorous clinical research, and the design of targeted prevention strategies.

Global and Regional Epidemiology of Sudden Cardiac Death

Sudden cardiac death constitutes one of the most formidable challenges in contemporary cardiovascular medicine and public health. Despite substantial advances in preventive cardiology, interventional cardiology, pharmacotherapy, and resuscitation science, the global burden of SCD remains enormous (Chugh, et al., 2014: 837–847). Accurate epidemiological assessment of SCD is, however, inherently complex, owing to heterogeneity in case definitions, variability in death certification practices, differences in autopsy rates, and the fundamental difficulty of distinguishing cardiac from non-cardiac sudden death in out-of-hospital settings where post-mortem investigation is incomplete (Kong, et al., 2011: 794–801).

Global Incidence and Burden

In the general adult population, the estimated annual incidence of SCD ranges between 50 and 100 cases per 100,000 persons, making it responsible for approximately 15–20% of all deaths in industrialized nations (Myerburg & Castellanos, 2008). On a global scale, SCD is estimated to cause between 4 and 5 million deaths annually, positioning it as one of the leading single causes of mortality worldwide — surpassing many cancers and infectious diseases in absolute terms (Chugh, et al., 2014: 837–847). However, these figures must be interpreted cautiously, as they are heavily

influenced by the quality and completeness of underlying data sources.

High-income countries generally contribute disproportionately to reported absolute case numbers, in part due to older population structures with a high prevalence of ischemic heart disease, and in part due to more robust death registration and emergency medical service documentation (Kong, et al., 2011: 794–801). Conversely, low- and middle-income countries — which collectively bear a large and growing share of the global cardiovascular disease burden — are substantially underrepresented in SCD epidemiology literature. Limited access to emergency medical infrastructure, low autopsy rates, and incomplete death certification systems in these regions almost certainly result in significant underreporting (Kong, et al., 2011: 794–801).

Regional Variations and Contributing Factors

Marked regional differences in SCD incidence reflect a complex interplay of cardiovascular risk profiles, healthcare system capacity, socioeconomic determinants, genetic background, and lifestyle factors. In Western Europe and North America, coronary artery disease remains the dominant substrate for SCD in adults over 35–40 years of age (Zipes & Wellens, 1998: 2334–2351). Paradoxically, despite significant reductions in acute myocardial infarction incidence attributable to improved primary prevention and aggressive interventional strategies, the corresponding decline in SCD has been comparatively modest. This dissociation suggests that the chronic sequelae of ischemic heart disease — myocardial fibrosis, left ventricular remodeling, and recurrent electrical instability — continue to drive a substantial arrhythmic burden independent of acute ischemic events (Stecker, et al., 2006: 1161–1166).

In East and Southeast Asian populations, the overall incidence of SCD appears lower relative to Western cohorts, potentially reflecting differences in coronary artery disease prevalence, body habitus, and dietary patterns (Noseworthy & Newton-Cheh, 2008: 1854–1863). Nevertheless, certain primary arrhythmia syndromes — most notably Brugada syndrome, which is more prevalent in populations of Southeast Asian descent — represent a relatively higher proportion of SCD cases in these regions compared with ischemic etiologies (Noseworthy & Newton-Cheh, 2008: 1854–1863). In South Asia and sub-Saharan Africa, the epidemiological landscape is shaped by high rates of untreated hypertension, rheumatic heart disease, and peripartum cardiomyopathy, making non-ischemic mechanisms of SCD proportionally more prominent.

Urban–rural disparities add another dimension of complexity. Survival from sudden cardiac arrest — and consequently the rate at which SCA events are recorded as SCD — is strongly dependent on emergency response infrastructure (Hasselqvist-Ax, et al., 2015: 2307–2315). Metropolitan areas with short EMS response times, high bystander CPR rates, and widespread AED deployment demonstrate substantially higher cardiac arrest survival rates than rural regions. As a result, two communities with identical SCA incidence rates may report markedly different SCD mortality figures, purely on the basis of resuscitation system performance.

Temporal Trends

Over recent decades, temporal trends in SCD incidence have demonstrated modest declines in several high-income countries, driven primarily by improved management of acute myocardial infarction, increased use of evidence-based secondary prevention pharmacotherapy (statins, beta-blockers, renin-angiotensin system

inhibitors, antiplatelets), and greater rates of coronary revascularization (Chugh, et al., 2008: 213–228). The Oregon Sudden Unexpected Death Study (SUDS), one of the largest and most methodologically rigorous community-based SCD registries, documented a gradual decline in annual SCD incidence over a nearly two-decade observation period (Chugh, et al., 2008: 213–228). Similar trends have been reported in Scandinavia, the United Kingdom, and parts of continental Europe.

However, these favorable trends have been partially or fully offset by counteracting forces. Population aging, increasing prevalence of diabetes mellitus, obesity, and the metabolic syndrome, as well as the growing burden of heart failure — itself a major substrate for arrhythmic death — have collectively sustained or even increased the absolute number of SCD events in many populations (Solomon, et al., 2005: 2581–2588). Most concerning, community-based studies consistently demonstrate that up to 50% of SCD cases occur as the first and only manifestation of underlying cardiac disease, meaning that these events fall entirely outside the reach of current secondary prevention frameworks and risk stratification tools (Chugh, et al., 2008: 213–228).

Epidemiology Across Age Groups

Age is among the most powerful and consistent determinants of SCD incidence. In older adults — particularly beyond the sixth and seventh decades of life — SCD is predominantly attributable to ischemic heart disease and its sequelae, including post-infarction ventricular scarring, ischemic cardiomyopathy, and systolic heart failure (Myerburg & Castellanos, 2008). Incidence increases exponentially with advancing age in this population, reflecting the cumulative accrual of atherosclerotic burden, myocardial damage, and electrophysiological remodeling.

In younger populations, including children, adolescents, and adults below age 35–40 years, SCD is rare in absolute terms but carries profound societal significance. Estimated incidence rates in this age group range from 0.5 to 2 per 100,000 person-years, varying by definition and ascertainment methodology (Winkel, et al., 2011: 983–990). Unlike older adults, SCD in the young is predominantly caused by inherited cardiomyopathies (particularly hypertrophic cardiomyopathy and arrhythmogenic cardiomyopathy), primary electrical syndromes (long QT syndrome, Brugada syndrome, CPVT), congenital coronary artery anomalies, and myocarditis. In a significant proportion of young SCD victims, autopsy findings reveal a structurally normal heart, suggesting an undetected channelopathy or missed toxicological diagnosis (Winkel, et al., 2011: 983–990).

Sex Differences in Epidemiology

Sex-related differences in SCD epidemiology are robustly and consistently observed across all studied populations. Men experience SCD at rates approximately two- to threefold higher than women across all adult age groups (Albert, et al., 2003: 2096–2101). This disparity is at least partially explained by the earlier onset and greater cumulative burden of coronary artery disease in men, sex-based differences in cardiac electrophysiology, and the cardioprotective effects of estrogen prior to menopause in women.

Nevertheless, SCD in women is increasingly recognized as a clinically distinct entity that has been historically under-investigated. Women who experience SCD are more likely than men to die in the absence of significant obstructive epicardial coronary artery disease, with microvascular dysfunction, non-ischemic cardiomyopathy, and channelopathies playing proportionally larger roles (Albert, et al., 2003: 2096–2101). Additionally, inherent sex differences in cardiac ion channel expression and repolarization — reflected in the longer

corrected QT interval physiologically present in women — confer distinct patterns of arrhythmic susceptibility. These biological differences, combined with the historical underrepresentation of women in major cardiovascular trials, have resulted in risk prediction models that may perform less accurately in female patients (Albert, et al., 2003: 2096–2101).

Methodological Challenges in Epidemiological Assessment

Accurate and reliable estimation of SCD incidence is hampered by a constellation of methodological challenges (Chugh, et al., 2014: 837–847). First, inconsistent application of temporal and definitional criteria across studies makes direct comparisons problematic. Second, reliance on death certificates — which systematically undercode sudden cardiac death and misclassify a proportion of cases as non-specific "cardiac arrest" or "unspecified cardiovascular disease" — introduces systematic underestimation. Third, the low and variable rates of systematic autopsy performance in out-of-hospital deaths limit the ability to confirm or refute cardiac causation, particularly in older individuals with multiple comorbidities. Fourth, improvements in resuscitation success rates over time blur the boundary between SCA and SCD in longitudinal incidence data. Finally, advances in ICD therapy and improved management of high-risk populations may reduce SCD incidence in treated subgroups while leaving the broader population burden unchanged.

Summary

Sudden cardiac death remains one of the leading causes of mortality worldwide, with significant geographic, demographic, and temporal variation. The absolute incidence is highest in older populations with established ischemic heart disease, but a critical and growing proportion of cases occur in individuals without prior cardiac diagnosis — underscoring the profound limitations of

current risk stratification paradigms. Addressing the epidemiological burden of SCD requires not only improvements in high-risk patient management but also population-level preventive strategies, enhanced death certification and autopsy practices, and expansion of epidemiological research to underrepresented geographic regions.

Age, Sex, and Demographic Differences in Sudden Cardiac Death

Sudden cardiac death is a heterogeneous phenomenon that does not distribute uniformly across populations. Its incidence, underlying etiology, arrhythmic mechanisms, and clinical context vary substantially according to age, biological sex, ethnicity, and a range of broader sociodemographic characteristics (Albert, et al., 2003: 2096–2101). These differences are not merely statistical curiosities — they reflect fundamental biological, genetic, and socioeconomic determinants that must be explicitly considered in the design of risk stratification tools, screening programs, and preventive interventions.

Age-Related Differences

Age is the single most powerful and consistent demographic determinant of SCD risk. The incidence increases exponentially with advancing age, closely mirroring the rising prevalence of structural heart disease, coronary artery disease, and left ventricular dysfunction (Zipes & Wellens, 1998: 2334–2351). In adults beyond the sixth decade of life, ischemic heart disease is the dominant etiological substrate, with acute plaque rupture, residual post-infarction scar tissue, and left ventricular systolic dysfunction serving as the principal arrhythmogenic substrates. The combination of myocardial fibrosis, impaired impulse conduction, and neurohumoral activation in this population creates a milieu highly permissive to re-entrant ventricular arrhythmias (Huikuri, Castellanos, & Myerburg, 2001: 1473–1482).

In stark contrast, SCD in the young occupies a fundamentally different etiological landscape. In children, adolescents, and young adults — generally defined as those below 35–40 years of age — SCD frequently occurs in the absence of atherosclerotic disease (Winkel, et al., 2011: 983–990). Inherited cardiomyopathies, particularly hypertrophic cardiomyopathy (HCM) and arrhythmogenic cardiomyopathy (ACM, formerly ARVC), account for a significant proportion of cases in Western populations. Congenital coronary artery anomalies — most notably anomalous origin of the left coronary artery from the right sinus of Valsalva — are an important and potentially correctable cause of exercise-related SCD in young athletes (Corrado, et al., 2006: 1593–1601). Myocarditis, whether viral or autoimmune in origin, may create a transient arrhythmogenic substrate even in previously healthy myocardium. Primary electrical disorders, including long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia, are particularly treacherous because they may remain entirely silent on standard resting evaluation until their first arrhythmic event (Schwartz, et al., 2009: 1761–1767).

A defining and clinically alarming characteristic of SCD in young individuals is that it frequently represents the first clinical manifestation of the underlying cardiac disorder — the sentinel event of a previously unsuspected disease (Winkel, et al., 2011: 983–990). This observation fundamentally challenges symptom-based or reactive approaches to risk identification in this population and reinforces the argument for structured pre-symptomatic screening.

Sex-Based Differences

Marked and consistent sex-based differences in SCD incidence have been documented across all studied populations and regions. Men experience SCD at rates approximately two- to threefold higher than women across all adult age groups, a disparity

that emerges in early adulthood and persists throughout the lifespan (Albert, et al., 2003: 2096–2101). This excess risk in men is partly explained by the earlier onset, higher prevalence, and greater severity of coronary artery disease — itself partially attributable to higher rates of traditional risk factors such as smoking and dyslipidemia, sex differences in autonomic nervous system tone, and the differential cardioprotective effects of gonadal hormones.

Despite their lower overall SCD incidence, women present with clinically and pathophysiologically distinct characteristics. Women who suffer SCD are more likely to do so in the absence of significant obstructive epicardial coronary artery disease; non-obstructive coronary disease, microvascular dysfunction, stress-induced (Takotsubo) cardiomyopathy, and autoimmune myocarditis contribute disproportionately to the arrhythmic substrate in women (Albert, et al., 2003: 2096–2101). Intrinsic biological differences — including longer corrected QT intervals at baseline related to sex differences in cardiac ion channel expression, particularly hERG (KCNH2) channel density — render women more susceptible to drug-induced QT prolongation and torsades de pointes (Darpo, et al., 2014: 522–531).

A critical and underappreciated issue is that women have been systematically underrepresented in landmark cardiovascular clinical trials and SCD risk stratification studies. The majority of evidence underpinning current ICD implantation criteria — derived from trials such as MADIT-II, SCD-HeFT, and MUSTT — enrolled predominantly male populations (Buxton, et al., 1999: 1882–1890). As a consequence, risk prediction models validated in male cohorts may have suboptimal performance when applied to women, potentially leading to both under-treatment of truly high-risk women and misclassification of lower-risk female patients. This knowledge gap represents a major equity challenge in SCD prevention.

Ethnic and Racial Differences

Ethnic and racial disparities in SCD incidence and outcomes are consistently documented, particularly in the United States where data are most granular. Individuals of African descent experience higher rates of SCD compared with White populations, and this excess risk persists after adjustment for traditional cardiovascular risk factors and socioeconomic covariates. The higher SCD burden in this population reflects a substantially elevated prevalence of hypertension, greater rates of hypertensive left ventricular hypertrophy, higher incidence of heart failure with both preserved and reduced ejection fraction, and marked disparities in access to preventive cardiology care, cardiovascular medications, and ICD therapy (Havranek, et al., 2015: 873–898).

Genetic factors may further contribute to ethnic differences in SCD susceptibility beyond classical risk factor distribution. Certain loss-of-function variants in SCN5A — the gene encoding the cardiac sodium channel Nav1.5 — appear more prevalent in populations of West African ancestry and have been proposed as contributors to increased ventricular arrhythmia susceptibility in this group (Plant, et al., 2006: 430–435). However, disentangling genetic from environmental and socioeconomic factors in explaining racial disparities in SCD remains methodologically challenging.

Socioeconomic and Environmental Determinants

Socioeconomic status exerts a powerful, multidimensional influence on SCD risk and outcomes. Lower socioeconomic position is associated with higher cardiovascular risk factor burden, reduced utilization of preventive medications and screenings, higher rates of undetected or undertreated cardiac disease, and residential segregation in neighborhoods with limited healthcare infrastructure. The consequences for SCD outcomes are compounded by neighborhood-level factors: areas with lower median income

demonstrate systematically lower rates of bystander CPR initiation, lower AED density, and longer EMS response times — all of which directly increase the probability that an SCA progresses to SCD (Marijon, et al., 2015: 1546–1554).

Urban–rural disparities in SCD outcomes are among the most robust and clinically important findings in cardiovascular epidemiology. Rural populations face extended EMS response times, often exceeding the critical therapeutic window for defibrillation, lower bystander CPR rates attributable to less widespread public training programs, and reduced access to tertiary cardiac care and electrophysiology centers. These systemic disadvantages translate into higher case fatality rates following cardiac arrest and higher population-level SCD mortality, independent of underlying cardiac disease prevalence (Marijon, et al., 2015: 1546–1554).

Demographic Differences in Special Populations

Patients with chronic kidney disease (CKD) represent a high-risk demographic subgroup in whom SCD risk is markedly elevated but incompletely captured by conventional risk scores calibrated to the general population. Mechanisms include accelerated cardiovascular calcification, chronic electrolyte dysregulation (hyperkalemia, hypomagnesemia), autonomic dysfunction, and a high prevalence of left ventricular hypertrophy and diastolic dysfunction (Genovesi, et al., 2009: 2529–2536). Similarly, patients with type 2 diabetes mellitus face a disproportionate SCD risk through mechanisms including autonomic neuropathy, ischemic preconditioning impairment, and proarrhythmic QT interval prolongation (Jouven, et al., 2005: 2142–2147). Patients with chronic systemic inflammatory conditions — including rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease — demonstrate excess cardiovascular mortality including

SCD, reflecting both accelerated atherosclerosis and direct myocardial inflammation (Lazou, et al., 2020: 5357–5374).

Summary

Sudden cardiac death is a demographically heterogeneous entity shaped by the interplay of biological, genetic, and socioeconomic forces. Older age and male sex are associated with higher overall incidence and ischemia-dominated mechanisms, while younger individuals and women often experience SCD through distinct and incompletely characterized pathways that challenge established risk stratification paradigms. Recognition of these multidimensional differences is fundamental to the development of equitable, evidence-based, and population-tailored prevention strategies.

Genetic Predisposition and Family History of Sudden Cardiac Death

Genetic factors occupy a pivotal and increasingly well-defined role in the pathogenesis of sudden cardiac death, particularly in younger individuals and in those without apparent structural heart disease on conventional imaging (Ackerman, et al., 2011: 1308–1339). The molecular revolution of the past three decades has revealed that inherited abnormalities affecting myocardial architecture, intercellular coupling, or the biophysical properties of cardiac ion channels can profoundly increase susceptibility to fatal ventricular arrhythmias. As a consequence, genetic evaluation has transitioned from a purely academic exercise to a clinically actionable tool with direct implications for patient management and family screening (Semsarian, et al., 2015: 1249–1254).

Inherited Cardiomyopathies

Genetically mediated cardiomyopathies collectively represent the leading cause of SCD in individuals below 35 years of

age in Western populations. Hypertrophic cardiomyopathy (HCM), caused by mutations in genes encoding sarcomeric proteins — most commonly MYH7 (beta-myosin heavy chain) and MYBPC3 (myosin-binding protein C) — is the prototype of this group (Maron, et al., 2000: 858–864). Its pathological hallmarks include disordered myocyte architecture (myocyte disarray), interstitial and replacement fibrosis, and abnormal intramural coronary arteries. These structural abnormalities create a complex electrophysiological substrate with heterogeneous conduction velocities and refractory periods, facilitating both triggered activity and macro-re-entrant circuits (Maron, Maron, & Semsarian, 2012: 705–715).

Arrhythmogenic cardiomyopathy (ACM) is caused by mutations primarily in desmosomal proteins — including PKP2 (plakophilin-2), DSP (desmoplakin), DSG2 (desmoglein-2), and DSC2 (desmocollin-2) — which are structural components critical for maintaining cardiomyocyte adhesion and mechanical integrity. Loss of desmosomal function triggers a cascade of cardiomyocyte apoptosis and replacement by fibrofatty tissue, predominantly in the right ventricular free wall but with recognized left ventricular and biventricular variants. The resulting fibrofatty infiltration creates slow, fragmented electrical conduction zones that are classically associated with exercise-triggered ventricular tachycardia and SCD, particularly in young athletes (Maron, et al., 2000: 858–864).

Dilated cardiomyopathy (DCM) has a familial etiology in approximately 25–30% of cases, with pathogenic variants identified in over 50 genes, the most common being TTN (titin), LMNA (lamin A/C), SCN5A, RBM20, and PLN (phospholamban). Lamin A/C mutations deserve specific emphasis, as they are associated with a particularly malignant arrhythmic phenotype including high-degree atrioventricular block, supraventricular and ventricular arrhythmias, and SCD — often preceding or disproportionate to the degree of systolic dysfunction. LMNA mutation carriers may qualify for

prophylactic ICD implantation at relatively preserved ejection fractions based on arrhythmic risk scoring (van Rijsingen, et al., 2012: 493–500).

Inherited Arrhythmia Syndromes (Channelopathies)

Primary electrical diseases — collectively termed channelopathies — are characterized by mutations in genes encoding cardiac ion channels or their regulatory subunits, resulting in abnormal membrane electrophysiology in the absence of macroscopic structural pathology detectable by standard imaging (Schwartz, et al., 2009: 1761–1767). These disorders are of particular clinical importance because the heart may appear entirely normal on echocardiography and cardiac MRI, yet the patient remains at risk of sudden death from malignant ventricular arrhythmias triggered by specific physiological stimuli.

Long QT syndrome (LQTS) encompasses a group of disorders characterized by delayed cardiac repolarization and susceptibility to torsades de pointes. The two most common subtypes are LQT1, caused by loss-of-function mutations in KCNQ1 (encoding the slow delayed rectifier potassium channel IKs), and LQT2, caused by loss-of-function mutations in KCNH2 (hERG, encoding the rapid delayed rectifier IKr) (Schwartz, et al., 2009: 1761–1767). LQT3 results from gain-of-function mutations in SCN5A. Each subtype has characteristic triggering conditions: LQT1 events are classically associated with exercise and swimming, LQT2 with auditory stimuli and emotional arousal, and LQT3 with rest and sleep (Moss, et al., 2007: 2481–2489).

Brugada syndrome — caused in approximately 20–25% of cases by loss-of-function mutations in SCN5A — manifests as a distinctive coved-type ST-segment elevation in the right precordial leads and carries risk of ventricular fibrillation, typically at rest or during fever (Antzelevitch, et al., 2005: 659–670). Its prevalence is

estimated at 1–5 per 10,000 in the general population, with significantly higher rates in populations of Southeast Asian ancestry, and the male-to-female ratio among symptomatic patients is approximately 8:1 (Antzelevitch, et al., 2005: 659–670). Catecholaminergic polymorphic ventricular tachycardia (CPVT) — most commonly caused by mutations in RYR2 (ryanodine receptor 2) — produces bidirectional or polymorphic VT specifically triggered by adrenergic stimulation during exercise or emotional stress, in the absence of any QT prolongation or structural abnormality (Priori, et al., 2002: 69–74). CPVT carries a particularly high mortality in untreated patients; antiadrenergic therapy with beta-blockers and, where necessary, flecainide and sympathetic denervation form the cornerstones of management.

Family History as a Risk Marker

A family history of unexplained sudden death — particularly when occurring in a first-degree relative under 40–45 years of age — constitutes one of the most potent clinical indicators of inherited arrhythmic risk. Familial aggregation of SCD may reflect a shared genetic substrate (inherited cardiomyopathy or channelopathy), shared environmental exposures, or both. Detailed and systematic pedigree construction, spanning at least three generations, is an essential component of the clinical evaluation of any patient presenting with unexplained syncope, documented VT/VF, or resuscitated cardiac arrest. When a pathogenic or likely pathogenic genetic variant is identified in a proband, cascade screening of first-degree relatives is strongly recommended by international guidelines (Semsarian, et al., 2015: 1249–1254).

Emerging Genetic Insights

Beyond rare, high-penetrance pathogenic mutations responsible for Mendelian forms of SCD risk, large-scale genome-wide association studies (GWAS) have identified numerous common

genetic variants at multiple loci that, in aggregate, modulate arrhythmic susceptibility in the general population. While individual common variants typically confer modest risk increments, polygenic risk scores — which aggregate the contributions of hundreds of variants — may identify subsets of the general population with substantially elevated background arrhythmic risk (Newton-Cheh, et al., 2009: 399–406).

Next-generation sequencing technologies — including whole exome sequencing and whole genome sequencing — have accelerated the discovery of novel arrhythmia-associated variants and have improved the genetic diagnostic yield in unexplained SCD cases referred for post-mortem molecular autopsy. In cases of sudden unexplained death (SUD) where autopsy and toxicology are unrevealing, genetic testing of stored tissue or blood can identify a causative mutation in approximately 20–30% of cases, with channelopathy-associated variants being most frequent. When a pathogenic variant is identified post-mortem, this finding has immediate implications for living relatives who can be screened and, if necessary, treated or monitored (Bagnall, et al., 2016: 2441–2452).

Summary

Genetic predisposition is a fundamental and clinically actionable determinant of SCD risk, particularly in younger populations and in the context of structurally normal hearts. Inherited cardiomyopathies and primary channelopathies represent mechanistically distinct but equally important genetic contributions to the arrhythmic death burden. A thorough family history, systematic post-mortem genetic evaluation, and cascade screening of relatives are integral components of contemporary SCD prevention.

Sudden Cardiac Death in Athletes

Sudden cardiac death in athletes represents a clinically and emotionally compelling entity that occupies a unique position within the broader landscape of SCD. Although numerically rare, the occurrence of SCA or SCD in young, apparently healthy, and physically elite individuals commands disproportionate medical and public attention (Corrado, et al., 2006: 1593–1601). It simultaneously highlights the limits of current cardiovascular screening methodologies, challenges the prevalent assumption that intensive physical fitness confers unconditional cardiac protection, and raises complex ethical and medicolegal questions around pre-participation evaluation.

Epidemiology and Risk Profile

The reported incidence of SCD in athletes varies considerably across studies, depending on the definition of "athlete," the age range and competitive level of the study population, the case ascertainment methodology (mandatory registry versus voluntary reporting versus media surveillance), and the geographic setting. Published estimates range from approximately 1 in 40,000 to 1 in 250,000 athlete-years, with the most methodologically rigorous registries reporting incidence rates at the higher end of this range when ascertainment is systematic and comprehensive (Corrado, et al., 2005: 516–524). Male athletes are disproportionately affected, accounting for approximately 70–90% of athletic SCD cases in most large series (Basso, et al., 2000: 1493–1501).

Underlying Causes

The etiological spectrum of SCD in athletes is strongly age-dependent. In younger athletes — generally defined as those under 35 years — inherited cardiomyopathies and primary electrical disorders dominate. In the United States, hypertrophic

cardiomyopathy has historically been cited as the most common cause of SCD in young athletes, accounting for approximately 30–40% of cases in autopsy-based series (Corrado, et al., 2006: 1593–1601). However, more recent prospective registry data and systematic autopsy studies from European cohorts suggest that arrhythmogenic cardiomyopathy (ACM) and idiopathic ventricular fibrillation may be more common in European populations than previously appreciated (Basso, et al., 2000: 1493–1501).

Congenital coronary artery anomalies — particularly anomalous origin of the left main or left anterior descending coronary artery from the opposite sinus of Valsalva — represent an important, potentially correctable cause of exercise-related SCD in young athletes, as the anomalous vessel may become compressed between the aorta and pulmonary artery during exercise-induced aortic root expansion. Myocarditis, whether acute or in the subclinical healing phase, represents a dynamic arrhythmogenic substrate in which inflammatory infiltrate, cardiomyocyte necrosis, and subsequent fibrosis create conditions conducive to triggered arrhythmias during physical stress (Harmon, et al., 2015: 10–19).

Commotio cordis — a non-structural, mechanically induced form of SCA resulting from a precisely timed low-energy chest wall impact during the vulnerable phase of the cardiac cycle — represents a rare but important and underappreciated cause of SCA in young athletes, particularly in contact sports and recreational activities involving projectiles. The absence of structural cardiac disease at autopsy in commotio cordis can lead to misclassification as unexplained SCA unless the clinical context is carefully evaluated (Maron, et al., 2002: 1142–1146).

In older athletes — masters athletes generally defined as those over 35 years — the dominant etiology shifts decisively toward occult or clinically unrecognized atherosclerotic coronary artery

disease, reflecting the cumulative accrual of traditional cardiovascular risk factors. Notably, physical fitness in older individuals does not immunize against atherosclerotic plaque development, even though it may reduce the risk of plaque-related events at equivalent plaque burdens (Basso, et al., 2000: 1493–1501).

Exercise as a Trigger and Cardioprotective Paradox

The relationship between physical exertion and SCA in susceptible athletes embodies what is sometimes termed the "exercise paradox": regular physical activity is one of the most effective interventions for reducing long-term cardiovascular risk and all-cause mortality at the population level, yet acute vigorous exercise transiently increases the immediate risk of cardiac arrest in individuals harboring vulnerable substrates. This paradox resolves when considered mechanistically: intense exercise activates the sympathoadrenal axis, dramatically increases heart rate and myocardial oxygen demand, elevates circulating catecholamines, and may induce coronary vasospasm or platelet aggregation. In a heart with an underlying arrhythmogenic substrate, these physiological perturbations may cross the threshold required to initiate ventricular arrhythmia (Thompson, et al., 2003: 3109–3116).

Prevention and Screening

Pre-participation cardiovascular screening programs aim to identify athletes at elevated risk of SCA/SCD before catastrophic events occur, enabling risk-stratified management — ranging from activity modification to ICD implantation. Screening strategies differ substantially between geographic regions, reflecting different regulatory frameworks, medicolegal contexts, and healthcare resource availability. In the United States, the AHA/ACC guidelines recommend a 14-element history and physical examination as the primary screening tool. By contrast, European practice — informed

significantly by the Italian Veneto experience, which demonstrated substantial reductions in athletic SCD rates following the introduction of mandatory ECG screening — has historically emphasized the incorporation of resting 12-lead ECG into pre-participation evaluation for competitive athletes (Maron, et al., 1996: 850–856).

The Seattle Criteria and their refinements have substantially improved the specificity of ECG interpretation in athletes by distinguishing physiological training-related ECG changes from pathological findings warranting further investigation (Drezner, et al., 2013: 122–124). Data from large sporting event registries consistently demonstrate that prompt bystander defibrillation — when delivered within 3–5 minutes of collapse — can achieve survival rates exceeding 70–80% in witnessed VF arrests, a survival rate dramatically higher than the population average for out-of-hospital cardiac arrest. These findings reinforce the principle that primary prevention through screening and secondary response capability through AED access are complementary rather than competing strategies.

Summary

Sudden cardiac death in athletes reflects the complex and sometimes tragic interaction between intense physical exertion and an underlying cardiac vulnerability — whether structural, electrical, or mechanical — that has eluded detection by prior clinical evaluation. Understanding its distinct epidemiology, age-dependent etiological spectrum, and the specific physiological triggers conferred by athletic competition is essential for designing screening programs, emergency response protocols, and management algorithms that appropriately balance the extraordinary cardiovascular benefits of physical activity against the rare but real risk of exercise-related sudden death.

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PATHOPHYSIOLOGICAL MECHANISMS OF ARRHYTHMIA AND SUDDEN CARDIAC DEATH

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Introduction

Sudden cardiac death (SCD) constitutes one of the most complex clinical presentations in cardiovascular medicine. It is an unexpected and natural death resulting from a sudden cessation of cardiac activity due to an electrical disturbance. The heart is a unique organ with its own intrinsic electrical conduction system, capable of converting these impulses into mechanical contractions that generate hemodynamic force. Although this flawless cycle functions efficiently for decades in most individuals, intrinsic (congenital) or acquired defects in the system can ultimately lead to the failure of mechanical pump function (Karpawich, 2015: 1003–1014). This dramatic event accounts for approximately 10% to 20% of all deaths worldwide (Konemann, et al., 2023). Characterized by the arrest of the heart's mechanical function shortly after the onset of symptoms, this condition is predominantly the result of malignant arrhythmias such as ventricular tachycardia (VT) or ventricular fibrillation (VF).

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The pathogenesis of cardiac arrhythmias and sudden cardiac death is the result of a dynamic interplay rather than an isolated factor. Current data indicate that SCD occurs as a result of a complex interaction among genetic predisposition, an underlying structural "substrate" (e.g., scar tissue), transient "triggers" (e.g., ischemia, electrolyte imbalance), and autonomic modulation (Goh, et al., 2025: 162–177).

The fundamental conceptual framework used to elucidate the pathogenesis of cardiac arrhythmias and sudden cardiac death is the model described by Philippe Coumel, widely known in the literature as "Coumel's Triangle" (Coumel, 1993: 338–355). According to this model, the simultaneous interaction of three main components is mandatory to trigger a malignant arrhythmia:

Arrhythmogenic Substrate: Structural or functional abnormalities that disrupt the homogeneity of electrical conduction (e.g., post-myocardial infarction scar tissue, hypertrophy, fibrosis, or genetic channelopathies).

Triggering Factor: The initiating event that destabilizes a steady rhythm (e.g., premature ventricular complex [PVC], bradycardia).

Modulating Factors: Transient physiological states that facilitate or exacerbate the interaction between the substrate and the trigger (e.g., autonomic nervous system imbalance, electrolyte imbalance, acute ischemia) (Coumel, 1993: 338–355; Zipes, 2003: 902–912).

The aim of this chapter is to establish a pathophysiological bridge between abnormalities in cellular electrophysiology and the clinical presentation of sudden cardiac death. The content will encompass the progression from isolated ion channel pathologies (channelopathies) to complex re-entry circuits within structurally damaged myocardial tissue. Elucidating the three fundamental

mechanisms of arrhythmogenesis—abnormal automaticity, triggered activity, and re-entry—plays a critical role both in the early identification of high-risk patients and in the development of targeted strategies, such as ablation and defibrillator therapies (Zeppenfeld, et al., 2022: 3997–4126).

Basic Electrophysiological Mechanisms: From the Cellular Level to Arrhythmogenesis

Arrhythmias are defined as deviations from the physiological heart rate and rhythm, and their underlying mechanisms are conventionally classified into two main categories: disorders of impulse formation (abnormal automaticity and triggered activity) and disorders of impulse conduction (re-entry and conduction block). A comprehensive understanding of these mechanisms relies on elucidating the effects of specific ion channels, such as sodium, potassium, and calcium, as well as intracellular calcium cycling, on the cardiac action potential (Tse, 2016: 75–81).

The Cardiac Action Potential and Ionic Basis

The action potential of ventricular myocytes consists of five distinct phases, as illustrated in Figure 1:

- Phase 0 (Rapid Depolarization): The abrupt rise of the membrane potential from its resting value (-85 mV) to positive values (+20 mV). This phase is driven by a sudden and massive influx of sodium through voltage-gated fast sodium (Na^+) channels. It is the primary determinant of conduction velocity (dV/dt); the slowing of this phase (e.g., in the presence of ischemia or due to the effects of Class I antiarrhythmic agents) provides a favorable substrate for conduction blocks and re-entry circuits.

- Phase 1 (Early Repolarization): Characterized by a "notch" appearance resulting from the inactivation of sodium (Na^+) channels and the activation of transient outward potassium (K^+) currents

(I_{to}).This is the phase where the pathophysiology of Brugada syndrome is concentrated.

- Phase 2 (Plateau): The period during which the membrane potential remains near the isoelectric line, facilitating the crucial calcium influx necessary for cardiac contraction. Calcium (Ca^{2+}) entering the cell through L-type calcium channels balances the outward potassium (K^+) currents. Excessive prolongation of this phase leads to early afterdepolarizations (EADs) and the presentation of *Torsades de Pointes*.

- Phase 3 (Rapid Repolarization): The return of the membrane potential to negative values following the closure of calcium channels and the predominance of outward K^+ currents (I_{Kr} and I_{Ks}). Loss of function in these channels plays a role in the subtypes of Long QT syndrome (LQT1 and LQT2).

- Phase 4 (Resting): The period during which the membrane potential remains stable throughout diastole (for ventricular cells) or undergoes slow depolarization (for pacemaker cells). The resting potential is primarily determined by the I_{K1} (inward rectifier) potential current (Antzelevitch & Burashnikov, 2011: 23–45).

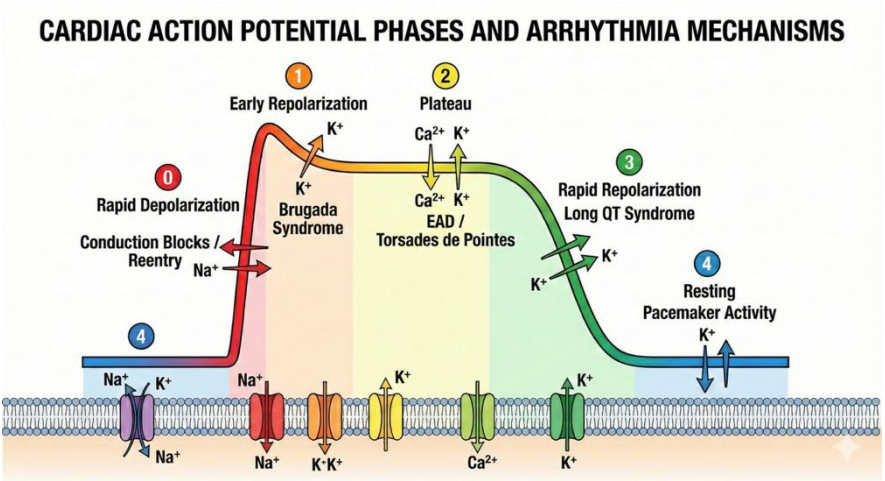

Figure 1. Phases of the ventricular myocyte action potential and principal ion currents. Phase 0 represents rapid depolarization driven by fast Na^+ influx; Phase 1 is early repolarization generated by a transient outward K^+ current (I_{to}); Phase 2 (Plateau) is the period where inward calcium through L-type Ca^{+2} channels balances outward potassium; Phase 3 is rapid repolarization, which occurs as K^+ efflux (I_{Kr}, I_{Ks}) becomes predominant; Phase 4 is the resting membrane potential, maintained primarily by I_{K1}. *(Abbreviations: I_{Na}: Fast sodium current; $I_{Ca,L}$: L-type calcium current; I_{to}: Transient outward potassium current; I_{Kr} and I_{Ks}: Rapid and slow delayed rectifier potassium currents; I_{K1}: Inward rectifier potassium current).*

Disorders of Impulse Formation

Automaticity: Voltage and Calcium Clocks

Under physiological conditions, the sinoatrial (SA) node functions as the dominant pacemaker of the heart due to its highest rate of automaticity. The spontaneous diastolic depolarization (Phase 4) of SA node cells occurs through the flawless integration of two fundamental mechanisms described as the "Voltage Clock" and the "Calcium Clock" (Antzelevitch & Burashnikov, 2011: 23–45).

Voltage Clock (I_f Current): The "funny" current (I_f), which occurs via hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, initiates the diastolic depolarization process.

Spontaneous calcium release from the sarcoplasmic reticulum (SR) contributes to membrane depolarization by activating the sodium-calcium exchanger (I_{NCX}) (Amos, et al., 1996: 31–50).

In pathological conditions such as ischemia or hypokalemia, when the resting membrane potential of atrial or ventricular myocytes—which do not normally possess pacemaker properties—rises to levels between -70 mV and -30 mV, a condition of "Depolarization-Induced Abnormal Automaticity" can develop (Groenke, et al., 2013: e81633).

Triggered Activity

This mechanism is characterized by membrane potential oscillations triggered by a preceding action potential and is referred to in the literature as "afterdepolarizations" (Antzelevitch & Burashnikov, 2011: 23–45).

Early Afterdepolarizations (EAD): Occur before the completion of the repolarization process (during Phase 2 or Phase 3). They typically develop secondary to the reactivation of L-type calcium channels under pathological conditions where the action potential duration (APD) is prolonged (Long QT syndrome, hypokalemia, bradycardia). EADs are the primary triggering mechanism, particularly for *Torsades de Pointes* (TdP) type polymorphic ventricular tachycardias (Nader, et al., 2007: 67–75).

Delayed Afterdepolarizations (DAD): Occur after repolarization is completely finished (during the Phase 4 resting stage). The fundamental pathophysiological mechanism is intracellular calcium overload (e.g., digitalis toxicity, catecholaminergic polymorphic VT - CPVT). Spontaneous calcium leak from the sarcoplasmic reticulum (SR) (via the ryanodine receptor - RyR2) activates the sodium-calcium exchanger current,

generating a transient inward current and bringing the membrane potential to the firing threshold (Guinamard, et al., 2004: 75–83).

Late Phase 3 EAD: In this specific mechanism described by Burashnikov and Antzelevitch; under conditions of abrupt APD shortening, such as the termination of atrial fibrillation (AF), the rapid completion of repolarization while SR calcium release continues leads to a robust electrophysiological activation at the cellular level and arrhythmic triggering (Burashnikov & Antzelevitch, 2003: 2355–2360, 2006: 290–295).

Disorders of Impulse Conduction: Re-entry

Re-entry is the phenomenon where an electrical impulse, instead of extinguishing, cyclically and repeatedly excites a specific region of the myocardium, and it is the most frequently encountered fundamental mechanism of clinical tachyarrhythmias (VT, AF, atrial flutter) (Janse & Wit, 1989: 1049–1169; Tabbah, Saliba, & Abi-Saleh, 2026: 100674).

Classical (Anatomical) Re-entry

It is based on the "Circus Movement" model described by George Mines. For this mechanism to occur, the simultaneous fulfillment of three fundamental electrophysiological conditions is mandatory: a closed conduction circuit rotating around an anatomical obstacle, unidirectional conduction block, and the slowing of the impulse's travel within the circuit to an extent that allows the tissue to complete its refractory period (G. R. Mines, 1913: 349–383; George Ralph Mines, 1914). Compact scar tissue developing after a myocardial infarction creates an electrically inactive and insulating center, constituting an ideal arrhythmic substrate for such anatomical re-entry circuits (Ripplinger, et al., 2009: 87–97).

Functional Re-entry

It occurs in the absence of a fixed anatomical obstacle, purely as a result of regional heterogeneity in the electrophysiological properties (refractory period and conduction velocity) of the tissue. Allessie's "Leading Circle" model and spiral wave (rotor) dynamics are investigated under this category (Ikeda, et al., 1996: 1962–1973). Spiral waves rotate around an electrically excitable but not yet excited core (phase singularity) and play a critical role, particularly in the maintenance of ventricular fibrillation (Allessie, Bonke, & Schopman, 1977: 9–18; Ikeda, et al., 1996: 1962–1973).

Phase 2 Re-entry

It is a cellular mechanism that does not involve a circus movement in the classical sense and is observed superficially as a focal activity, yet fundamentally harbors re-entrant dynamics (Krishnan & Antzelevitch, 1993: 562–572; Lukas & Antzelevitch, 1996: 593–603). t is the fundamental arrhythmic source in the pathophysiology of Brugada syndrome and Early Repolarization Syndrome (ERS). Due to the dense expression of the transient outward potassium current (I_{to}) in the right ventricular epicardium, a regional loss of the epicardial "dome" structure in the action potential can occur. Local electrical currents occurring at the cellular level from regions where the dome is maintained to regions where it is lost can pave the way for a very early extrasystole (R-on-T phenomenon) during phase 2, thereby triggering polymorphic VT or VF (Lukas & Antzelevitch, 1996: 593–603; Yan & Antzelevitch, 1999: 1660–1666; Yan, et al., 2003: 401–409).

Reflection

It is the condition where electrical conduction is unidirectionally blocked along an ionically depressed or ischemically damaged myocardial segment, but subsequently returns

via electrotonic (passive) currents across this segment to re-excite the proximal tissue (Antzelevitch, Jalife, & Moe, 1980: 182–191; Schmitt & Erlanger, 1928: 326–347). This mechanism does not require a physical circuit; it emerges through the forward and backward electrotonic interaction of the impulse along the same linear pathway (McDowell, et al., 2011: 1307–1315; Xie, et al., 2009: 1641–1649).

Electrical and Structural Remodeling

The electrical stability of the heart possesses the capacity to reorganize specific ion channels (I_{to} ,I_{Kr}) and gap junction proteins (Connexin 43) by exhibiting a cellular adaptation to altered activation patterns (e.g., ventricular pacing) through a phenomenon described as "Cardiac Memory" (Oros, Beekman, & Vos, 2008: 168–178; Stambler, 2006: 1378–1381). During the secondary remodeling process observed in structural heart diseases, pathological changes at the tissue level, such as increased fibrosis and myofibroblast-myocyte coupling, slow down electrical conduction, thereby creating a permanent substrate for re-entrant arrhythmias (McDowell, et al., 2011: 1307–1315; Xie, et al., 2009: 1641–1649).

Modulatıng Factors In Arrhythmogenesıs: Neural And Inflammatory Interactıon

The pathogenesis of cardiac arrhythmias does not solely originate from the intrinsic electrical anomalies of the heart; the autonomic nervous system and inflammatory processes play a critical initiating role by "triggering" an existing arrhythmic substrate into a clinical arrhythmia.

Neurocardiology and The Heart-Brain Axis

The heart and the brain are in continuous, bidirectional communication via the autonomic nervous system. In this integrated

mechanism, defined in the literature as the "Heart-Brain Axis," the insular cortex (particularly the right hemisphere) constitutes the primary center for sympathetic regulation (Tahsili-Fahadan & Geocadin, 2017: 559–572).

Acute Neurological Events: In acute conditions such as ischemic stroke or intracranial hemorrhage, a massive catecholamine discharge occurs alongside the abrupt disruption of autonomic balance. This condition can lead to the clinical picture of "neurogenic stunned myocardium" and secondary repolarization abnormalities (QT interval prolongation), thereby triggering malignant ventricular arrhythmias(Seifert, et al., 2015: 1182–1190).

Stellate Ganglion Remodeling: Following a myocardial infarction, pathological nerve sprouting and cellular enlargement (hypertrophy) are observed in the stellate ganglia that innervate the heart. This resulting structural remodeling significantly lowers the ventricular fibrillation threshold by augmenting sympathetic nerve discharge (Nguyen, et al., 2012: 143–148).

Inflammation and The NLRP3 Inflammasome

Inflammation is one of the fundamental pathogenic factors driving both structural (fibrosis) and electrical (ion channel dysfunction) remodeling during the process of arrhythmogenesis. In particular, the activation of the NLRP3 inflammasome robustly triggers the release of mature interlökin-1β (IL-1β) by facilitating the cleavage of inactive pro-cytokines via the caspase-1 pathway (Chen, et al., 2018: 1115).

• Calcium Leak :IL-1β, disrupts the functional integrity of ryanodine receptors (RyR2) located on the sarcoplasmic reticulum, causing an abnormal calcium leak during the diastolic phase. This pathological calcium leak provides a cellular substrate for "triggered

activity" mechanisms, which initiate atrial fibrillation and malignant ventricular arrhythmias (Heijman, et al., 2020: 1036–1055).

• Fibrosis: The chronic inflammatory process accelerates myocardial fibrosis by activating cardiac fibroblasts and provides a permanent substrate for the formation of re-entrant circuits by slowing electrical conduction (L. Li, et al., 2025: 101244).

Arrhythmıc Substrates in Structural Heart Dıseases

Arrhythmogenic mechanisms observed in structural heart diseases exhibit dramatic pathophysiological differences depending on the underlying etiology (ischemic or non-ischemic pathologies) and left ventricular function (ejection fraction).

Ischemic Heart Disease and Scar-Related Re-entry

Coronary artery disease is the most frequently encountered etiological cause of sudden cardiac death (SCD). In this clinical presentation, the mechanisms triggering malignant arrhythmias vary according to the stage of myocardial infarction:

Acute Phase: Intracellular potassium accumulation and tissue acidosis developing in myocytes subjected to ischemia generate myocardial "injury currents." This pathological cellular environment initiates arrhythmic events by triggering focal ectopic beats in the electrically stable, adjacent healthy tissues (Varro, et al., 2021: 1083–1176).

Chronic Phase (Scar Re-entry): The fibrotic scar formed following a myocardial infarction constitutes an electrically insulating and inactive anatomical obstacle. However, surviving myocyte bundles in the border zone, where the scar tissue intersects with the healthy myocardium, create pathological "conducting channels." The slowing of the electrical impulse within these channels and its entry into an anatomical circuit around the scar tissue give rise to macro-reentrant waves, which are the fundamental

mechanism of monomorphic ventricular tachycardia (VT) (Tschabrunn, et al., 2016: 262–273).

Divergent Mechanisms of Death in Heart Failure Phenotypes (HFrEF vs. HFpEF)

Recent studies have demonstrated that the mechanisms of sudden cardiac death (SCD) in heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) are based on entirely distinct pathophysiological foundations (X. Huang, et al., 2024; Sobue, et al., 2025: 37048).

HFrEF (Reduced EF, EF < 40%): The majority of fatal events in this group (46-68%) originate from ventricular tachyarrhythmias (VT/VF). Extensive macroscopic scar tissue and ventricular myocardial stretch create an ideal substrate for re-entrant waves, leading to electrical instability. This physiological basis explains why the HFrEF patient group derives the highest clinical benefit from implantable cardioverter-defibrillator (ICD) therapy (Zile, et al., 2010: 1393–1405).

HFpEF (Preserved EF, EF ≥ 50%): The incidence of SCD in HFpEF patients is lower compared to the general HF population (approximately 5.9%); however, the mechanism of death observed in this group is strikingly characterized by bradyarrhythmic and mechanical events rather than ventricular tachyarrhythmias (Sobue, et al., 2025: 37048).

Asystole as the Predominant Mechanism: Current prospective data indicate that approximately 53% of sudden cardiac deaths in HFpEF patients occur due to asystole or pulseless electrical activity (PEA).

QTc Prolongation and Microvascular Dysfunction: In the myocardial architecture of these patients, rather than a focal fibrotic scar, microvascular dysfunction, diffuse interstitial fibrosis, and

metabolic inflammation are prominent. Pathological prolongation of the QTc interval, representing an electrical manifestation of increased inflammatory burden and cellular dysfunction, has been identified as an independent and robust risk factor for sudden cardiac death in HFpEF patients [4]. he predisposition to QTc prolongation and the predominance of asystole/pulseless electrical activity (PEA) as the mechanism of death clearly elucidate why conventional antiarrhythmic devices, such as implantable cardioverter-defibrillators (ICDs), offer a limited survival benefit in HFpEF cases (C. Y. Huang, et al., 2024: e0308999; X. Huang, et al., 2024; Sobue, et al., 2025: 37048; Zile, et al., 2010: 1393–1405).

Hypertrophic Cardiomyopathy (HCM)

Hypertrophic cardiomyopathy (HCM) is one of the most frequently identified etiologies of sudden cardiac death (SCD), particularly in young adults and competitive athletes; it possesses a complex and multi-layered pathophysiology where electrical and structural abnormalities are intertwined (Marian & Braunwald, 2017: 749–770).

Myocyte Disarray: It is the phenomenon where myocardial muscle fibers lose their physiological, parallel, and orderly architecture, exhibiting a chaotic organization. This pathological remodeling at the tissue level creates an extremely high-risk substrate for malignant re-entrant waves by paving the way for regional slowing in electrical impulse conduction and functional conduction blocks (Marian & Braunwald, 2017: 749–770).

Cellular Calcium (Ca^{+2}) Overload and Electrophysiological Remodeling: Even in HCM cases where prominent macroscopic fibrosis has not developed, fatal arrhythmias can be observed. This condition is closely associated with sarcomeric protein mutations pathologically increasing the calcium sensitivity of myofilaments. The increased intracellular calcium

burden hyperactivates sarcolemmal sodium-calcium exchanger (I_{NCX}) currents, thereby inducing the formation of delayed afterdepolarizations (DADs). These abnormal electrical triggerings (triggered activity) occurring at the cellular level rank among the primary initiating mechanisms of ventricular tachyarrhythmias (Coppini, et al., 2013: 575–584).

Apical Aneurysm Formation: Left ventricular apical aneurysms, detected in a specific subset (2-5%) of HCM patients, stand out as a high-risk factor in the clinical presentation. The dense fibrotic scar tissue surrounding the aneurysm sac and serving as a transition zone (border zone) with the healthy myocardium functions as an anatomical arrhythmogenic focus with an extremely high risk for monomorphic ventricular tachycardia (VT) episodes (Rowin, et al., 2017: 761–773).

Primary Electrical Dıseases (Channelopathıes)

Primary electrical diseases or channelopathies encompass a group of genetic syndromes in which the heart appears macroscopically and structurally completely normal, yet malignant ventricular arrhythmias and sudden cardiac death (SCD) develop secondary to specific ion channel mutations at the molecular level (Wilde, et al., 2022: 1307–1367).

Long QT Syndrome (LQTS)

It is the most frequently encountered channelopathy in clinical practice, characterized by a pathological prolongation of ventricular repolarization on the surface electrocardiogram.

Mechanism: The fundamental pathophysiology relies on the prolongation of the cellular action potential duration as a result of loss-of-function mutations in potassium (K^+) channels (e.g., KCNQ1, KCNH2) or gain-of-function mutations in the sodium (Na^+) channel (e.g., SCN5A). The resulting delay in repolarization

increases secondary calcium (Ca^{+2}) influx into the myocyte, thereby triggering the formation of early afterdepolarizations (EADs) (Schwartz, Crotti, & Insolia, 2012: 868–877).

Torsades de Pointes (TdP): The developing EADs lead to the "R-on-T" phenomenon on the electrocardiogram, initiating the characteristic polymorphic ventricular tachycardia referred to as *Torsades de Pointes* (TdP). The pathological increase in the difference in repolarization duration among the distinct myocardial layers of the heart (M cells, epicardium, and endocardium), known as transmural dispersion of repolarization, is the principal proarrhythmic substrate that maintains this malignant arrhythmia (Schwartz, Crotti, & Insolia, 2012: 868–877).

Brugada Syndrome (BrS)

It is a genetic arrhythmia syndrome that can lead to SCD in individuals without structural heart disease, characterized by a specific *coved-type* ST-segment elevation predominantly observed in the right precordial leads (V1-V3).

Mechanism: Loss-of-function mutations in the Na^{+} channel within the SCN5A gene are held responsible in a significant portion of cases. Two main hypotheses stand out in the literature regarding the pathophysiological substrate:

Repolarization Hypothesis: It is the epicardial and endocardial voltage gradient (Phase 2 re-entry) resulting from the pathological deepening of the epicardial action potential notch (Phase 1) and the loss of the plateau "dome" in the right ventricular outflow tract (RVOT).

Depolarization Hypothesis: It refers to the conduction defects created by regional conduction slowing, the development of microscopic interstitial fibrosis, and connexin (Cx43) dysfunction in the RVOT region (Antzelevitch & Patocskai, 2016: 7–57).

Clinical Triggers: Arrhythmogenic events frequently exhibit a tendency to be triggered during sleep periods when parasympathetic (vagal) tone is predominant, or during episodes of febrile illness (Antzelevitch & Patocskai, 2016: 7–57).

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

It is a highly aggressive channelopathy in which the heart appears completely normal structurally and on the resting electrocardiogram; however, malignant arrhythmias are triggered under conditions of intense adrenergic discharge, such as physical exercise or acute emotional stress.

Mechanism: Specific mutations occurring in the ryanodine receptor (RyR2) or calsequestrin (CASQ2) genes lie at the foundation of its pathophysiology. Under increased adrenergic stimulation, these mutations lead to an uncontrolled, leak-like pathological diastolic calcium release (*diastolic calcium leak*) from the sarcoplasmic reticulum into the cytosol (Priori & Chen, 2011: 871–883).

Clinical Consequence: This abnormal increase in intracellular free calcium (Ca^{+2}) concentration activates the sarcolemmal sodium-calcium exchanger (NCX), thereby triggering the formation of delayed afterdepolarizations (DADs). These cellular triggerings result in bidirectional or polymorphic ventricular tachycardias (VT), which are considered pathognomonic for CPVT in the clinical presentation, frequently culminating in sudden cardiac death (SCD) (Priori & Chen, 2011: 871–883).

Electrical Storm and The Autonomıc Vicious Cycle

One of the most dramatic and life-threatening clinical manifestations of arrhythmogenesis is the presentation of "Electrical Storm," characterized by the occurrence of three or more consecutive

episodes of sustained ventricular tachycardia (VT), ventricular fibrillation (VF), or appropriate ICD shocks within a 24-hour period (Zeppenfeld, et al., 2022: 3997–4126). This acute clinical presentation is triggered by the pathological hyperactivation of "modulating factors" described in Coumel's Triangle, specifically the autonomic nervous system.

Adrenergic Discharge and Substrate Destabilization

During an electrical storm, the myocardial tissue is exposed to massive local and systemic catecholamine discharge. This adrenergic storm paves the way for intracellular calcium (Ca^{+2}) overload secondary to the overstimulation of beta-adrenergic receptors, and consequently, to delayed afterdepolarization (DAD)-mediated triggered activities (Vaseghi & Shivkumar, 2008: 404–419). Simultaneously, the pain and profound anxiety generated by recurrent malignant arrhythmias and ICD shocks further amplify the autonomic tone via the central nervous system. This condition creates a fatal "sympathetic vicious cycle" that cannot be broken without external neuromodulatory intervention (e.g., beta-blockers or sedation).

Pathophysiological Role of Stellate Ganglia and Neural Remodeling

In the setting of chronic ischemic heart disease and heart failure, structural hypertrophy occurs in the cervicothoracic (stellate) ganglia innervating the heart, alongside pathological nerve sprouting in the infarct border zones [3]. During an electrical storm episode, this hyperactive and asymmetrically distributed sympathetic network creates significant heterogeneity in myocardial refractoriness around the scar tissue.

This regional electrophysiological mismatch stimulates slow conduction zones, leading to the activation of silent ("dormant")

anatomical re-entry circuits and perpetuating the arrhythmic storm (Y. L. Li, 2022).

From Pathophysıology to Rısk Stratification: Current Approaches

Predicting the risk of sudden cardiac death (SCD) remains one of the most challenging clinical hurdles that has persisted for decades in cardiology practice. The traditional risk stratification criterion based solely on a "Left Ventricular Ejection Fraction (LVEF) ≤ %35" falls short of the modern understanding of arrhythmogenesis; a significant proportion of SCD victims possess relatively preserved EF values, and an arrhythmic substrate can develop independently of LVEF (Tabbah, Saliba, & Abi-Saleh, 2026: 100674). Therefore, current guidelines are shifting towards pathophysiology-focused risk assessment strategies rather than purely anatomical measurements.

Imaging of Myocardial Scar (Cardiac MRI)

Cardiac Magnetic Resonance (CMR) is currently the gold standard imaging modality for the detection of anatomical obstacles (fibrotic scar tissue) underlying re-entrant arrhythmias. Utilizing the Late Gadolinium Enhancement (LGE) technique, the extent, location (endocardial, transmural, or mid-myocardial), and distribution of scar tissue within the myocardium can be mapped with high resolution.

The myocardial fibrosis burden detected by LGE is recognized as one of the most robust anatomical predictors of arrhythmic sudden death risk, independent of a reduced or preserved EF (Tabbah, Saliba, & Abi-Saleh, 2026: 100674).

Molecular Autopsy and Genetic Testing

In cases of Idiopathic VF or Sudden Arrhythmic Death Syndrome (SADS) occurring in structurally completely normal hearts, the most critical diagnostic approach is post-mortem genetic testing. The sequencing of specific genes encoding sodium, calcium, or potassium channels (e.g., SCN5A, RyR2, KCNH2) through a "molecular autopsy" performed on DNA isolated from blood or tissue samples of sudden death victims is of paramount importance. This approach not only elucidates the cellular pathophysiology underlying the fatal event but also plays a life-saving role through the screening of asymptomatic first-degree relatives (*cascade screening*) and the development of prophylactic strategies (Wilde, et al., 2022: 1307–1367).

Mechanism-Targeted Therapeutic Strategies

The most concrete reflection of arrhythmogenesis theories in clinical practice is mechanism-targeted therapeutic modalities that directly address the arrhythmic substrate or autonomic triggers.

Elimination of Re-entry Circuits via Catheter Ablation

Macro-reentrant circuits developing after a myocardial infarction are the primary target of catheter ablation today. With the assistance of three-dimensional electroanatomical mapping systems, the slow conduction channels (isthmuses) located at the borders of the scar tissue, which perpetuate the arrhythmia, are electrophysiologically identified.

By applying radiofrequency energy to these regions, electrical isolation is achieved, and the cyclical (re-entrant) activity that allows the impulse to repeatedly re-excite the same tissue is terminated. Currently, catheter ablation has a strong indication not only in cases refractory to antiarrhythmic drugs but also in the earlier

stages of the disease to prevent implantable cardioverter-defibrillator (ICD) shocks (Zeppenfeld, et al., 2022: 3997–4126).

Autonomic Neuromodulation

Modification of the heart's autonomic innervation is a life-saving approach, particularly in genetic channelopathies such as Long QT Syndrome (LQTS) and Catecholaminergic Polymorphic VT (CPVT), as well as in presentations of refractory electrical storm developing secondary to ischemic cardiomyopathy.

Stellate Ganglion Blockade and Denervation: Left cardiac sympathetic denervation (LCSD) is the surgical resection procedure of the lower half of the left stellate ganglion along with the T2-T4 (second to fourth thoracic) sympathetic ganglia (Schwartz, et al., 2004: 1826–1833).

This procedure significantly eliminates the triggering adrenergic (norepinephrine) burden on the ventricular myocardium, thereby robustly suppressing the formation of pathogenic early and delayed afterdepolarizations (EADs and DADs).

Specific Ion Channel Modulators (Pharmacotherapy)

Elucidating the specific ion current defects underlying the pathophysiology of arrhythmias at the cellular level has enabled the use of targeted and rational pharmacotherapy. For example:

In Brugada Syndrome and Idiopathic VF: Quinidine, which suppresses the excessive and unbalanced transient outward potassium current (I_{to}) that deepens the epicardial action potential notch and balances the transmural action potential duration, is a highly effective therapeutic agent (Belhassen, Glick, & Viskin, 2004: 1731–1737).

In Catecholaminergic Polymorphic VT (CPVT): Flecainide, which directly blocks the calcium leak from the ryanodine receptor

(RyR2) in the sarcoplasmic reticulum into the cytosol during diastole, constitutes the cornerstone of clinical management when combined with beta-blocker therapy (van der Werf, et al., 2011: 2244–2254).

Conclusion

Arrhythmia and sudden cardiac death (SCD) are not merely clinical coincidences; they represent a fatal intersection of biophysical, molecular, and structural factors. While this pathological process initiates at the cellular level as genetic ion channel abnormalities or calcium leaks, it transforms into complex re-entry substrates at the tissue level via scar areas and fibrotic insulating obstacles (Tabbah, Saliba, & Abi-Saleh, 2026: 100674). The interaction of inflammatory signaling pathways (e.g., NLRP3) and permanent adaptations in the autonomic nervous system (nerve sprouting) with this substrate pulls the ultimate trigger leading to the failure of mechanical pump function (Y. L. Li, 2022). In the future, risk management will move away from relying solely on macroscopic parameters such as left ventricular ejection fraction; it will open the doors to a new, more "personalized" and mechanism-oriented era integrating cellular imaging (cardiac MRI), genomic profiling (molecular autopsy), and neuromodulatory therapies. Ultimately, fully unraveling these complex mechanisms underlying arrhythmogenesis will serve as the most powerful key to transforming sudden cardiac death from an unpredictable fate into a clinically preventable entity at the cellular level.

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CARDIOVASCULAR RISK FACTORS, CORONARY ARTERY DISEASE, ACUTE AND CHRONIC MYOCARDIAL ISCHEMIA, ACUTE MYOCARDIAL INFARCTION AND SUDDEN CARDIAC DEATH

SEFA ERDİ ÖMÜR[1]

Introduction

In the contemporary landscape of global public health, cardiovascular diseases (CVD) persistently occupy the position as the foremost drivers of both morbidity and mortality across diverse populations worldwide. Despite significant advancements in medical technology, the overarching burden of these conditions requires proactive intervention. A substantial proportion of these adverse cardiovascular events are fundamentally preventable through the early identification and the subsequent, highly effective management of modifiable risk factors that accumulate within an individual across their entire life course (Visseren, et al., 2021: 3227–3337).

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Cardiovascular risk factors

Conceptual framework and clinical relevance

The vast majority of the population-level burden of cardiovascular disease is directly attributable to modifiable lifestyle and metabolic risk factors. The early recognition of these factors is paramount, as it enables the precise quantification of individual patient risk, the critical personalization of therapeutic lifestyle interventions, and the timely initiation of appropriate pharmacotherapy, yielding profound benefits across both primary and secondary prevention paradigms (Visseren, et al., 2021: 3227–3337). In real-world clinical practice, the management of risk factors achieves optimal efficacy when it adheres to three core principles: it must be (i) holistic (addressing multiple concurrent risks simultaneously rather than in isolation), (ii) target-oriented (establishing clear, evidence-based goals for critical parameters, including blood pressure, lipid profiles, glycemic control, body weight, and smoking cessation), and (iii) iterative (requiring short-interval follow-up consultations paired with the prompt intensification of treatment regimens whenever established therapeutic targets are not met)

Modern risk assessment: from single factors to total risk

Historically, preventive cardiology often isolated single parameters; however, rather than focusing predominantly on an isolated metric (such as strictly monitoring blood pressure or LDL-cholesterol alone), contemporary prevention paradigms utilize the comprehensive concept of total cardiovascular risk. This modern model integrates a multitude of variables, including age, biological sex, smoking history, lipid profiles, systemic glucose levels, blood pressure, body weight, sleep hygiene, and psychosocial determinants. The American Heart Association's *Life's Essential 8* framework serves as a foundational tool in this regard, supporting

structured and effective risk communication by jointly addressing critical health behaviors and health factors: diet, physical activity, nicotine exposure, sleep health, body mass index, lipids, glucose, and blood pressure (Lloyd-Jones, et al., 2022: e18–e43). Beyond strictly biomedical variables, clinicians must recognize that adherence barriers, patient health literacy, socioeconomic constraints, and underlying mental health conditions often serve as the ultimate determinants of long-term patient outcomes. Consequently, a brief, repeated, and iterative risk conversation that actively translates abstract clinical targets into tangible, actionable steps is usually significantly more effective than a single, exhaustive counseling session.

Risk stratification with SCORE2 / SCORE2-OP

Accurate risk estimation is the cornerstone of primary prevention (Table 1). For European populations, the SCORE2 algorithm reliably estimates the 10-year risk of both fatal and non-fatal cardiovascular events in adult populations aged 40 to 69 years. This tool leverages updated longitudinal cohort data alongside country-specific calibration, thereby vastly improving the accuracy of risk classification into distinct low-moderate, high, and very high-risk categories (S. w. group & collaboration, 2021: 2439–2454). However, in individuals aged 70 years and older, the dynamics of risk estimation become inherently more complex. To address this demographic, SCORE2-OP was explicitly developed for older adult populations to better reflect the incident event risk across various European geographical risk regions (S. O. w. group & collaboration, 2021: 2455–2467). At the clinical bedside, the fundamental key to success is selecting the age-appropriate predictive model and judiciously interpreting the statistical results within the broader context of the patient's existing comorbidities, overall frailty, and competing mortality risks, thereby actively avoiding both the pitfalls of undertreatment and overtreatment.

Improving risk estimation in practice (risk modifiers)

Although validated risk scores greatly facilitate clinical decision-making, they are inherently limited and cannot fully capture the nuanced risk profile of every individual patient. Therefore, sound clinical judgment must be supported by the integration of established risk modifiers, such as a detailed family history of premature CVD, the presence of chronic inflammatory conditions, chronic kidney disease (CKD), specific metabolic phenotypes, markers of subclinical atherosclerosis, and the patient's historical adherence profile. When clinical uncertainty remains regarding the optimal path forward (particularly within the nebulous intermediate-risk range), the deployment of subclinical atherosclerosis imaging or specialized systemic biomarkers may help clinicians refine the precise intensity of preventive therapy, provided that these diagnostic results will tangibly alter the management plan.

Table 1. Practical steps for SCORE2/SCORE2-OP-based risk assessment.

Step	What to do	Example output
1	Confirm prevention context: primary prevention vs secondary prevention.	Appropriate pathway is selected
2	Select the appropriate model: SCORE2 (age 40–69) or SCORE2-OP (≥70).	Correct risk chart is chosen
3	Collect core variables: sex, age, smoking status, systolic BP, and non-HDL cholesterol (or total + HDL).	Inputs are complete and reliable
4	Choose the regional risk chart/tool and calculate 10-year risk.	Numerical 10-year risk estimate
5	Assign a risk category and communicate absolute risk clearly.	Risk category + shared plan
6	Consider risk modifiers when they are likely to change management (family history, CKD, inflammatory disease, Lp(a), metabolic phenotype).	Risk estimate refined
7	Use subclinical atherosclerosis imaging selectively (e.g., CAC) to reclassify intermediate risk when uncertainty remains.	Treatment intensity individualized
8	Define targets (BP, LDL-C, glycemia, weight, smoking) and a follow-up plan; reassess after major changes.	Documented targets + follow-up schedule

Hypertension

Hypertension acts as a profound catalyst for vascular pathogenesis, aggressively increasing the risk of coronary artery disease and subsequent stroke through mechanisms encompassing

endothelial dysfunction, left ventricular hypertrophy, deleterious microvascular injury, and accelerated states of atherosclerosis. The comprehensive 2023 European Society of Hypertension (ESH) guideline places heavy emphasis on ensuring accurate blood pressure measurement techniques, utilizing out-of-office monitoring methodologies, implementing aggressive lifestyle interventions, utilizing appropriate combination pharmacotherapy, and achieving target-oriented blood pressure control to mitigate severe downstream complications (Mancia, et al., 2023: 1874–2071). Common clinical pitfalls frequently include relying solely on a single office-based reading, providing inadequate therapeutic titration, and experiencing low patient adherence due to the prescription of highly complex medication regimens. The strategic use of single-pill combinations alongside structured home blood pressure monitoring protocols can substantially and sustainably improve long-term disease control.

Dyslipidemia and atherogenic lipoproteins

In the realm of primary prevention, the critical decision to initiate statin therapy must be meticulously individualized, hinging upon the patient's distinct risk factors and their overall computed risk trajectory. The authoritative recommendation from the USPSTF robustly supports the net clinical benefit of initiating statin therapy in adult cohorts aged 40-75 years who possess at least one prominent risk factor coupled with a sufficient 10-year atherosclerotic risk profile (Force, et al., 2022: 746–753). In high-risk scenarios involving established ASCVD, when aggressive LDL-C goals remain unachieved despite maximum tolerated statin therapy, non-statin pharmacological options—such as ezetimibe, PCSK9 inhibitors, or bempedoic acid—can be systematically added in a stepwise fashion to drive down lipid levels. The 2022 ACC decision pathway rigorously details scenario-based selection criteria and outlines effective treatment intensification strategies (Writing, et al., 2022: 1366–1418). Furthermore, Lipoprotein(a) [Lp(a)] has

emerged as a critical factor, being causally linked directly to severe atherothrombotic events and the development of aortic stenosis. The 2022 EAS consensus vehemently recommends the measurement of Lp(a) levels at least once during adulthood, and—when found to be elevated—urges clinicians to pursue substantially more intensive risk factor optimization and, when clinically appropriate, initiate comprehensive family screening protocols (Kronenberg, et al., 2022: 3925–3946).

Platelet activation and aspirin: balancing benefit and bleeding in primary prevention

The paradigm regarding prophylactic aspirin has shifted; it is definitively not appropriate for universal application in primary prevention due to the concurrent, non-trivial risk of major bleeding events. The updated USPSTF framework recommends highly individualized decision-making specifically for selected adult populations aged 40-59 years who exhibit a sufficient 10-year ASCVD risk, while strongly discouraging the routine initiation of aspirin in adults aged 60 years and older (Force, et al., 2022: 1577–1584). In daily practice, this complex decision should seamlessly integrate a review of prior bleeding episodes, any concomitant use of anticoagulation, the patient's frailty status, underlying gastrointestinal risk factors, and explicit patient preferences, and it must be actively revisited as the patient's physiological risk profile evolves over time.

Diabetes and cardiometabolic risk

Diabetes mellitus profoundly amplifies cardiovascular vulnerability, aggressively increasing the risk of manifesting coronary disease, developing heart failure, and sustaining critical renal complications via a trifecta of endothelial dysfunction, systemic inflammation, and a highly prothrombotic biological milieu. The highly influential ADA 2024 Standards of Care provide

distinct, phenotype-based algorithms (stratified by ASCVD, HF, and CKD presence) specifically designed for selecting optimal glucose-lowering therapies and for precisely aligning lipid and blood pressure targets with overarching cardioprotection goals (American Diabetes Association Professional Practice, 2024: S179–S218). The most practical clinical approach is to conceptualize and treat diabetes as a complex, multisystem cardiometabolic condition: physicians must target not only strictly numeric glycemia but also aggressively manage patient weight, blood pressure parameters, lipid panels, structural kidney function, and baseline physical activity—while preferentially utilizing therapies with proven, evidence-based organ-protective effects whenever indicated.

Obesity, weight management, and GLP-1-based strategies

Obesity is a profound metabolic disruptor that seamlessly clusters together hypertension, detrimental dyslipidemia, profound insulin resistance, and chronic systemic inflammation. The 2025 ACC expert consensus statement provides an indispensable, practical framework that holistically integrates targeted lifestyle adjustments, advanced anti-obesity pharmacotherapy, and surgical bariatric approaches directly into cardiovascular risk optimization (Gilbert, et al., 2025: 536–555). Groundbreaking data from the SELECT trial demonstrated that the administration of semaglutide 2.4 mg significantly reduced the incidence of major adverse cardiovascular events in adult populations presenting with overweight or obesity, established clinical CVD, and an absence of diabetes, reinforcing the concept of weight management as a primary cardiovascular therapeutic target (Lincoff, et al., 2023: 2221–2232). In routine clinical practice, achieving sustainable weight reduction typically mandates a multifaceted strategy encompassing improvements in nutrition quality, physical activity, sleep, behavioral support, and—when deemed clinically appropriate—pharmacotherapy and/or metabolic surgery.

Subclinical atherosclerosis: coronary artery calcium score

The Coronary Artery Calcium (CAC) score serves as a direct radiographic reflection of calcified plaque burden and stands as an exceptionally strong independent risk marker. A unified message across contemporary guidelines is that CAC imaging can significantly aid in risk reclassification for individuals in the intermediate-risk category. A finding of CAC=0 is overwhelmingly associated with a remarkably low short-term risk of adverse events, whereas high CAC numerical values provide robust support for the initiation of significantly more intensive lipid-lowering regimens and aggressive lifestyle interventions (Golub, et al., 2023: 98–117). CAC scanning should be utilized selectively—most appropriately when the derived score will tangibly alter the clinical management trajectory and when the patient demonstrates a clear willingness to act definitively upon the results.

Key messages

- A total-risk approach is more effective than correcting a single risk factor in isolation.
- SCORE2/SCORE2-OP should be interpreted together with risk enhancers.
- Blood pressure and LDL control are core pillars of event prevention.
- In diabetes/obesity, the cardiometabolic axis should be managed with multiple targets.
- In uncertain intermediate risk, CAC may guide treatment intensity.

Coronary artery disease

Definition and phenotypes

It is critical to recognize that coronary artery disease (CAD) is emphatically not limited merely to the presence of obstructive epicardial stenosis or complete vessel occlusion. Alternative

pathophysiological mechanisms, including epicardial vasospasm, severe microvascular dysfunction, and spontaneous plaque erosion or rupture, substantially contribute to the heterogeneous clinical presentations observed in modern practice. Chronic coronary syndromes must be conceptualized as a dynamic spectrum that requires continuous reclassification directly according to the patient's symptom stability and risk profile (Vrints, et al., 2024: 3415–3537). Importantly, a subset of patients may exhibit objective signs of ischemia or experience debilitating angina while maintaining entirely non-obstructive coronary arteries on imaging (INOCA/ANOCA). Recognizing these diverse phenotypic variations prevents underdiagnosis and directly supports targeted, mechanism-specific therapy.

Core goals in chronic coronary disease

The comprehensive 2023 AHA/ACC guideline explicitly highlights three overarching goals in the management of chronic coronary disease (Table 2): (i) improving the patient's overall quality of life via stringent angina control, (ii) substantially reducing the incidence of future adverse events via secondary prevention, and (iii) executing strategic revascularization specifically in selected high-risk clinical settings defined by their anatomic or ischemic severity. Treatment paradigms must remain fiercely individualized according to the patient's unique symptom presentation, documented ischemia burden, anatomic extent of the disease, left ventricular functional status, and confounding comorbidities (Virani, et al., 2023: e9–e119).

Table 2. Core goals and components in chronic coronary disease

Goal	Components	Practical tip
Symptom control	Antianginal therapy; lifestyle; cardiac rehabilitation; treat comorbidities	Match therapy to symptoms, heart rate/BP, and comorbidity profile.
Event prevention	Lipid/BP/diabetes/obesity management; antithrombotic strategy when indicated; smoking cessation	Intensify according to total risk and track target attainment over time.
Revascularization (selected patients)	Heart Team decision-making; PCI/CABG selection; physiology- and imaging-guided strategy	Integrate anatomy, ischemia burden, procedural risk, and patient preferences.

Clinical assessment: chest pain and equivalents

In practice, presentations of chest pain must be rigorously classified (typical, possible, unlikely), and critical anginal equivalents—such as dyspnea, a sudden reduction in baseline exercise capacity, epigastric discomfort, or unexplained syncope—must never be overlooked. The 2021 AHA/ACC chest pain guideline logically structures diagnostic test selection (Algorithm 1) heavily based on pretest probability, identified risk factors, baseline ECG and troponin findings, and the broader clinical context (Gulati, et al., 2021: e368–e454). A structured history should comprehensively capture symptom triggers, relief patterns, functional limitation, and absolute clinical red flags such as rest pain, syncope, or overt signs of heart failure

Biomarkers: rapid triage with high-sensitivity troponin

In suspected acute coronary syndromes, high-sensitivity troponin assays coupled with serial sampling definitively support rapid rule-out or rule-in diagnostic strategies. Clinical interpretation

must carefully account for biological variation, recognized etiologies of chronic biomarker elevation (CKD, HF, myocarditis), and the integrated clinical context to systematically avoid initiating unnecessary invasive procedures while simultaneously minimizing missed MI (Sandoval, et al., 2022: 569–581).

Anatomical testing: coronary CT angiography (CCTA)

CCTA provides rapid, non-invasive anatomic assessment, particularly useful in selected low-to-intermediate risk acute chest pain presentations. The SCCT expert consensus notes that, in appropriately selected patients, CCTA imaging can strongly support safe early discharge decisions, reduce the volume of unnecessary hospital admissions, and reveal alternative pathological diagnoses (Maroules, et al., 2023: 146–163).

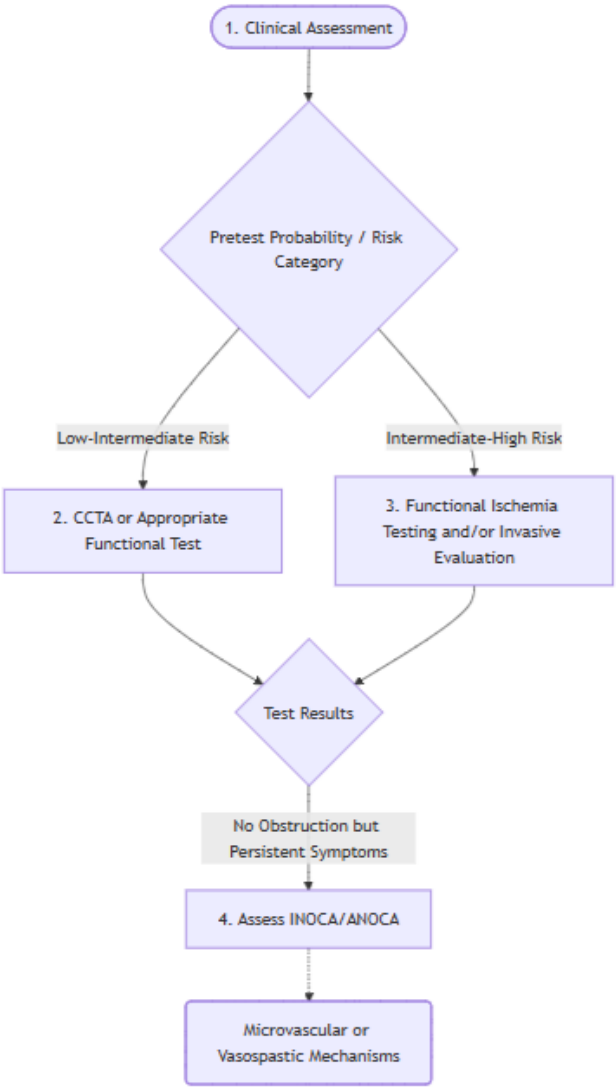
Functional anatomy: CT-derived fractional flow reserve (FFR-CT)

FFR-CT computationally estimates the true hemodynamic significance of identified anatomic stenoses entirely non-invasively, holding the profound potential to reduce unnecessary invasive angiography. Strict adherence to optimal image quality, patient heart rate control, and standardized reporting are absolutely critical for reliable clinical decision-making (Rajiah, et al., 2022: 340–358).

Revascularization decisions: who, when, and how?

Indications driving the decision for revascularization are firmly based upon optimizing symptom control, the quantified burden of myocardial ischemia, and the anatomic extent of the disease. The 2021 ACC/AHA/SCAI guideline summarizes evidence-based preferences for PCI vs CABG in multivessel disease, left main coronary disease, concurrent diabetes, left ventricular dysfunction, and complex anatomy, explicitly emphasizing the multidisciplinary Heart Team approach (Lawton, et al., 2022: e18–

e114). Beyond anatomy, patient values, expected quality-of-life gains, procedural risks, and the feasibility of complete revascularization should be explicitly discussed.



Algorithm 1. Test selection in suspected CAD/chronic coronary syndromes (summary).

Step 1. Exclude acute coronary syndrome or other unstable features.

Step 2. Perform structured clinical assessment (symptom phenotype, risk factors, ECG ± troponin) and estimate pre-test probability.

Step 3. Choose the initial test based on probability and patient factors:

• Low probability: consider no immediate cardiac testing; focus on risk-factor optimization and alternative diagnoses.

• Intermediate probability: coronary CT angiography is often preferred when image quality is expected to be high; use functional imaging when CT quality is limited or contraindicated.

• High probability or high-risk clinical features: functional ischemia testing or invasive angiography with physiologic assessment as appropriate.

Step 4. Add physiology when anatomy is equivocal (e.g., CT-FFR or invasive FFR/iFR) to reduce unnecessary procedures.

Step 5. If no obstructive disease but symptoms persist, consider INOCA (microvascular dysfunction/vasospasm) and tailor therapy.

Key messages

- CAD is not limited to obstructive stenosis; vasospasm and microvascular dysfunction are important phenotypes.
- Test selection should be guided by clinical risk and pretest probability.
- In chronic CAD, aim for symptom control + event prevention + revascularization in selected patients.
- Revascularization decisions should integrate anatomy, ischemia burden, and patient preferences.

Acute and chronic myocardial ischemia

Physiology of ischemia: supply-demand balance and the 'ischemic cascade'

Myocardial ischemia is the direct consequence of a fundamental mismatch: a reduced oxygen supply (coronary stenosis, spasm, thrombus, hypotension) and/or a pathologically increased demand (tachycardia, hypertension, fever, thyrotoxicosis). In the ischemic cascade, early diastolic dysfunction and regional wall motion abnormalities may manifest before detectable ECG changes, followed by biomarker elevation and eventual necrosis. Understanding this cascade helps intelligently guide the choice and timing of anatomical vs functional diagnostic testing. Clinically, differentiating acute plaque-related ischemia from demand-driven ischemia (type 2 mechanisms) is essential because management priorities differ vastly.

Microvascular ischemia and microvascular angina

Patients may present clinically with classic exertional chest pain or objective ischemia despite absolutely no significant stenosis upon standard angiography. Microvascular angina is deeply associated with pathologically increased microvascular resistance, profound endothelial dysfunction, and distinct vasomotor abnormalities. Contemporary reviews highlight the diagnostic role of stress imaging, invasive coronary flow reserve assessment, and highly individualized antianginal pharmacotherapy (Spione, et al., 2022: 800918). Controlling traditional risk factors and explicitly avoiding false reassurance based merely on a 'normal angiography' are key tenets of care.

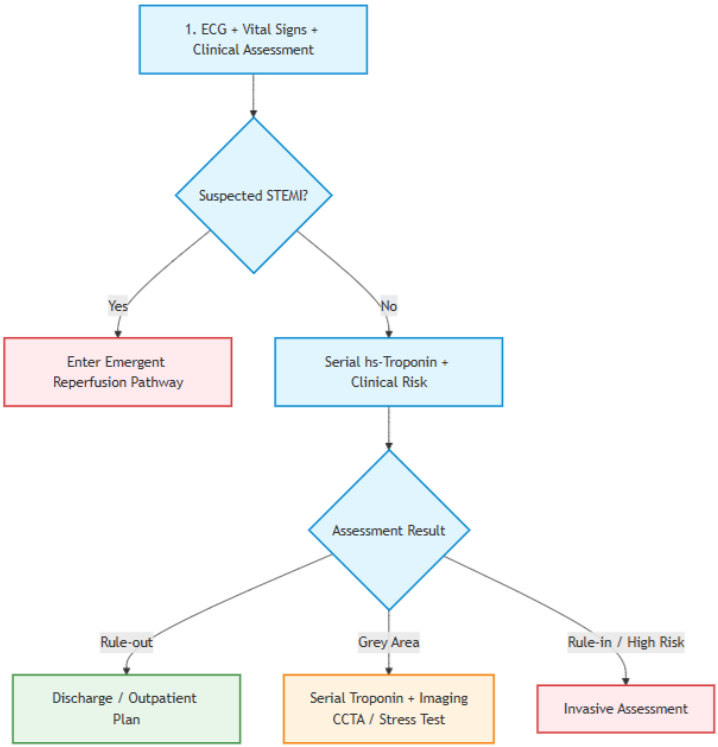
INOCA: current concepts in diagnosis and management

Ischemia with Non-Obstructive Coronary Arteries (INOCA) is a highly heterogeneous clinical syndrome, most often mechanistically driven by underlying microvascular dysfunction

and/or profound vasospastic mechanisms. Modern imaging-focused analyses emphasize accurate patient phenotyping (microvascular vs vasospastic), rigorous systemic risk factor optimization, and the deployment of mechanism-targeted pharmacotherapy to improve patient symptoms and potentially alter outcomes (Reynolds, et al., 2023: 63–74).

Rapid risk stratification in the emergency department: 0/1-hour algorithms

Accelerated diagnostic algorithms (Algorithm 2) relying on high-sensitivity troponin assays have been rigorously tested within real-world emergency settings. A comprehensive, multi-center analysis evaluated the performance of the validated ESC 0/1-hour diagnostic algorithm across diverse patient subgroups (accounting for variations in age, sex, and comorbidities), providing practical, actionable insights for safe, rapid rule-out protocols and appropriate clinical escalation in uncertain cases (Ashburn, et al., 2023: 347–356).



***Algorithm 2**; Emergency Chest Pain Triage and Early ACS Management*

Step 1. Immediate assessment: vitals, focused history, and 12-lead ECG as early as possible; treat hypoxemia and severe pain while obtaining diagnostics.

Step 2. Obtain high-sensitivity troponin at 0 h and repeat at 1–2 h per validated pathways; interpret alongside ECG and clinical context.

Step 3. STEMI or very high-risk NSTEMI: activate reperfusion/early invasive strategy and manage complications (arrhythmia, shock).

Step 4. Intermediate risk/unclear diagnosis: observe with serial ECG/troponin; consider early coronary CT angiography in suitable patients.

Step 5. Low-risk rule-out: provide return precautions, arrange timely follow-up, and optimize risk factors.

Key messages

- Rapid triage in acute ischemia relies on ECG + high-sensitivity troponin + clinical risk assessment.
- In selected patients, CCTA provides speed and diagnostic clarity; FFR-CT may add physiology when needed.
- In chronic ischemia, symptom burden and event risk should be targeted separately.
- In INOCA/ANOCA, microvascular and vasospastic mechanisms should be considered.

Acute myocardial infarction and sudden cardiac death

Clinical approach in acute myocardial infarction: early diagnosis, early reperfusion

Acute myocardial infarction (AMI) is a time-critical emergency in which outcomes are largely determined by the speed and quality of diagnosis and reperfusion. Most events arise from abrupt reduction in coronary flow following plaque rupture or erosion with superimposed thrombosis. The practical workflow can be summarized as: stabilize, diagnose, risk-stratify, reperfuse/revascularize, prevent complications, and initiate secondary prevention before discharge.

Initial assessment should prioritize airway, breathing, and circulation, while simultaneously obtaining a focused history, rapid vital signs, and continuous rhythm monitoring. Hemodynamic status (hypotension, shock, pulmonary edema), ongoing or recurrent ischemia, and malignant arrhythmias identify patients who require immediate escalation. In parallel, bleeding risk and contraindications

to antithrombotic therapy should be screened (recent major bleeding, hemorrhagic stroke history, severe thrombocytopenia, or recent high-risk surgery).

Diagnosis rests on the integration of symptoms, ECG findings, and serial troponin. A single early troponin may be negative, particularly if symptom onset is recent; therefore, serial sampling and dynamic change are essential. ECG should be obtained as early as possible and repeated when clinical suspicion persists, because evolving ischemia may be missed on a single recording. Posterior infarction, right ventricular involvement, and new conduction disturbances may require additional leads or targeted assessment.

Once AMI is suspected, the next decision is whether the presentation is consistent with ST-elevation MI (STEMI) or a non-ST-elevation acute coronary syndrome with myocardial infarction (NSTEMI). In STEMI (or STEMI-equivalent patterns), the priority is immediate reperfusion, ideally via primary percutaneous coronary intervention (PCI). When timely access to PCI is not feasible, reperfusion strategies may need to be adapted according to local logistics and patient-level contraindications.

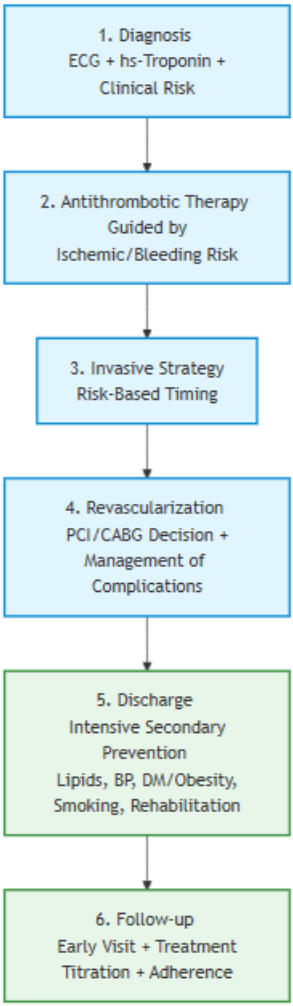
In NSTEMI, the approach is risk-based. Patients with hemodynamic instability, refractory angina, dynamic ECG changes, life-threatening arrhythmias, acute heart failure, or substantial biomarker elevation typically benefit from early invasive evaluation, whereas clinically stable patients can undergo invasive assessment according to their overall risk profile and procedural/bleeding risk.

Antithrombotic treatment is central to AMI care but must be individualized. The goal is to prevent thrombus propagation and stent thrombosis while minimizing major bleeding. Practical considerations include patient age, renal function, body weight, history of bleeding, need for long-term oral anticoagulation (e.g.,

atrial fibrillation), and planned access strategy. Dose adjustments and shortened periods of combined therapy may be appropriate in high bleeding-risk settings.

Early complication surveillance is mandatory. Ventricular tachyarrhythmias can occur abruptly and require prompt defibrillation and advanced life support. Bradyarrhythmias or atrioventricular block, particularly in inferior infarction, may necessitate temporary pacing. Acute heart failure and pulmonary edema should be managed according to hemodynamic profile, and mechanical complications (acute severe mitral regurgitation, ventricular septal rupture, free wall rupture) should be suspected in cases of sudden deterioration, new murmurs, or shock - triggering urgent echocardiography and surgical consultation.

Finally, AMI management (Algorithm 3) does not end with successful reperfusion. Before discharge, secondary prevention should be initiated as a structured plan: aggressive lipid lowering, blood pressure optimization, diabetes/weight management, smoking cessation, cardiac rehabilitation referral, and clear follow-up. Early outpatient review helps titrate therapy to targets, reinforce adherence, and detect recurrent ischemia or heart failure symptoms in the vulnerable post-MI period (Byrne, et al., 2023: 3720–3826).



Algorithm 3; *Integrated Management Pathway for Acute Coronary Syndromes (Diagnosis to Follow-Up)*

Phase A (minutes–hours): confirm diagnosis, initiate antithrombotic and anti-ischemic therapy, and deliver reperfusion/early invasive management when indicated.

Phase B (in-hospital): quantify LV function, treat complications, and start evidence-based secondary prevention.

Phase C (discharge planning): define antithrombotic duration/bleeding strategy, intensify lipid lowering as needed, prescribe cardiac rehabilitation, and schedule early follow-up.

Phase D (post-MI risk mitigation): monitor for heart failure, recurrent ischemia, and medication adherence; intensify cardiometabolic risk reduction.

Phase E (arrhythmia and cardiac arrest readiness): reassess LVEF for ICD candidacy; ensure effective CPR/ALS response systems.

Heart failure risk after acute MI and SGLT2 inhibitors

Heart failure during the vulnerable early post-MI period remains a remarkably dominant cause of ongoing morbidity. The EMPACT-MI clinical trial rigorously evaluated the therapeutic effect of empagliflozin on clinical outcomes in patients determined to be at a high risk of developing heart failure following an acute MI (Butler, et al., 2024: 1455–1466). Concurrently, the DAPA-MI trial thoroughly examined the efficacy of dapagliflozin explicitly in acute MI patients who lacked a prior diagnosis of diabetes or chronic heart failure, focusing on overarching cardiometabolic outcomes. Together, these pivotal studies strongly indicate an actively expanding cardiometabolic strategy within the post-MI clinical setting (James, et al., 2024: EVIDoa2300286).

Guideline-directed long-term therapy: heart failure and secondary prevention

To improve a patient's long-term prognostic trajectory after an MI, the implementation of high-intensity lipid-lowering agents, robust RAAS blockade, beta-blockers, targeted mineralocorticoid receptor antagonists when appropriate, and comorbidity-focused

management strategies is essential. The 2022 AHA/ACC/HFSA heart failure guideline meticulously details guideline-directed medical therapy (GDMT) for ischemic heart failure and firmly supports multidisciplinary follow-up models (Heidenreich, et al., 2022: e895–e1032). In clinical practice, early initiation followed by rapid up-titration (executed strictly as tolerated) is documented to be significantly more effective than delayed, stepwise escalation.

Special phenotype: premature MI

Premature MI represents a distinct phenotype in which underlying genetic predisposition factors (familial hypercholesterolemia, elevated Lp(a)), intense smoking, severe obesity, profound insulin resistance, and states of chronic systemic inflammation play a substantially more prominent etiologic role. A state-of-the-art JACC review heavily emphasizes the need for a thorough etiologic work-up and the immediate deployment of exceptionally aggressive secondary prevention strategies (Rallidis, et al., 2022: 2431–2449).

MINOCA and heterogeneous mechanisms

Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA) encompasses a remarkably diverse array of underlying pathophysiological mechanisms, including spontaneous plaque disruption, severe epicardial coronary spasm, severe microvascular dysfunction, coronary embolism, inflammatory myocarditis, or Takotsubo syndrome. The PROMISE trial formally evaluated the efficacy of applying stratified, mechanism-targeted treatment within the MINOCA patient population (Montone, et al., 2025). The central clinical principle is to systematically investigate and identify the most likely driving mechanism (e.g., utilizing intracoronary imaging, cardiac MRI, or targeted vasoreactivity testing when appropriate) and strictly tailor the subsequent medical therapy accordingly. Contemporary medical reviews summarize

these nuanced diagnostic sets and management strategies in a highly structured manner (Tamis-Holland, et al., 2019: e891–e908).

Sudden cardiac death (SCD): mechanisms, risk assessment, and prevention

Sudden Cardiac Death (SCD) most commonly results directly from the onset of malignant ventricular tachycardia/fibrillation, or advanced bradyarrhythmias. The comprehensive 2022 ESC guideline on ventricular arrhythmias and the prevention of SCD provides crucial updates on Implantable Cardioverter-Defibrillator (ICD) indications, identifies novel risk markers, clarifies the role of targeted catheter ablation, and details optimized pharmacologic options suitable for patients suffering from both ischemic and non-ischemic cardiomyopathies (Zeppenfeld, et al., 2022: 3997–4126).

Basic and advanced life support: time is the key determinant

In out-of-hospital cardiac arrest, the immediate provision of early bystander CPR, early defibrillation, and highly organized advanced life support protocols remain the absolute main determinants of patient survival. The ERC 2021 advanced life support guideline rigorously updates clinical standards for delivering high-quality chest compressions, executing optimal electrical rhythm management, identifying reversible causes (the 4H-4T framework), and managing complex post-resuscitation care (Soar, et al., 2021: 115–151).

Practical 'final recommendations': a rapid checklist

Estimate total risk (SCORE2/SCORE2-OP) and align treatment intensity with risk level.

Address lifestyle systematically: smoking cessation, Mediterranean-style diet, regular exercise, sleep health, and weight management.

Use accurate blood pressure measurement and an early combination-therapy strategy when needed; confirm target attainment during follow-up.

Define an LDL-C strategy: statin -> add non-statin therapy when necessary; in high Lp(a), intensify risk factor management early.

In acute chest pain, use serial ECG + hs-troponin algorithms for rule-out/rule-in; consider CCTA/FFR-CT in appropriate patients.

In chronic CAD, manage symptom control and secondary prevention together; plan revascularization with a Heart Team and evidence-based criteria.

After MI, do not delay GDMT; ensure close follow-up in those at high risk of heart failure and build a comorbidity-focused plan.

Structure SCD risk assessment (LVEF, arrhythmia history, scar burden); do not delay ICD/ablation strategies when indicated.

Key messages

- ACS care is time-critical; reperfusion and appropriate antithrombotic therapy are major determinants of mortality.
- Intensive secondary prevention after discharge (lipids, BP, diabetes/obesity, smoking, rehabilitation) improves long-term outcomes.
- Post-MI heart failure and arrhythmia risks require close surveillance.
- SCD prevention relies on structured risk stratification and ICD strategies in appropriate patients.
- At the population level, early CPR and defibrillation are the most critical links in survival.

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STRUCTURAL HEART DISEASE AND SUDDEN CARDIAC DEATH: MECHANISMS AND CARDIOMYOPATHIES

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Introduction

Sudden cardiac death (SCD) continues to represent a major global public health concern and accounts for a significant proportion of cardiovascular mortality worldwide (Zeppenfeld, et al., 2022: 3997–4126). Although coronary artery disease remains the most frequent underlying cause overall, structural heart diseases constitute a substantial share of non-ischaemic substrates and play a pivotal role across different age groups and clinical contexts (Bagnall, et al., 2016: 2441–2452; Zeppenfeld, et al., 2022: 3997–4126). Structural abnormalities—including cardiomyopathies, valvular heart disease, and congenital heart disease—provide the anatomical and electrophysiological framework that predisposes to malignant ventricular arrhythmias and remain central to contemporary concepts of SCD.

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The relative contribution of structural heart disease varies considerably according to age and population characteristics. In younger individuals, inherited cardiomyopathies and congenital heart disease predominate, whereas degenerative valvular disease and advanced myocardial remodeling are more frequently implicated in older populations (Bagnall, et al., 2016: 2441–2452; Zeppenfeld, et al., 2022: 3997–4126). These patterns underscore the heterogeneity of structural substrates and highlight the importance of disease-specific etiological perspectives in SCD.

Despite differences among disease entities, several pathological features are consistently shared across structural heart diseases. Myocardial fibrosis, ventricular dilation, hypertrophy, and scar formation promote electrical heterogeneity and create a substrate capable of sustaining ventricular arrhythmias (Disertori, Mase, & Ravelli, 2017: 363–372; Gulati, et al., 2013: 896–908) . This chapter examines structural heart diseases as major causes of sudden cardiac death, focusing on cardiomyopathies, valvular heart disease, and congenital heart disease within a contemporary clinical framework.

Cardiomyopathies

Cardiomyopathies represent one of the most important non-ischaemic structural causes of sudden cardiac death and account for a substantial proportion of SCD cases, particularly among younger and middle-aged populations (Bagnall, et al., 2016: 2441–2452; Zeppenfeld, et al., 2022: 3997–4126). These disorders comprise a heterogeneous group of myocardial diseases characterized by structural and functional abnormalities not explained solely by coronary artery disease, hypertension, valvular disease, or congenital defects (Elliott, et al., 2008: 270–276).

Across cardiomyopathy phenotypes, shared structural abnormalities—including myocardial fibrosis, myocyte disarray,

ventricular dilation, and scar formation—create an arrhythmogenic substrate capable of sustaining malignant ventricular arrhythmias (Disertori, Mase, & Ravelli, 2017: 363–372; Gulati, et al., 2013: 896–908). Although the degree of risk varies across specific cardiomyopathy subtypes, these disorders consistently represent major contributors to non-ischaemic sudden death across diverse populations.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is among the most common inherited cardiovascular disorders and remains a leading structural cause of sudden cardiac death, particularly in adolescents, young adults, and athletes (Bagnall, et al., 2016: 2441–2452; Maron, Maron, & Semsarian, 2012: 705–715). It is defined by otherwise unexplained left ventricular hypertrophy, most commonly involving the interventricular septum, and demonstrates substantial phenotypic variability (Elliott, et al., 2008: 270–276).

The structural basis of SCD in HCM is complex and multifactorial. Histopathological hallmarks—including myocyte hypertrophy, myofibrillar disarray, and interstitial fibrosis—contribute to electrical instability and predispose to malignant ventricular arrhythmias (Disertori, Mase, & Ravelli, 2017: 363–372; Zeppenfeld, et al., 2022: 3997–4126). Microvascular dysfunction and ischemia may further promote myocardial injury and fibrosis, thereby increasing arrhythmogenic susceptibility. These abnormalities often coexist with dynamic left ventricular outflow tract obstruction, which can exacerbate hemodynamic stress (Zeppenfeld, et al., 2022: 3997–4126).

Clinical manifestations vary widely, ranging from asymptomatic individuals to those with severe heart failure or malignant arrhythmias. Sudden cardiac death may occur at rest or during exertion and is frequently the initial presentation in younger

patients (Bagnall, et al., 2016: 2441–2452; Maron, Maron, & Semsarian, 2012: 705–715). Structural features such as marked hypertrophy, myocardial fibrosis, and adverse remodeling remain consistently associated with arrhythmic risk across observational studies.

Overall, HCM illustrates the intricate relationship between structural myocardial abnormalities and arrhythmogenesis, reinforcing its central role among cardiomyopathies associated with sudden cardiac death.

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) represents another major structural cause of sudden cardiac death across a wide age spectrum and is characterized by left ventricular dilation and systolic dysfunction in the absence of abnormal loading conditions or significant coronary artery disease. The condition encompasses diverse etiologies—including genetic, inflammatory, toxic, and idiopathic mechanisms—that contribute to the development of an arrhythmogenic myocardial substrate (Elliott, et al., 2008: 270–276; Zeppenfeld, et al., 2022: 3997–4126).

The structural basis of SCD in DCM is closely related to progressive myocardial remodeling and fibrosis. Ventricular dilation, wall thinning, and replacement fibrosis promote conduction delay and electrical heterogeneity, facilitating re-entrant ventricular arrhythmias (Disertori, Mase, & Ravelli, 2017: 363–372; Gulati, et al., 2013: 896–908). Myocardial scar formation, in particular, has been consistently linked with malignant ventricular arrhythmias and sudden death across observational cohorts. Additional contributors such as neurohormonal activation and mechanical stretch may further enhance arrhythmogenic vulnerability in advanced disease stages.

Clinical presentation ranges from asymptomatic ventricular dysfunction to advanced heart failure and life-threatening arrhythmias. Sudden cardiac death may occur at any stage and is not confined to patients with severely reduced ejection fraction. Structural abnormalities, particularly myocardial fibrosis and adverse remodeling, remain central determinants of arrhythmic risk in DCM.

Overall, DCM highlights the close association between progressive myocardial remodeling and arrhythmogenesis, underscoring its importance among structural causes of sudden cardiac death.

Arrhythmogenic Cardiomyopathy

Arrhythmogenic cardiomyopathy (ACM) is an inherited myocardial disorder characterized by progressive fibro-fatty myocardial replacement and represents a major structural cause of sudden cardiac death, particularly in younger individuals and athletes(Corrado, Link, & Calkins, 2017: 61–72; Zeppenfeld, et al., 2022: 3997–4126). Although initially described as a right ventricular disease, ACM is now recognized as a broader spectrum involving the right ventricle, left ventricle, or both.

The structural substrate underlying SCD in ACM includes fibrofatty infiltration, regional wall thinning, and ventricular dilation, all of which contribute to conduction delay and electrical instability. Patchy myocardial involvement further enhances electrical heterogeneity and facilitates re-entrant ventricular arrhythmias (Corrado, Link, & Calkins, 2017: 61–72). Clinically, ACM may manifest with palpitations, syncope, or ventricular arrhythmias, although sudden death may be the initial presentation, particularly in young individuals during exertion.

Overall, ACM exemplifies how progressive structural myocardial changes closely parallel arrhythmic risk in inherited cardiomyopathies.

Restrictive and Infiltrative Cardiomyopathies

Restrictive and infiltrative cardiomyopathies represent less common but clinically relevant structural causes of sudden cardiac death. These conditions are characterized by increased myocardial stiffness, impaired ventricular filling, and progressive atrial enlargement, often with preserved systolic function in earlier disease stages (Elliott, et al., 2008: 270–276; Zeppenfeld, et al., 2022: 3997–4126). Cardiac amyloidosis and cardiac sarcoidosis are among the most frequently implicated disorders in arrhythmia related mortality.

Diffuse myocardial infiltration, fibrosis, and conduction system involvement constitute the primary structural mechanisms underlying SCD in these conditions. In amyloidosis, extracellular protein deposition contributes to restrictive physiology and electrical instability, whereas granulomatous inflammation and scar formation in sarcoidosis are strongly associated with ventricular arrhythmias (Zeppenfeld, et al., 2022: 3997–4126). Although less common than in hypertrophic or dilated cardiomyopathy, infiltrative myocardial disease remains an important etiological consideration in advanced structural heart disease.

Takotsubo Cardiomyopathy

Takotsubo cardiomyopathy (TCM), also known as “broken heart syndrome” or stress-induced cardiomyopathy, is a clinical condition characterized by transient and reversible left ventricular systolic dysfunction, typically triggered by intense emotional or physical stress (Ahmad, Khalid, & Ibrahim, 2026). First described in Japan in 1990, the syndrome derives its name from the characteristic systolic configuration of the left ventricle, which resembles a

traditional Japanese octopus trap known as a takotsubo, marked by apical ballooning with basal hyperkinesis (McKenzie & Bargout, 2025).

Clinically, TCM often mimics acute coronary syndrome (ACS), presenting with chest pain, electrocardiographic changes, and elevated cardiac biomarkers. However, a defining feature is the absence of obstructive coronary artery disease on coronary angiography. Approximately 90% of cases occur in postmenopausal women, and the estimated annual incidence ranges between 15 and 30 cases per 100,000 individuals (Hanmandlu, et al., 2025: e70138).

Pathophysiology and the Brain–Heart Axis

The principal mechanism underlying TCM is believed to be a sudden and excessive surge in circulating catecholamines, particularly epinephrine and norepinephrine (Rossi, et al., 2025: 45857). This catecholamine storm leads to myocardial stunning through several interconnected mechanisms:

Adrenergic Receptor Signaling Switch: Extremely elevated epinephrine levels induce a functional shift in β_2-adrenergic receptor signaling from the stimulatory Gs pathway to the inhibitory Gi pathway. Although this shift may represent a protective mechanism against catecholamine-induced myocyte necrosis, it simultaneously results in profound myocardial contractile depression (McKenzie & Bargout, 2025).

Microvascular Dysfunction: Catecholamine excess may provoke epicardial coronary vasospasm and diffuse microvascular constriction, leading to transient myocardial ischemia and impaired perfusion (McKenzie & Bargout, 2025).

Neurocardiogenic Interaction: Advanced neuroimaging studies have demonstrated transient alterations in the autonomic regulatory networks and stress-processing centers of the brain,

including the limbic system and amygdala, in patients during the acute phase of TCM. These findings support the concept of a brain–heart axis contributing to disease pathogenesis (Huang, et al., 2024: e772).

Risk Factors for Sudden Cardiac Death and Acute Complications

Although historically considered a benign condition, contemporary studies indicate that patients with TCM carry an in-hospital mortality rate of approximately 4–5%, which is comparable to that observed in cohorts with acute coronary syndromes (Hanmandlu, et al., 2025: e70138). The risk of SCD primarily arises from several acute complications:

Life-Threatening Ventricular Arrhythmias: Ventricular tachycardia (VT) and ventricular fibrillation (VF) occur in approximately 4–10% of patients, particularly within the first 24 hours, and represent the leading cause of sudden cardiac death during the acute phase (Rossi, et al., 2025: 45857).

QTc Interval Prolongation: Catecholamine-mediated disturbances in ventricular repolarization frequently result in QTc prolongation. A QTc interval exceeding 490 ms is considered a strong predictor of malignant arrhythmias, including torsades de pointes, and may increase the risk of sudden death (Rossi, et al., 2025: 45857).

Cardiogenic Shock and Hemodynamic Collapse: Cardiogenic shock develops in approximately 6–10% of patients, with a higher incidence observed in individuals with right ventricular involvement (McKenzie & Bargout, 2025).

Left Ventricular Outflow Tract Obstruction (LVOTO): Apical akinesis combined with compensatory basal hyperkinesis may produce dynamic LVOT obstruction, resulting in reduced

cardiac output. In such cases, the administration of inotropic agents can further exacerbate the obstruction (McKenzie & Bargout, 2025).

Acute Mitral Regurgitation: Dynamic mitral regurgitation occurs in 17–25% of patients and significantly increases the risk of hemodynamic instability and mortality (Rudd, et al., 2024: 100797).

Risk Stratification and Long-Term Prognosis

Early risk stratification is essential to prevent sudden cardiac death and optimize clinical outcomes. The InterTAK Diagnostic Score, which incorporates factors such as sex, triggering stressors, and electrocardiographic findings, can assist clinicians in differentiating TCM from acute coronary syndromes (McKenzie & Bargout, 2025). In addition, elevated C-reactive protein (CRP) levels exceeding 33 mg/L at discharge have been identified as an independent predictor of one-year mortality (Faucher, et al., 2025: 1427–1436).

Long-term prognosis in TCM appears less benign than previously assumed. Although left ventricular ejection fraction (LVEF) typically normalizes within weeks, many patients continue to exhibit persistent heart failure–like symptoms, including exercise intolerance and fatigue. Moreover, subtle myocardial dysfunction may persist despite apparent recovery of global systolic function. Longitudinal studies have demonstrated that five-year mortality rates are comparable to those observed in patients with myocardial infarction (Rudd, et al., 2024: 100797).

Management Strategies

Management strategies should be individualized in order to minimize the risk of sudden cardiac death and other complications:

Close Hemodynamic and Rhythm Monitoring: Patients with significant QTc prolongation or markedly reduced LVEF should undergo continuous cardiac monitoring in an intensive care setting

for at least 48–72 hours due to the increased risk of malignant arrhythmias (Hanmandlu, et al., 2025: e70138).

Pharmacological Therapy: Angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs) may improve long-term survival. Although the role of beta-blockers remains debated, they may be beneficial in reducing arrhythmic events and in-hospital complications (Rudd, et al., 2024: 100797).

Avoidance of Catecholaminergic Inotropes: In patients presenting with cardiogenic shock, left ventricular outflow tract obstruction must be excluded before initiating inotropic therapy. If LVOTO is present, vasopressin or phenylephrine may be preferable to catecholamine-based inotropes (Ahmad, Khalid, & Ibrahim, 2026).

Peripartum Cardiomyopathy

Peripartum cardiomyopathy (PPCM) is a life-threatening form of heart failure that develops during the last month of pregnancy or within the first five months postpartum, in the absence of any other identifiable cause of cardiomyopathy. It is characterized by left ventricular systolic dysfunction with a left ventricular ejection fraction (LVEF) below 45%. PPCM is fundamentally a diagnosis of exclusion, and patients typically have no prior history of structural heart disease before the onset of symptoms (De Backer, et al., 2025: 4462–4568).

The global incidence of PPCM is estimated to be approximately 1 case per 2,000 live births, although substantial geographic and ethnic variability exists. For instance, the reported incidence is approximately 1 in 100 births in Nigeriaand 1 in 1,000 births in the United States. PPCM accounts for nearly 60% of pregnancy-associated cardiogenic shock cases, making it one of the

most significant causes of maternal morbidity and mortality worldwide (Seidman, Sathi, & Frishman, 2025).

Pathophysiology

Although the exact etiology of PPCM remains incompletely understood, the currently accepted "two-hit" modelhighlights the interaction between genetic susceptibility and pregnancy-related hormonal injury (Rodriguez Ziccardi & Siddique, 2026).

Hormonal Injury and Oxidative Stress: Increased oxidative stress in cardiomyocytes during late pregnancy activates the enzyme cathepsin D, which cleaves the hormone prolactin into a smaller 16-kDa prolactin fragment. This fragment is highly cardiotoxic, pro-apoptotic, and anti-angiogenic, leading to endothelial dysfunction and microvascular rarefaction, ultimately contributing to myocardial dysfunction and heart failure (De Backer, et al., 2025: 4462–4568).

Angiogenic Imbalance: During the third trimester, the placenta releases elevated levels of soluble fms-like tyrosine kinase-1 (sFlt-1), a circulating inhibitor of vascular endothelial growth factor (VEGF). Excessive sFlt-1 disrupts angiogenic balance and promotes endothelial dysfunction, a mechanism that significantly overlaps with the pathophysiology of preeclampsia (De Backer, et al., 2025: 4462–4568).

Genetic Predisposition: Approximately 15–20% of patients with PPCM carry pathogenic variants in genes associated with cardiomyocyte structural integrity, particularly mutations in the TTN (titin) gene. This observation supports the hypothesis that PPCM may represent a pregnancy-triggered manifestation of an underlying dilated cardiomyopathy phenotype (Goli, et al., 2021: 1852–1862).

Risk Factors for Sudden Cardiac Death and Arrhythmias

During the clinical course of PPCM, SCD represents a significant threat, particularly during the acute phase and in patients with severe left ventricular dysfunction.

Arrhythmogenic Substrate: Catecholamine surges, myocardial inflammation, and myocardial edema may create a substrate conducive to VT and VF (De Backer, et al., 2025: 4462–4568).

Clinical Risk Factors: Several maternal characteristics are associated with increased PPCM risk and consequently a higher likelihood of SCD, including advanced maternal age (>30–35 years), multiple gestation (approximately 2.6-fold increased risk), the presence of preeclampsia or eclampsia (approximately 3.3-fold increased risk), obesity, and African ancestry (Dewi, et al., 2025: 775).

Prognostic Indicators: Severe cardiac dysfunction at presentation strongly predicts adverse outcomes. Specifically, an LVEF below 30–35% and a left ventricular end-diastolic diameter exceeding 60 mm (or >2.7cm/m²) are associated with lower recovery rates and increased mortality risk (Sliwa, et al., 2021: 3094–3102).

Clinical Management and Prevention of Mortality

Early diagnosis and appropriate management are crucial to reducing the risk of sudden cardiac death in PPCM. Diagnostic evaluation typically includes electrocardiography, cardiac biomarkers (particularly BNP or NT-proBNP), and transthoracic echocardiography, which remains the gold standard for diagnosis (Jackson, et al., 2023: 5128–5141).

Pharmacological Therapy: In addition to guideline-directed medical therapy for heart failure, bromocriptine, a dopamine D2 receptor agonist that inhibits prolactin secretion, has

emerged as a disease-specific therapeutic option for PPCM (Sliwa, et al., 2021: 3094–3102).

Device Therapy and Monitoring: Patients with LVEF below 35%, who are considered at elevated risk of sudden cardiac death, may benefit from wearable cardioverter-defibrillators (WCDs) as a temporary protective strategy during the recovery phase (Saltzberg, Szymkiewicz, & Bianco, 2012: 21–27).

Pregnancy Heart Team Approach: Optimal management requires a multidisciplinary Pregnancy Heart Team, typically consisting of cardiologists, obstetricians, and anesthesiologists, to guide treatment decisions and peripartum care.

Subsequent Pregnancies and Risk of Recurrence

Management of future pregnancies in women with a history of PPCM remains challenging. Even in patients whose cardiac function completely recovers (LVEF >50%), the recurrence risk in subsequent pregnancies is approximately 24%. In contrast, women with persistent left ventricular dysfunction face a recurrence risk of approximately 36%, with mortality or heart transplantation rates approaching 10% (Man, et al., 2025: 1009–1025).

Therefore, even after apparent recovery, patients should receive comprehensive counseling regarding recurrence and sudden cardiac death risk, and they should undergo close cardiologic follow-up during and after any future pregnancies.

Left Ventricular Non-Compaction Cardiomyopathy

Left ventricular non-compaction cardiomyopathy (LVNC) is a rare structural myocardial abnormality characterized by prominent trabeculations and deep intertrabecular recesses that communicate directly with the ventricular cavity. The traditional pathogenetic concept attributes LVNC to an arrest in the myocardial compaction process during embryogenesis, which normally occurs between

the 5th and 8th weeks of gestation. According to this model, the developing myocardium fails to undergo the normal transition from a spongy network of trabeculations to a compacted myocardial layer, resulting in the persistence of a highly trabeculated ventricular structure (Martinez-Tittonel, et al., 2025; Z. Zhou, et al., 2025).

However, accumulating evidence suggests that LVNC may not exclusively represent a congenital developmental defect. Similar trabeculated morphologies have been observed in athletes, pregnant women, and individuals with chronic anemia, where increased preload conditions may induce adaptive and potentially reversible myocardial remodeling. This dual nature has led to the recognition that LVNC may represent a morphological phenotype within a broader cardiomyopathy spectrum, rather than a completely distinct disease entity (Martinez-Tittonel, et al., 2025).

Genetic Basis and Phenotypic Heterogeneity

LVNC is genetically heterogeneous, and identifiable pathogenic variants are detected in approximately 30–45% of cases (Lehman, et al., 2025: 39044). The most frequently implicated genes include:

Sarcomeric Genes: Mutations in MYH7, MYBPC3, and TNNT2 are commonly associated with overlapping phenotypes of HCM or DCM (Singh, et al., 2026).

Cytoskeletal Genes: Truncating variants in TTN gene are particularly important and are associated with a higher risk of progressive systolic dysfunction and heart failure (Hershberger, et al., 2018: 281–302).

Ion Channel and Developmental Genes: Mutations in SCN5A and HCN4 are linked to cardiac arrhythmias and conduction abnormalities, whereas genes such as GATA4 and BMP10 are

directly involved in the regulation of embryonic myocardial compaction (Lehman, et al., 2025: 39044).

This genetic diversity contributes to the marked phenotypic variability observed in LVNC, ranging from asymptomatic individuals to patients with severe heart failure and malignant arrhythmias.

Diagnostic Challenges and the Importance of "Injury Markers"

The diagnosis of LVNC primarily relies on transthoracic echocardiography using criteria such as the Jenni or Chin criteria and cardiac magnetic resonance imaging (CMR) with established parameters such as the Petersen or Jacquier criteria (Cuevas, et al., 2022: 529–539).

Nevertheless, reliance solely on morphological criteria, particularly the non-compacted to compacted myocardium ratio (NC/C ratio), presents a substantial risk of overdiagnosis, as increased trabeculation can be observed in up to 20% of healthy individuals and athletes (Singh, et al., 2026).

Recent expert consensus statements emphasize that, particularly in individuals with low pre-test probability, morphological findings should be accompanied by additional "injury markers" to support the diagnosis. These include:

Late Gadolinium Enhancement (LGE): Detected on CMR, LGE indicates myocardial fibrosis, reflecting structural myocardial injury (Jacquier, et al., 2010: 1098–1104).

Reduced LVEF or Abnormal Myocardial Strain: Evidence of impaired systolic function (Martinez-Tittonel, et al., 2025).

Clinical Complications: The presence of malignant arrhythmias or systemic thromboembolic events.

The integration of structural, functional, and tissue-characterization data is therefore essential for establishing a clinically meaningful diagnosis.

Risk Factors for Sudden Cardiac Death and Arrhythmias

The risk of SCD in LVNC is determined less by the degree of trabeculation itself and more by the associated clinical phenotype and myocardial substrate (Z. Zhou, et al., 2025).

Arrhythmogenic Substrate: The characteristic deep intertrabecular recesses may facilitate infiltration of Purkinje fibers into the myocardial wall, resulting in heterogeneous electrical conduction, abnormal depolarization, and delayed repolarization. This environment predisposes patients to VT and VF (Miyake & Kim, 2015: 319–330).

Myocardial Fibrosis (LGE): The presence of late gadolinium enhancement on CMR is among the most powerful independent predictors of malignant arrhythmias, sudden cardiac death, and major adverse cardiovascular events (MACE) (Z. Q. Zhou, et al., 2022: 25).

Thromboembolism: Blood stasis within the deep recesses can promote ventricular thrombus formation, potentially leading to ischemic stroke or systemic embolic events (Huang, et al., 2024: e772).

Risk Stratification and Management Strategies

Careful risk stratification is essential for preventing sudden cardiac death in patients with LVNC. Individuals with isolated LVNC and preserved systolic function generally have a favorable prognosis. In contrast, patients with complex phenotypes, particularly those overlapping with dilated or hypertrophic cardiomyopathy, exhibit substantially higher morbidity and mortality (Singh, et al., 2026).

Implantable Cardioverter-Defibrillator (ICD) Therapy: Current guidelines recommend ICD implantation for LVNC patients with LVEF below 35% or documented malignant ventricular arrhythmias. ICD therapy may also be considered in patients with preserved systolic function who exhibit extensive myocardial fibrosis, unexplained syncope, or a family history of sudden cardiac death (Bennett & Freudenberger, 2016: 5172308).

Anticoagulation Therapy: Lifelong anticoagulation preferably with direct oral anticoagulants (DOACs) is recommended in patients with atrial fibrillation or significantly impaired systolic function (LVEF <40%) to reduce the risk of thromboembolic complications (Huang, et al., 2024: e772).

Conclusion

Left ventricular non-compaction cardiomyopathy represents far more than a simple trabeculated myocardial appearance. When accompanied by systolic dysfunction, myocardial fibrosis, and electrical instability, it constitutes a clinically significant condition associated with an increased risk of sudden cardiac death. Diagnostic approaches should avoid an exclusive focus on morphological criteria; instead, tissue characterization, functional assessment, and genetic risk profiling should guide clinical decision-making and long-term management.

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VALVULAR HEART DISEASE AND SUDDEN CARDIAC DEATH, MECHANISMS, IMAGING, AND PREVENTION STRATEGIES

ARİF ARISOY[1]

Introduction

Sudden cardiac death (SCD) is defined as an unexpected death from a cardiac cause occurring within one hour of symptom onset, or unwitnessed death in a person who was last seen alive and in a stable condition within the preceding 24 hours. It constitutes one of the leading causes of cardiovascular mortality worldwide, accounting for approximately 50% of all cardiac deaths (Nishimura, et al., 2014: 2440–2492; Vahanian, et al., 2022: 561–632).

Valvular heart disease (VHD) represents a heterogeneous group of structural abnormalities that can directly precipitate or contribute to the risk of SCD through various pathophysiological mechanisms. While ischaemic heart disease and primary cardiomyopathies dominate the epidemiology of SCD, VHD is responsible for a clinically significant and often underappreciated proportion of cases. The spectrum ranges from severe aortic stenosis

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(AS) — which alone causes several thousand deaths annually in the general population — to the increasingly recognised arrhythmic mitral valve prolapse (MVP) syndrome (Nkomo, et al., 2006: 1005–1011; Priori, et al., 2016: 176).

With the advent of transcatheter structural interventions, refined imaging techniques including three-dimensional echocardiography and cardiac magnetic resonance (CMR), and evolving risk stratification tools, the cardiologist now has a rich armamentarium to identify high-risk patients and intervene before the occurrence of a fatal arrhythmia. This chapter provides a comprehensive review of the valvular conditions associated with SCD, their arrhythmogenic mechanisms, the role of multimodality imaging in risk stratification, and the medical and interventional strategies available for prevention.

Epidemiology and Pathophysiological Overview

The prevalence of moderate or severe VHD in the general population is approximately 2.5%, rising to over 13% in individuals aged 75 years and above (Nkomo, et al., 2006: 1005–1011). Among patients presenting with SCD or resuscitated cardiac arrest, valvular abnormalities are identifiable in 4–8% of cases, a figure that likely underestimates true prevalence owing to incomplete post-mortem evaluation.

The arrhythmogenic mechanisms linking VHD to SCD are multifactorial and condition-specific. Common pathways include: (1) pressure and volume overload leading to pathological myocardial hypertrophy and fibrosis; (2) mechanical stretch-induced ion channel dysregulation (mechano-electrical feedback); (3) autonomic imbalance, particularly sympathetic activation; (4) ischaemia secondary to increased myocardial oxygen demand and impaired coronary perfusion; (5) conduction system disease resulting from annular calcification or abscess formation in infective endocarditis

(IE); and (6) atrial fibrillation (AF) serving as a substrate for haemodynamic deterioration or thromboembolism (Myerburg & Junttila, 2012: 1043–1052; Nishimura, et al., 2014: 2440–2492; Priori, et al., 2016: 176).

A critical concept in VHD-related SCD is the notion of 'silent' myocardial remodelling that precedes clinically overt decompensation. Subclinical left ventricular (LV) dysfunction, quantified by global longitudinal strain (GLS) and late gadolinium enhancement (LGE) on CMR, identifies a high-risk phenotype before the onset of symptoms or significant LVEF reduction — the two classical thresholds guiding surgical timing in current guidelines (Koskenvuo, et al., 2009: 229–240; Lancellotti, et al., 2013: 611–644; M. S. Maron, et al., 2009: 220–228).

Aortic Stenosis

Mechanisms of SCD

Aortic stenosis is the most common acquired valvular lesion in developed countries and carries the highest absolute burden of SCD among VHD entities (Coffey, Cox, & Williams, 2014: 2852–2861; Genereux, et al., 2016: 2263–2288). The classic triad of symptoms — angina, syncope, and heart failure — each signals a dramatically worsened prognosis with an average survival of 5, 3, and 2 years respectively, and a SCD rate of 15–20% per year in the symptomatic phase.

The principal mechanisms of SCD in AS include: severe LV outflow tract obstruction causing fixed reduced stroke volume; concentric LVH with resultant diastolic dysfunction and elevated filling pressures; subendocardial ischaemia from reduced coronary perfusion pressure; baroreceptor-mediated paradoxical vasodilation during exercise (the substrate for exertional syncope); and ventricular arrhythmias — particularly ventricular tachycardia (VT)

and ventricular fibrillation (VF) — arising from the hypertrophied and fibrotic myocardium (Genereux, et al., 2016: 2263–2288; Pibarot & Dumesnil, 2012: 169–180).

In patients with paradoxical low-flow, low-gradient (LFLG) AS — a clinically challenging subgroup with AVA ≤1.0 cm², mean gradient <40 mmHg, and preserved ejection fraction — the risk of SCD is driven by LV remodelling and concentric geometry rather than outflow obstruction alone, making echocardiographic phenotyping essential (Clavel, et al., 2014: 1202–1213; Pibarot & Dumesnil, 2012: 169–180).

Echocardiographic Assessment

Transthoracic echocardiography (TTE) remains the cornerstone of AS assessment. Key parameters include the aortic valve area (AVA) by continuity equation (severe: ≤1.0 cm²; very severe: ≤0.6 cm²), mean transvalvular gradient (severe: >40 mmHg), peak jet velocity (severe: >4 m/s), and dimensionless velocity index (DVI <0.25) (Lancellotti, et al., 2013: 611–644; Pibarot & Dumesnil, 2012: 169–180).

Beyond stenosis quantification, echocardiographic evaluation must include assessment of LVEF by biplane Simpson's method, relative wall thickness (RWT), LV mass index (LVMI), and importantly, GLS. A GLS value less negative than −18% in the setting of preserved LVEF is a marker of subclinical myocardial dysfunction associated with adverse outcomes. Aortic valve calcium (AVC) scoring by multidetector computed tomography (MDCT) can adjudicate discordant AS grading and provides incremental prognostic information (Clavel, et al., 2014: 1202–1213; Pibarot & Dumesnil, 2012: 169–180).

Stress echocardiography (low-dose dobutamine stress echo, DSE) is valuable in low-flow, low-gradient AS with reduced EF,

distinguishing true severe AS (AVA fails to increase >1.0 cm^2) from pseudo-severe AS (gradient-limited by reduced flow alone). It also assesses contractile reserve, a key prognostic indicator for surgical risk (Lancellotti, et al., 2016: 1191–1229).

Preventive Strategies

There are no proven medical therapies that halt the progression of calcific AS or directly reduce SCD risk in the absence of intervention. Aggressive management of cardiovascular risk factors — particularly hypertension and dyslipidaemia — may slow progression (Genereux, et al., 2016: 2263–2288).

Aortic valve replacement (AVR), whether surgical (SAVR) or transcatheter (TAVR), is the definitive treatment and substantially reduces SCD risk. Current guidelines (ESC 2021, AHA/ACC 2014) recommend intervention for all symptomatic severe AS (Class I) and selected high-risk asymptomatic patients with very severe AS (AVA ≤0.6 cm^2, peak velocity ≥5.5 m/s) or those with declining LVEF (Class IIa) (Nishimura, et al., 2014: 2440–2492; Vahanian, et al., 2022: 561–632).

The landmark PARTNER and CoreValve trials demonstrated mortality equivalence or superiority of TAVR over SAVR in high-, intermediate-, and low-risk surgical patients, expanding access to definitive intervention (Mack, et al., 2019: 1695–1705; Smith, et al., 2011: 2187–2198). Post-TAVR regression of LVH and improvement in GLS are well-documented, correlating with reduced ventricular arrhythmia burden. ICD implantation should be considered in patients with LVEF <35% who are awaiting or ineligible for valve intervention, in keeping with general SCD prevention guidelines (Priori, et al., 2016: 176).

Aortic Regurgitation

Mechanisms of SCD

Chronic severe aortic regurgitation (AR) imposes combined volume and pressure overload on the LV, leading to progressive eccentric hypertrophy, myocardial fibrosis, and ultimately systolic dysfunction. SCD in AR typically results from ventricular arrhythmias in the setting of significantly dilated and fibrotic ventricles (Thornton, et al., 2025: 1829–1839). Acute AR — most commonly from aortic dissection or infective endocarditis — causes sudden haemodynamic collapse without prior LV adaptation, carrying an exceptionally high mortality.

Risk stratification in chronic AR hinges on serial monitoring of LVEF and LV dimensions. An LVEF below 50% or an LV end-systolic diameter (LVESD) exceeding 50 mm (or 25mm/m² indexed to body surface area) identifies patients at heightened risk of irreversible myocardial damage and SCD (Baumgartner, et al., 2018: 110; Nishimura, et al., 2014: 2440–2492).

Echocardiographic and Imaging Assessment

TTE quantification employs vena contracta width (severe: >6 mm), pressure half-time (<200 ms for severe AR), holodiastolic flow reversal in the descending aorta, and the regurgitant fraction (severe: ≥50%). Proximal isovelocity surface area (PISA) provides additional regurgitant volume estimation (Lancellotti, et al., 2013: 611–644; Zoghbi, et al., 2009: 975–1014; quiz 1082–1014).

CMR has emerged as the gold standard for AR quantification, particularly in patients with suboptimal acoustic windows. CMR-derived regurgitant fraction correlates more strongly with outcomes than Doppler-based measurements, and LGE-CMR identifies myocardial fibrosis as an independent predictor of post-surgical

ventricular arrhythmia (Koskenvuo, et al., 2009: 229–240; M. S. Maron, et al., 2009: 220–228).

Preventive Strategies

Vasodilator therapy with ACE inhibitors or dihydropyridine calcium channel blockers may reduce LV afterload in chronic AR, particularly in hypertensive patients, but has not demonstrated mortality benefit as a primary endpoint (Thornton, et al., 2025: 1829–1839).

Surgical AVR is indicated when LVEF falls below 50%, LVESD exceeds 50 mm, or when symptoms develop (Class I, ESC 2021). Pre-emptive surgery in asymptomatic patients with rapidly progressive LV dilation (Class IIa) aims to prevent irreversible fibrosis. Beta-blockade is warranted for rate control when AF supervenes (Baumgartner, et al., 2018: 110; Vahanian, et al., 2022: 561–632).

Mitral Valve Disease

Mitral Valve Prolapse and Arrhythmic SCD

MVP affects approximately 2–3% of the general population and was long considered a benign entity. However, a distinct arrhythmic MVP syndrome has been delineated, characterised by frequent ventricular ectopy, polymorphic VT, and SCD predominantly affecting young women (Basso, et al., 2015: 556–566; Delling & Vasan, 2014: 2158–2170).

The pathological substrate includes mitral annular disjunction (MAD) — a separation between the posterior mitral annulus and the LV posterior wall — papillary muscle fibrosis detectable on LGE-CMR, and mechanical stretch-induced triggered activity in the papillary muscles and basal LV. MAD ≥1 mm on TTE

parasternal long-axis view is a key imaging marker (Basso, et al., 2015: 556–566).

Additional risk features include bileaflet prolapse, QTc prolongation on ECG, T-wave inversions in the inferolateral leads, frequent PVCs (>500/24 hours), and complex ventricular ectopy on Holter monitoring. ICD implantation is appropriate in high-risk MVP patients with unexplained syncope, resuscitated VF, or sustained VT (Basso, et al., 2015: 556–566; Priori, et al., 2016: 176).

Mitral Regurgitation

Severe mitral regurgitation (MR) — whether primary (degenerative) or secondary (functional) — creates chronic LV volume overload with progressive dilatation and eccentric hypertrophy. The incidence of SCD in severe MR is approximately 0.8–1.8% per year, driven by ventricular arrhythmias and sudden decompensation (Enriquez-Sarano, et al., 2005: 875–883; Grigioni, et al., 2008: 133–141).

LV function assessment in MR requires integration of multiple parameters: LVEF by biplane Simpson (surgical threshold <60%), LVESD >40 mm (Class I surgical indication), GLS (<-18% identifies subclinical dysfunction), and volumetric parameters by 3D echocardiography. High-intensity mitral regurgitant jet area, vena contracta >7 mm, and regurgitant volume ≥60 mL/beat indicate haemodynamically severe MR (Enriquez-Sarano, et al., 2005: 875–883; Lancellotti, et al., 2013: 611–644).

Mitral valve repair is preferred over replacement in degenerative MR and is associated with superior preservation of LV function and superior long-term survival. The MitraClip (transcatheter edge-to-edge repair, TEER) demonstrated mortality benefit in functional MR in the COAPT trial, establishing a new

interventional pathway for patients ineligible for surgery (Stone, et al., 2018: 2307–2318).

Mitral Stenosis

Rheumatic mitral stenosis (MS) predisposes to SCD primarily through AF-mediated haemodynamic deterioration, systemic thromboembolism including coronary embolism, and pulmonary hypertension-related right ventricular (RV) failure. Direct ventricular arrhythmia is less prominent than in other valvular conditions (Mangoni, et al., 2002: 90–94).

Severe MS is defined by an MVA ≤1.0cm² (≤1.5cm² in symptomatic patients). Percutaneous balloon mitral commissurotomy (PBMC) is the treatment of choice for suitable anatomy (Wilkins score ≤8) and is highly effective at reducing the arrhythmia burden when AF converts to sinus rhythm post-procedure (Mangoni, et al., 2002: 90–94).

Hypertrophic Cardiomyopathy with Left Ventricular Outflow Tract Obstruction

HCM with LVOTO represents the most common genetic cause of SCD in young athletes and occupies a unique position at the intersection of cardiomyopathy and functional valvular disease. Dynamic LVOTO, caused by systolic anterior motion (SAM) of the mitral valve against the hypertrophied septum and Venturi effect, generates a characteristic left ventricular outflow tract (LVOT) gradient(Authors/Task Force, et al., 2014: 2733–2779; B. J. Maron, et al., 2022: 372–389; Ommen, et al., 2020: e159–e240).

SCD mechanisms include: (1) exercise-induced LVOT gradient augmentation causing syncope and haemodynamic collapse; (2) ischaemia from microvascular dysfunction and intramural coronary artery compression by hypertrophied myocardium; (3) myocardial fibrosis (LGE extent >15% of LV mass

on CMR is an independent SCD risk factor); (4) AF initiating haemodynamic deterioration; and (5) primary VT/VF from fibrotic substrates(B. J. Maron, et al., 2022: 372–389; M. S. Maron, et al., 2009: 220–228; Ommen, et al., 2020: e159–e240).

The SCD-HCM risk calculator (ESC 2023) integrates: family history of SCD, unexplained syncope, maximal wall thickness, LVOT gradient, non-sustained VT, and LA diameter to compute a 5-year SCD risk score. A score ≥6% indicates ICD implantation (Class IIa, Level B). The AHA/ACC 2020 guidelines adopt a more liberal ICD recommendation, particularly for patients with prior resuscitation or unexplained syncope (Authors/Task Force, et al., 2014: 2733–2779; Ommen, et al., 2020: e159–e240).

Septal reduction therapy — surgical myectomy (Morrow procedure) or alcohol septal ablation (ASA) — abolishes resting gradients in >90% of patients and significantly reduces arrhythmia burden. Mavacamten, a selective cardiac myosin inhibitor, has recently demonstrated efficacy in reducing LVOT gradients and symptoms in OBHCM (obstructive HCM), representing a landmark in pharmacological management (B. J. Maron, et al., 2022: 372–389; Nishimura & Holmes, 2004: 1320–1327).

Bicuspid Aortic Valve and Aortopathy

Bicuspid aortic valve (BAV) is the most common congenital cardiac anomaly, affecting 1–2% of the population, and is associated with progressive AS, AR, aortopathy (dilatation and dissection), and a modestly elevated SCD risk (Andreini, et al., 2014: 332–339; Stout, et al., 2019: e81–e192). SCD mechanisms include haemodynamic consequences of valve dysfunction, as described in sections 3 and 4, and acute aortic dissection precipitating SCD from coronary ostial involvement or cardiac tamponade.

Aortic surveillance with TTE and MDCT aortography forms the cornerstone of management. Prophylactic aortic root/ascending aorta surgery is recommended when the maximal aortic diameter exceeds 55 mm, or 50 mm in patients with rapid dilation (>3 mm/year), a family history of dissection, or high-risk coarctation co-existence (Baumgartner, et al., 2018: 110; Vahanian, et al., 2022: 561–632).

Infective Endocarditis

Infective endocarditis (IE) is a life-threatening condition carrying in-hospital mortality of 15–30%, with SCD risk arising from multiple concurrent mechanisms: acute severe regurgitation (haemodynamic emergency); perivalvular abscess extending to the conduction system causing complete heart block or VT/VF; septic embolism to coronary arteries; and embolic stroke (Habib, et al., 2015: 963–1027).

Echocardiography — both TTE and TEE — is pivotal in the diagnosis and surgical decision-making in IE. TEE provides superior sensitivity (>90%) for vegetations, perivalvular extension, fistulae, and prosthetic valve involvement. Three-dimensional TEE delineates complex anatomy and guides surgical planning (Habib, et al., 2015: 963–1027; Pepi, et al., 2010: 461–476).

18F-FDG PET/CT has become an important adjunctive imaging tool in prosthetic valve IE, demonstrating high sensitivity for perivalvular infection and distant embolic foci. Early surgery — ideally within 24–48 hours in acute heart failure — is associated with improved outcomes and is the most effective SCD prevention strategy in active IE (Habib, et al., 2015: 963–1027).

Multimodality Imaging in Risk Stratification

Table 1. Valvular Conditions Associated with SCD: Risk Profile and Key Interventions

Aortic Stenosis (severe)	High	LV outflow obstruction, LVH, ischemia	AVR/TAVR; ICD if EF <35%
Hypertrophic Cardiomyopathy (LVOTO)	Very High	Dynamic obstruction, fibrosis, VT/VF	Septal reduction, ICD implant
Aortic Regurgitation (severe)	Moderate	Volume overload, LV dilation, arrhythmia	AVR when EF <55% or symptomatic
Mitral Regurgitation (severe)	Moderate	LA dilation, AF, LV dysfunction	MV repair/replacement; rate control
Mitral Valve Prolapse	Low-Moderate	Mitral annular disjunction, VT, fibrosis	ICD in high-risk MVP; beta-blocker
Mitral Stenosis (severe)	Low-Moderate	AF-mediated thromboembolism, PHT	PBMC/MVR; anticoagulation
Bicuspid Aortic Valve	Moderate	Aortopathy, stenosis, regurgitation	Surveillance; AVR/aortic surgery
Infective Endocarditis	High	Emboli, abscess, acute regurgitation	Early surgery; hemodynamic support

Cardiac Magnetic Resonance

CMR is the most comprehensive structural imaging tool in VHD. Its primary strengths for SCD risk stratification lie in: (1) LGE-CMR for myocardial fibrosis quantification — the most powerful tissue-level marker of arrhythmic risk; (2) precise volumetric assessment of LV/RV remodelling; (3) four-dimensional flow CMR for accurate quantification of regurgitant volumes and aortic flow Dynamics (B. J. Maron, et al., 2022: 372–389); and T1-

mapping and extracellular volume (ECV) fraction for diffuse fibrosis quantification, complementing focal LGE (Koskenvuo, et al., 2009: 229–240; M. S. Maron, et al., 2009: 220–228).

In MVP, LGE in the papillary muscles and inferobasal wall is the most robust imaging predictor of VT and SCD, identified in up to 45% of patients with arrhythmic MVP. In HCM, LGE >15% of LV mass doubles the 5-year SCD risk. In severe AR and MR, myocardial fibrosis on LGE predicts persistent LV dysfunction even after successful valve surgery (Basso, et al., 2015: 556–566; Koskenvuo, et al., 2009: 229–240; M. S. Maron, et al., 2009: 220–228).

Computed Tomography

MDCT provides high-resolution anatomical data essential for TAVR planning (aortic root dimensions, annular sizing, iliofemoral access), BAV aortopathy surveillance, and assessment of AVC load (Agatston score). AVC scoring by MDCT provides the most accurate AS severity classification in discordant haemodynamic groups (Andreini, et al., 2014: 332–339; Clavel, et al., 2014: 1202–1213). Coronary CT angiography (CCTA) is valuable for ruling out concomitant CAD prior to valve intervention in patients with intermediate pre-test probability.

Nuclear Imaging

SPECT myocardial perfusion imaging identifies reversible ischaemia as a contributing SCD mechanism in AS-related angina. 18F-FDG PET/CT, as noted above, is a key modality in prosthetic and native IE for delineating metabolic activity of infection. Rubidium PET offers superior diagnostic performance for ischaemia in patients with prior calcium scoring suggesting moderate-to-severe CAD (Habib, et al., 2015: 963–1027).

Table 2. ICD Implantation Indications in Valvular Heart Disease

Severe AS + LVEF <35%	IIa	B	Bridge to AVR or TAVR; reassess post-intervention
HCM + ≥1 major risk factor	IIa	B	SCD-HCM risk score ≥6% at 5 years; ICD implant
MVP with MAD + unexplained syncope/VT	IIa	C	High-risk MVP phenotype; EP study may guide decision
Severe AR + LVEF <35% + NYHA III-IV	IIb	C	Consider AVR first; ICD if surgery deferred
Severe MR + LVEF <30% + non-surgical	IIb	C	CRT-D if LBBB present; reassess after MV intervention
IE with recurrent VT post-surgery	I	C	Structural substrate; mandatory ICD evaluation

Table 3. Multimodality Imaging in Valvular SCD Risk Stratification — Comparative Overview

TTE	First-line; widely available	Limited acoustic windows	All valvular lesions; LV function	No
TEE	Superior resolution; intraoperative	Invasive; sedation required	Endocarditis; mitral apparatus	Minimal
CMR	Gold standard volumes; fibrosis (LGE)	Pacemaker/ICD contraindication; cost	AR/MR severity; myocardial fibrosis	No
CT (MDCT)	Aortic root anatomy; calcium scoring	Radiation; contrast; no real-time	TAVR planning; BAV aortopathy	Yes
Nuclear (SPECT/ PET)	Ischemia; inflammation (endocarditis)	Radiation; limited structural detail	Valve-related ischemia; IE activity	Yes

Medical Treatment for SCD Prevention

Beta-Blockers

Beta-adrenergic blockade is a cornerstone of medical management across multiple VHD contexts. In HCM with LVOTO, beta-blockers reduce dynamic gradient augmentation during exercise, suppress triggered arrhythmias, and improve symptoms. In MVP with frequent VPBs, beta-blockade reduces ectopy burden and may lower the risk of fatal arrhythmias. In AS with preserved EF, non-vasodilating beta-blockers (metoprolol, bisoprolol) attenuate sympathetically driven arrhythmia substrates (Authors/Task Force, et al., 2014: 2733–2779; Delling & Vasan, 2014: 2158–2170; B. J. Maron, et al., 2022: 372–389).

Antiarrhythmic Therapy

Amiodarone remains the most effective antiarrhythmic agent for suppressing VT/VF in structural heart disease and VHD-associated arrhythmias. However, its significant extracardiac toxicity profile limits long-term use, and it should be viewed as adjunctive therapy to ICD rather than a substitute. Sotalol offers an alternative in patients without significant LV dysfunction. Disopyramide, with its negative inotropic properties, may reduce LVOT gradients in symptomatic OBHCM (Authors/Task Force, et al., 2014: 2733–2779; Ommen, et al., 2020: e159–e240; Priori, et al., 2016: 176).

Anticoagulation

Anticoagulation with vitamin K antagonists (target INR 2.5–3.5 for mechanical valves) or direct oral anticoagulants (DOACs, for AF in native VHD or bioprosthetic valves beyond 3 months) significantly reduces thromboembolic SCD risk. The AFIRE trial demonstrated the safety of rivaroxaban monotherapy in AF patients with stable coronary artery disease, with relevance to VHD patients with complex indications (Baumgartner, et al., 2018: 110; Butchart, et al., 2005: 2463–2471; Vahanian, et al., 2022: 561–632).

Renin-Angiotensin-Aldosterone System Blockade

ACE inhibitors and ARBs reduce LV afterload and attenuate adverse remodelling in VHD-related LV dilation, particularly in AR and functional MR. Sacubitril/valsartan (ARNI) is beneficial in HFrEF of any aetiology including post-valvular surgery, reducing SCD risk in this population (Baumgartner, et al., 2018: 110).

Novel Pharmacotherapy: Cardiac Myosin Inhibitors

Mavacamten (Camzyos) — an allosteric inhibitor of cardiac myosin ATPase — reduces LVOT gradients, SAM severity, and MR

in OBHCM. The EXPLORER-HCM and VALOR-HCM trials demonstrated its efficacy in reducing gradients and improving functional class. Its impact on the arrhythmia substrate and SCD risk is under active investigation (B. J. Maron, et al., 2022: 372–389).

Interventional and Device-Based SCD Prevention

Implantable Cardioverter-Defibrillator (ICD)

The ICD remains the only proven life-saving device therapy for SCD prevention in structural heart disease. In VHD patients, ICD indications follow general SCD prevention guidelines (LVEF ≤35% after optimised medical therapy for ≥3 months) with VHD-specific modifications detailed in Table 3 (Priori, et al., 2016: 176). Key principles include:

(1) Post-valve surgery reassessment of ICD eligibility after myocardial recovery (typically 3–6 months); (2) The 'bridge to intervention' ICD strategy in symptomatic severe VHD with reduced EF when surgery is planned but delayed; (3) In HCM, the SCD-HCM risk calculator drives ICD threshold decisions, with a 5-year risk ≥6% favoring implantation regardless of LVEF (Ommen, et al., 2020: e159–e240; Priori, et al., 2016: 176).

Subcutaneous ICD (S-ICD) may be preferred in patients without bradycardia or anti-tachycardia pacing needs, avoiding the risks of transvenous leads in patients with prosthetic valves. Remote monitoring of ICD devices allows timely detection of appropriate and inappropriate shocks and arrhythmia trends (Priori, et al., 2016: 176).

Cardiac Resynchronisation Therapy (CRT)

CRT-D (combined CRT and defibrillator) is indicated in patients with VHD-related HFrEF (EF ≤35%), NYHA class II-IV, and LBBB with QRS ≥150 ms (Class I, ESC 2021). In functional

MR secondary to dilated cardiomyopathy, CRT reduces the severity of MR by restoring LV synchrony and improving papillary muscle coordination, potentially deferring or complementing transcatheter MV interventions (Priori, et al., 2016: 176; Stone, et al., 2018: 2307–2318).

Catheter Ablation

Radiofrequency catheter ablation (RFCA) targeting the ectopic foci in the papillary muscles and inferobasal LV wall has demonstrated effectiveness in arrhythmic MVP, particularly in patients with frequent PVCs and drug-refractory VT. Ablation serves as an important adjunct to ICD therapy, reducing appropriate shock burden and improving quality of life (Basso, et al., 2015: 556–566; Priori, et al., 2016: 176).

In HCM with VT, endocardial and epicardial RFCA targeting the fibrotic substrate can suppress VT recurrence, though success rates are variable and operator-experience dependent. Integration of electroanatomical mapping with CMR fibrosis data (LGE-guided ablation) improves target identification and procedural outcomes (B. J. Maron, et al., 2022: 372–389; Ommen, et al., 2020: e159–e240).

Surgical and Transcatheter Valve Interventions as SCD Prevention

Definitive treatment of the underlying valvular lesion remains the most effective SCD prevention strategy in VHD. Surgical AVR in severe symptomatic AS reduces the 5-year SCD risk from approximately 15–20% to <2%. TAVR achieves comparable arrhythmia risk reduction in surgical and high-risk patients with the additional benefit of improved haemodynamic recovery in frail patients (Mack, et al., 2019: 1695–1705; Smith, et al., 2011: 2187–2198).

MV repair in degenerative severe MR restores LV geometry, reduces arrhythmia burden, and prevents irreversible LV dysfunction. TEER with MitraClip/PASCAL devices is an alternative for non-surgical patients. In OBHCM, surgical myectomy (the gold standard) or ASA provide lasting LVOT gradient reduction with proven SCD risk reduction, particularly in centres with high-volume expertise (B. J. Maron, et al., 2022: 372–389; Ommen, et al., 2020: e159–e240; Stone, et al., 2018: 2307–2318).

Wearable Cardioverter Defibrillator (WCD)

The WCD (LifeVest) provides temporary external defibrillation capability in the period between VHD diagnosis (or post-valve surgery) and definitive ICD implantation, particularly when LV dysfunction is severe and recovery uncertain. Current guidelines support WCD use as a bridge to ICD re-evaluation at 3 months in newly diagnosed HFrEF of any aetiology (Priori, et al., 2016: 176).

Integrated Clinical Decision-Making: A Multidisciplinary Approach

Optimal SCD prevention in VHD requires a Heart Valve Team (HVT) approach integrating echocardiographers, interventional cardiologists, electrophysiologists, and cardiac surgeons. The clinical decision pathway should be guided by: (1) accurate grading of VHD severity using multimodality imaging; (2) assessment of LV/RV systolic and diastolic function including subclinical markers (GLS, CMR-ECV, LGE); (3) arrhythmia risk profiling by Holter monitoring, signal-averaged ECG, and electrophysiology study where indicated; (4) evaluation of procedural risk and patient preferences; and (5) guideline-concordant implementation of valve intervention, device therapy, and pharmacological treatment (Baumgartner, et al., 2018: 110; Priori, et al., 2016: 176; Vahanian, et al., 2022: 561–632).

Timing of valve intervention remains the most debated aspect of VHD management. The emerging consensus favours earlier intervention before irreversible subclinical LV remodelling occurs, guided by CMR-fibrosis and GLS data rather than LVEF and LV dimensions alone. This paradigm shift has significant implications for SCD prevention: myocardial fibrosis is the arrhythmogenic substrate, and its prevention through timely valve repair may ultimately be the most effective population-level SCD prevention strategy (Basso, et al., 2015: 556–566; Koskenvuo, et al., 2009: 229–240; M. S. Maron, et al., 2009: 220–228).

Conclusion

Valvular heart disease encompasses a spectrum of conditions that contribute meaningfully to the global burden of sudden cardiac death. Each condition presents distinct arrhythmogenic mechanisms — from the pressure-overloaded fibrotic myocardium in aortic stenosis to the papillary muscle triggered activity in arrhythmic MVP. Modern multimodality imaging, led by echocardiography and CMR, enables early identification of high-risk phenotypes before clinically overt decompensation.

SCD prevention in VHD demands an integrated strategy combining timely valve intervention, guideline-directed ICD therapy, catheter ablation of arrhythmic substrates, and optimised pharmacological management. The evolution of transcatheter technologies has dramatically expanded the treatable patient population, offering SCD risk reduction to patients previously deemed inoperable. Continued advances in CMR-based fibrosis quantification, AI-enhanced echocardiographic strain analysis, and wearable monitoring technologies promise to further refine risk stratification and personalise prevention strategies in the years ahead.

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CONGENITAL HEART DISEASES AND SUDDEN CARDIAC DEATH

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Introduction

Sudden cardiac death (SCD) in young individuals is one of the most devastating events in clinical cardiology, carrying significant psychological, social, and medicolegal consequences. Although coronary artery disease accounts for the majority of SCD events in adults older than 35 years, congenital heart diseases (CHDs) represent a disproportionately important and potentially preventable cause of SCD in children, adolescents, and young adults (Harmon, et al., 2015: 10–19). Advances in surgical techniques and postoperative care over the past five decades have dramatically improved survival for patients born with complex structural cardiac defects; however, this success has created a growing population of adults with congenital heart disease (ACHD) who carry lifelong arrhythmic risk (Khairy, et al., 2010: 1149–1157; Verheugt, et al., 2010: 1220–1229).

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The spectrum of CHDs associated with SCD is broad and encompasses structural anomalies (e.g., tetralogy of Fallot, Ebstein's anomaly, congenital aortic stenosis), coronary artery anomalies (e.g., anomalous left coronary artery from the pulmonary artery – ALCAPA), and primary electrical disorders (e.g., congenital long QT syndrome, catecholaminergic polymorphic ventricular tachycardia – CPVT, and Brugada syndrome) (Silka & Bar-Cohen, 2012: 452–460; Walsh, 2014: 1735–1742). Each entity has a distinct pathophysiological substrate, clinical presentation, and management strategy, yet all share the potential for fatal ventricular arrhythmias (Gatzoulis, et al., 2000: 975–981).

This chapter provides a comprehensive, clinically focused review of the CHDs most commonly implicated in SCD, with particular attention to symptomatology, physical examination, echocardiographic and advanced imaging findings, and both medical and interventional treatment modalities. Risk stratification tools and current guideline recommendations are integrated throughout, and appropriate use of implantable cardioverter-defibrillator (ICD) therapy is addressed for each condition (Priori, et al., 2013: e85–108; Zeppenfeld, et al., 2022: 3997–4126).

Epidemiology and Pathophysiology

CHDs occur in approximately 8–10 per 1,000 live births, making them the most common congenital malformations worldwide (van der Linde, et al., 2011: 2241–2247). The prevalence of ACHD is estimated at more than 1.4 million in the United States alone, and this population is growing at approximately 5% per year (Marelli, et al., 2014: 749–756). SCD represents 15–26% of all deaths in patients with CHD, and is particularly prevalent in those with repaired complex defects such as tetralogy of Fallot (TOF), D-transposition of the great arteries (D-TGA) after atrial switch

procedures, and single-ventricle physiology after Fontan palliation (Gallego, et al., 2012: 109–117; Verheugt, et al., 2010: 872–878).

In population-based studies of SCD in the young (age 1–35 years), CHD accounts for approximately 3–5% of all cases, whereas hypertrophic cardiomyopathy (HCM) and coronary artery anomalies each account for 10–15% (Corrado, et al., 1998: 364–369). In competitive athletes who experience SCD, the proportion attributable to HCM, coronary anomalies, and channelopathies is considerably higher (B. J. Maron, et al., 2009: 1085–1092). The common pathophysiological final pathway to SCD in CHD is ventricular fibrillation (VF), typically initiated by ventricular tachycardia (VT) arising from anatomical substrates (postoperative scar, myocardial hypertrophy, fibrosis) or triggered by acute ischemia, channelopathy-mediated action potential instability, or hemodynamic decompensation (Ghai, et al., 2002: 1675–1680; Khairy, et al., 2004: 1994–2000).

***Table 1**: Overview of Congenital Heart Diseases Associated with Sudden Cardiac Death*

Tetralogy of Fallot	1:3,600 live births	0.2–0.5	VT/VF, RBBB, scar-related re-entry
Hypertrophic Cardiomyopathy	1:500	0.5–1.0 (high-risk: >5)	LVOTO, VF, diastolic failure
Congenital Long QT Syndrome	1:2,000	0.3–0.9	Torsades de pointes → VF
Ebstein's Anomaly	1:20,000	0.1–0.3	WPW, SVT degenerating to VF
Aortic Stenosis (congenital)	1:3,500	0.4–1.0	LVOTO, subendocardial ischemia, VF
Coronary Artery Anomalies	~1% of population	Variable (high during exercise)	Ischemia, VF
D-Transposition (post-Mustard/ Senning)	1:3,500	0.5–1.5	AV block, sinus node dysfunction, VT
Brugada Syndrome (congenital SCN5A)	1:2,000 (higher in Asia)	0.5–2.0 (symptomatic)	VF, nocturnal sudden death
CPVT	1:10,000	2–4 (untreated)	Bidirectional VT, VF (adrenergic)

Symptoms, Clinical Presentation, and Physical Examination

The clinical presentation of CHD associated with SCD risk is heterogeneous. A careful history is paramount: up to 30% of young SCD victims have had prior warning symptoms, most often syncope or near-syncope, that were either unreported or misattributed (Drago, Battipaglia, & Di Mambro, 2018: 397–412). The clinician must distinguish between benign vasovagal syncope and the malignant syncope of arrhythmic or hemodynamic origin. Key red flags include: syncope during physical exertion or emotional stress, preceded by palpitations, in the absence of prodromal symptoms, or

associated with a family history of SCD at a young age (B. J. Maron, Zipes, & Kovacs, 2015: 2343–2349).

Tetralogy of Fallot

TOF is the most common cyanotic CHD, comprising approximately 10% of all CHD (Apitz, Webb, & Redington, 2009: 1462–1471). Prior to repair, children manifest exertional cyanosis, hypercyanotic spells ("Tet spells" – characterized by sudden hyperpnea, cyanosis, and loss of consciousness), and a compensatory squatting posture. Post-repair, the dominant concerns are pulmonary regurgitation (PR) leading to progressive right ventricular (RV) dilation and dysfunction, and macro-reentrant VT arising from the RVOT scar (Therrien, et al., 2005: 779–782). The electrocardiographic finding of QRS duration ≥180 ms on 12-lead ECG is one of the most powerful predictors of SCD in post-repair TOF (Gatzoulis, et al., 1995: 231–237).

Physical examination in repaired TOF reveals a midline sternotomy scar, often a single or softened P2 (indicating residual pulmonic stenosis or absent PV), and a soft diastolic decrescendo murmur (PR). A palpable RV heave and elevated JVP suggest significant RV pressure or volume overload. Detection of a new pansystolic murmur may indicate VSD patch leak or tricuspid regurgitation (Baumgartner, et al., 2021: 563–645).

Hypertrophic Cardiomyopathy

HCM is defined by unexplained left ventricular wall thickness ≥15 mm (or ≥13 mm in first-degree relatives) in the absence of loading conditions (Ommen, et al., 2020: e159–e240). It is the most common inherited cardiac disorder and a leading cause of SCD in athletes under 35 years. The classic symptomatic triad includes exertional chest pain, dyspnea, and syncope. Syncope in HCM may be due to dynamic LVOT obstruction, arrhythmia, or

inappropriate vasodilatory response to exercise (M. S. Maron, et al., 2003: 295–303).

The hallmark physical examination finding is a harsh, crescendo-decrescendo systolic murmur heard best at the left lower sternal border, which increases in intensity with maneuvers that decrease preload (Valsalva, standing) or afterload (amyl nitrite), and decreases with maneuvers that increase preload (squatting, passive leg raise). A bisferiens (double-peaked) carotid pulse may be present with significant LVOT obstruction. A fourth heart sound (S4) reflects reduced LV compliance (Sherrid, et al., 2005: 1251–1258).

Congenital Long QT Syndrome

Congenital LQTS encompasses at least 17 genetic subtypes, the most common being LQTS1 (KCNQ1 mutation, triggered by swimming/exercise), LQTS2 (KCNH2 mutation, triggered by sudden auditory stimuli), and LQTS3 (SCN5A mutation, arrhythmias at rest/sleep) (Wilde & Amin, 2018: 569–579). Clinical presentation may be a seizure-like episode (due to sudden cerebral hypoperfusion during torsades de pointes – TdP), unexplained syncope, or aborted SCD. A family history of unexplained drowning or sudden death in a young family member should raise suspicion. Jervell and Lange-Nielsen syndrome, characterized by LQTS combined with bilateral sensorineural deafness, follows an autosomal recessive pattern and carries particularly high SCD risk (Schwartz, Crotti, & Insolia, 2012: 868–877).

Catecholaminergic Polymorphic Ventricular Tachycardia

CPVT is a highly malignant channelopathy caused predominantly by mutations in the ryanodine receptor gene (RYR2, autosomal dominant) or calsequestrin-2 (CASQ2, autosomal recessive) (Napolitano, et al., 1993). The characteristic feature is exercise- or emotion-triggered bidirectional or polymorphic VT,

which may degenerate to VF. The resting ECG and echocardiogram are typically normal. CPVT should be suspected in any young patient with exertional syncope and a normal resting cardiac evaluation. Untreated, SCD risk may reach 30–50% by age 35 (van der Werf, Zwinderman, & Wilde, 2012: 175–183).

Coronary Artery Anomalies

Anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) is a rare but often fatal defect, accounting for up to 15% of infant SCD. In infancy, symptoms include irritability, diaphoresis during feeding, and failure to thrive; older patients may present with chest pain, exertional syncope, or SCD. Anomalous origin of the right (ARCA) or left (ALCA) coronary artery from the opposite sinus of Valsalva with an interarterial or intramural course is the most common cause of exercise-related SCD in young athletes (Brothers, et al., 2017: 1440–1457). Physical examination is typically unremarkable; a mitral regurgitation murmur may be present in ALCAPA due to papillary muscle dysfunction (Yau, et al., 2011: 204–210).

Table 2: *Symptoms, Clinical Red Flags, and Physical Examination Findings in CHD Associated with SCD*

Tetralogy of Fallot	Exertional dyspnea, cyanosis, squatting, hypercyanotic spells, palpitations	Cyanosis, clubbing, harsh systolic ejection murmur (RVOT), single S2, RV heave
HCM	Exertional syncope, pre-syncope, chest pain, dyspnea, palpitations, family SCD history	Harsh systolic murmur (increases with Valsalva), S4, sustained LV impulse, bisferiens pulse
Congenital LQTS	Seizure-like syncope triggered by emotion/exercise/loud noise, family history of SCD or drowning	Usually normal; sensorineural deafness in Jervell-Lange-Nielsen syndrome
Ebstein's Anomaly	Palpitations, exertional fatigue, cyanosis (variable), tachyarrhythmias	Widely split S1, triple/quadruple rhythm, holosystolic murmur (TR), peripheral cyanosis
Congenital AS	Classic triad: angina, syncope, heart failure; exertional symptoms dominant	Harsh systolic ejection murmur (aortic area), thrill, narrow pulse pressure, delayed carotid upstroke
ALCAPA / ARCAPA	Infantile: irritability, diaphoresis, feeding difficulty; adult: chest pain, syncope, SCD	Mitral regurgitation murmur, signs of heart failure in infants
Brugada Syndrome	Nocturnal agonal respiration, polymorphic VT/VF, fever-triggered syncope	Normal physical exam; fever may precipitate ECG changes
CPVT	Exercise or emotion-triggered syncope/SCD in young patients; family history of SCD	Normal physical exam; normal resting ECG (except in some subtypes)

Echocardiography

Transthoracic echocardiography (TTE) is the cornerstone of diagnostic evaluation in patients with suspected CHD. It is non-invasive, widely available, and provides real-time anatomical and hemodynamic data. Transesophageal echocardiography (TEE) and three-dimensional (3D) echocardiography offer superior resolution

for specific anatomical questions. Speckle-tracking echocardiography (STE) with myocardial strain analysis provides incremental prognostic information beyond conventional parameters (Lancellotti, et al., 2013: 611–644).

Tetralogy of Fallot (Post-Repair)

In post-repair TOF, the primary echocardiographic concerns are the degree of pulmonary regurgitation, RV dilation, and systolic function. RVOT anatomy and residual RVOT gradient should be quantified. The RV end-diastolic volume index (RVEDVi) is a key determinant of timing for pulmonary valve replacement (PVR); CMR-derived RVEDVi >160 mL/m² or RVEF <45% are widely cited thresholds for intervention (Therrien, et al., 2000: 1670–1675). Echocardiographic surrogates include TAPSE, RV FAC, and 3D RV EF. Systemic LV function and residual VSD should also be assessed (Geva, 2011: 9).

Hypertrophic Cardiomyopathy

The echocardiographic hallmark of HCM is asymmetric septal hypertrophy (ASH), with an IVS/PW ratio >1.3. Wall thickness ≥30 mm, diffuse hypertrophy, and the presence of an apical aneurysm are independent SCD risk markers (Authors/Task Force, et al., 2014: 2733–2779). Systolic anterior motion (SAM) of the mitral valve leaflets, typically the anterior leaflet tip engaging the interventricular septum, produces dynamic LVOT obstruction and a posteriorly directed MR jet. Peak LVOT gradient ≥50 mmHg at rest or with provocation (Valsalva/exercise) is considered hemodynamically significant and associated with increased symptoms and mortality (B. J. Maron, et al., 2009: 276–280).

Left atrial (LA) enlargement (LA area >25 cm²) is a risk factor for AF and thromboembolic stroke. Advanced echocardiographic techniques, including myocardial strain (global

longitudinal strain, GLS <–15%), and 3D left atrial volumetry, augment risk stratification. Recent data suggest that LV apical aneurysm, detected in 2–3% of HCM patients, confers particularly high risk for VT and SCD (M. S. Maron, et al., 2008: 1541–1549).

Ebstein's Anomaly

The echocardiographic diagnosis of Ebstein's anomaly rests on the demonstration of apical displacement of the septal tricuspid leaflet (STL) ≥8 mm/m² body surface area (Attenhofer Jost, et al., 2007: 277–285). The elongated, sail-like anterior leaflet, the 'atrialized' portion of the RV, RA enlargement, and the degree of tricuspid regurgitation are key parameters. An interatrial communication (ASD or PFO) is present in approximately 50% of cases and may facilitate right-to-left shunting if right atrial pressure is elevated. Associated Wolff-Parkinson-White (WPW) syndrome, present in 25% of patients, is the principal mechanism of arrhythmic SCD and must be carefully sought on ECG and electrophysiologic study (Sherwin, Triedman, & Walsh, 2013: 1032–1040).

Advanced Cardiac Imaging

Cardiovascular Magnetic Resonance Imaging

Cardiovascular magnetic resonance (CMR) has emerged as the gold standard for volumetric assessment of both ventricles, myocardial tissue characterization, and evaluation of complex CHD anatomy (Fratz, et al., 2013: 51). In post-repair TOF, CMR provides definitive quantification of RV volumes, RVEF, and PR fraction, which are critical for timing PVR. In HCM, late gadolinium enhancement (LGE) is present in approximately 60% of patients and represents replacement fibrosis; LGE extent >15% of LV mass is associated with 2- to 3-fold increased SCD risk and is now formally incorporated into the 2023 HCM guideline risk assessment (Chan, et al., 2014: 484–495).

In suspected arrhythmogenic right ventricular cardiomyopathy (ARVC), CMR reveals RV dilation, wall motion abnormalities, and fatty/fibrous replacement of the RV free wall. T1 mapping, T2-STIR, and extracellular volume (ECV) fraction analysis permit characterization of acute myocarditis, infiltrative disease, and diffuse fibrosis beyond what gadolinium LGE alone can provide (Marcus, et al., 2010: 1533–1541).

Computed Tomography Angiography

Coronary computed tomography angiography (CCTA) is the imaging modality of choice for delineating coronary artery anomalies (Grani, et al., 2017: 471–481). The critical anatomical features that predict ischemic risk include: (1) interarterial course between the aorta and pulmonary artery, (2) acute angle of take-off from the aorta, (3) intramural (intraseptal) course within the aortic wall, and (4) slit-like ostial orifice. CCTA also permits assessment of RVOT anatomy, aortic root dimensions in bicuspid aortic valve disease, and complex three-dimensional CHD anatomy for surgical/interventional planning (Angelini, Velasco, & Flamm, 2002: 2449–2454).

Electrophysiology Study and Ambulatory Monitoring

Invasive electrophysiology study (EPS) with programmed ventricular stimulation (PVS) plays a role in risk stratification for post-repair TOF and selected CHD. In TOF, inducibility of sustained VT at EPS is an independent predictor of clinical VT/VF events and guides ICD decision-making (Alexander, et al., 1999: 1033–1044). For suspected CPVT, exercise treadmill testing (ETT) with target heart rate ≥130 bpm is both diagnostic (reproducing bidirectional/polymorphic VT) and used to assess treatment efficacy. Implantable loop recorders (ILR) are valuable for prolonged rhythm monitoring in patients with unexplained syncope, enabling

correlation between symptoms and arrhythmias over months to years (Steinberg, et al., 2016).

Table 3: *Advanced Imaging Modalities in CHD-Related SCD Risk Stratification*

CMR	ARVC, HCM, myocardial fibrosis/LGE, congenital anomalies, RV/LV volumes, systemic RV	LGE extent (SCD predictor in HCM/ARVC), RVEF, LVEF, tissue characterization	Cost, availability, pacemaker/ICD restrictions
CT Angiography	Coronary artery anomalies (ALCAPA, ARCAPA, high-risk course), aortic root anatomy, RVOT evaluation	Ostial anatomy, intramural course, interarterial course, angle of take-off	Radiation, iodinated contrast, lower temporal resolution
Cardiac Catheterization	Hemodynamic assessment (Qp:Qs, PVR), coronary visualization when CT/CMR inconclusive, electrophysiology study (EPS)	PA pressure, PVR, shunt fraction, LVOT gradient, coronary anatomy	Invasive, radiation, nephrotoxicity
Nuclear Imaging (SPECT/PET)	Myocardial perfusion/viability in complex CHD with suspected ischemia, ALCAPA post-repair	Regional perfusion defects, viability, sympathetic innervation (I-123 MIBG)	Radiation, resolution, limited use in children
Exercise Stress Testing	CPVT provocation, risk stratification in LQTS (QTc response), HCM evaluation, TOF post-repair	Arrhythmia provocation, BP response, QTc prolongation, functional capacity (METS)	Requires careful monitoring; contraindicated in severe AS/HCM with gradient >100 mmHg

Medical and Interventional Treatment

General Principles

Treatment of SCD risk in CHD requires individualized risk stratification followed by a stepwise approach incorporating: (1) correction of reversible hemodynamic substrate, (2) pharmacological suppression of arrhythmic triggers, and (3) device-based therapy (ICD) for primary or secondary prevention in high-risk patients (Silka, et al., 1998: 245–251). The decision to implant an ICD must balance the benefits of protection against SCD against the significant risks of inappropriate shocks, lead complications, and the psychological burden of device therapy, particularly in young patients who may live with an ICD for decades (Yap, et al., 2007: 1854–1861).

Tetralogy of Fallot

Complete intracardiac repair (VSD patch closure + RVOT reconstruction) performed in the first year of life has transformed the prognosis of TOF, with 30-year survival exceeding 85% (Murphy, et al., 1993: 593–599). However, surgical scar tissue in the RVOT creates a substrate for macro-reentrant VT. Pulmonary valve replacement (PVR) for significant PR is recommended to reverse RV dilation and may reduce VT burden. Catheter ablation of the critical isthmus between the VSD patch and the pulmonary annulus (RVOT isthmus) is now a viable adjunct in patients with documented VT (Kapel, et al., 2015: 102–109).

ICD implantation for secondary prevention (post-VF or hemodynamically unstable VT) is a Class I indication. For primary prevention, current guidelines recommend considering ICD in post-repair TOF patients with at least two of the following risk factors: QRS duration ≥180 ms, extensive RVOT scar by CMR/EPS, LV

dysfunction (EF <40%), nonsustained VT on Holter, or inducible sustained VT at EPS (Khairy, et al., 2008: 363–370).

Hypertrophic Cardiomyopathy

Beta-blockers (metoprolol succinate) are the first-line pharmacological therapy for HCM, primarily for symptom relief in patients with LVOTO and exertional symptoms. Verapamil or diltiazem may be substituted in patients who do not tolerate beta-blockers. Disopyramide, a negative inotrope with class IA antiarrhythmic properties, is effective in reducing LVOT gradient and symptoms, particularly in combination with beta-blockers (Sherrid, et al., 2013: 694–702).

Mavacamten, a first-in-class selective cardiac myosin inhibitor, was approved by the FDA in 2022 for obstructive HCM (LVOT gradient ≥50 mmHg) and has demonstrated significant reductions in LVOT gradient, symptom burden, and improvement in exercise capacity in the EXPLORER-HCM and VALOR-HCM trials (Olivotto, et al., 2020: 759–769). Septal myectomy (Morrow procedure) remains the gold standard for refractory obstructive HCM at experienced centers, with surgical mortality <1% and >90% symptom relief (Nishimura, Seggewiss, & Schaff, 2017: 771–783).

ICD implantation for primary prevention in HCM is guided by the ACC/AHA 2020 HCM guideline and the 2022 ESC HCM guideline, which both incorporate multiple risk factors. The ESC approach uses the HCM Risk-SCD calculator (estimates 5-year SCD risk); an ICD is recommended when the 5-year risk is ≥6% (Class IIa), and may be considered at 4–6% (Class IIb) (O'Mahony, et al., 2014: 2010–2020). The ACC/AHA uses a parallel risk factor-based approach: a single major risk factor (prior cardiac arrest, spontaneous sustained VT, SCD in a first-degree relative, LV wall thickness ≥30 mm, unexplained syncope, LV apical aneurysm, LVEF

<50%) supports ICD implantation (B. J. Maron, et al., 2015: 757–764).

Congenital Long QT Syndrome

Beta-blockers are the cornerstone of LQTS therapy, particularly effective in LQTS1 (QTc response to exercise attenuated) and LQTS2, with a significant reduction in symptomatic events and mortality (Moss, et al., 2000: 616–623). Patients must strictly avoid QT-prolonging medications (www.crediblemeds.org provides a regularly updated list) and electrolyte derangements (hypokalemia, hypomagnesemia). Potassium supplementation (K+ target 4.5–5.0 mEq/L) is particularly important in LQTS2 (Schwartz, et al., 2013: 169–180).

Left cardiac sympathetic denervation (LCSD), achieved by video-assisted thoracoscopic resection of the left stellate ganglion and upper thoracic ganglia (T1–T4), is an effective adjunct for patients with recurrent events despite beta-blockers, those intolerant of beta-blockers, or as an adjunct to ICD to reduce shocks (Schwartz, et al., 2004: 1826–1833). ICD is indicated for secondary prevention (prior aborted SCD or syncope despite beta-blockers) and for high-risk primary prevention (LQTS3, QTc >550 ms, Jervell-Lange-Nielsen syndrome, 2:1 AV block) (Ackerman, et al., 2011: 1308–1339).

CPVT

Beta-blockers are the foundation of CPVT therapy, with complete suppression of exercise-induced arrhythmias in approximately 50–60% of patients (Priori, et al., 2002: 69–74). Flecainide, a sodium channel blocker with additional RYR2 channel-blocking properties, has demonstrated synergistic antiarrhythmic efficacy when added to beta-blockers in the CASQ2 trial and observational cohorts (van der Werf, et al., 2011: 2244–2254).

Verapamil has also been used as an adjunct. LCSD provides substantial protection against sympathetically triggered VT/VF in patients with refractory CPVT, and may allow reduction in ICD shocks (De Ferrari, et al., 2015: 2185–2193).

Brugada Syndrome

The ICD is the only proven therapy for prevention of SCD in symptomatic Brugada syndrome (Brugada & Brugada, 1992: 1391–1396). Quinidine (class IA agent) normalizes the Brugada ECG pattern by blocking the transient outward potassium current (Ito) and may reduce VF storm; it is used as a pharmacological alternative in patients who refuse ICD or as adjunct therapy. Isoproterenol infusion is the emergency treatment of choice for VF storm. Epicardial catheter ablation of the arrhythmogenic substrate in the RVOT epicardium has emerged as a promising curative strategy in selected patients with recurrent VF (Nademanee, et al., 2011: 1270–1279).

Fever is a major VF trigger in Brugada syndrome due to temperature-dependent loss-of-function of sodium channels; patients must be counseled to aggressively treat febrile illness with antipyretics. Medications that block sodium channels (class IC antiarrhythmics, tricyclic antidepressants, cocaine) should be avoided absolutely (Antzelevitch, et al., 2005: 429–440).

Table 4: *Summary of Medical and Interventional Treatment Strategies for CHD-Related SCD*

Tetralogy of Fallot	Beta-blockers (for arrhythmia suppression), ACE inhibitors (post-repair RV dysfunction)	Complete repair (VSD closure + RVOT reconstruction), PVR for significant PR, catheter ablation for VT	Secondary prevention; primary: EPS-induced sustained VT, QRSD >180ms + other risk factors

HCM	Beta-blockers (first line), verapamil/diltiazem, disopyramide (LVOT gradient), mavacamten (novel myosin inhibitor)	Septal myectomy (gold standard for refractory LVOTO), alcohol septal ablation, cardiac transplantation	Secondary prevention; primary: ≥1 major SCD risk factor (SCD-HCM Risk Score ≥6%/5-year)
Congenital LQTS	Beta-blockers (mainstay, especially LQTS1/2), avoid QT-prolonging drugs, K+/Mg2+ supplementation	Left cardiac sympathetic denervation (LCSD) for refractory cases or ICD-intolerant patients, gene-specific approaches	Secondary prevention; primary: high-risk (QTc >500ms, prior syncope on beta-blockers, LQTS2/3 with QTc >500ms)
Ebstein's Anomaly	Beta-blockers, AAD for accessory pathway (WPW), anticoagulation if atrial arrhythmias	Cone repair (surgical), TV repair/replacement, accessory pathway ablation (catheter/surgical)	Secondary prevention after VF/sustained VT; symptomatic WPW with rapid conduction
Congenital AS	No specific medical therapy to delay disease progression; diuretics for HF symptoms	Ross procedure/surgical AVR (young patients), balloon valvuloplasty (neonates/infants), TAVI (selected adults)	Post-repair VT/VF survivors; selected with severe residual LVOTO and syncope
Brugada Syndrome	Quinidine (ICD adjunct, fever management), isoproterenol (VF storm), avoid sodium channel blockers/fever	Catheter ablation (epicardial RVOT substrate), subcutaneous ICD vs transvenous ICD	Secondary prevention; primary: spontaneous type 1 pattern + syncope/nocturnal agonal breathing
CPVT	Beta-blockers, flecainide (adjunct), verapamil	LCSD, catheter ablation of VT triggers (limited efficacy), cardiac transplantation (refractory)	Secondary prevention (VF/syncope on beta-blockers); primary: only if high-risk and symptomatic on maximal therapy

Risk Stratification and ICD Decision-Making

Risk stratification for SCD in CHD remains challenging due to the heterogeneity of underlying conditions, the relatively low absolute event rates in individual entities, and the limitations of existing risk models. Shared risk factors across multiple CHD entities include: unexplained syncope (particularly exertional), a family history of premature SCD, significant ventricular hypertrophy or dilation, reduced ventricular ejection fraction, non-sustained VT on ambulatory monitoring, and electrophysiologic inducibility of sustained ventricular arrhythmias (Khairy, et al., 2014: e102–165).

For all CHD patients at potential SCD risk, the following minimum evaluation is recommended: (1) 12-lead ECG (QRS duration, QTc, conduction defects, epsilon waves, delta waves), (2) 24-hour Holter or extended rhythm monitoring, (3) comprehensive echocardiography, (4) CMR with gadolinium when echo is insufficient or tissue characterization is needed, (5) CCTA for coronary anatomy when anomalous origin is suspected, and (6) formal EPS in selected high-risk patients (Balaji, et al., 2014: 576–581).

The subcutaneous ICD (S-ICD) is an attractive option in young CHD patients who do not require pacing, as it avoids endovascular leads; however, careful screening for T-wave oversensing and the absence of a pacing indication are prerequisites (Frommeyer, et al., 2016: e003181). Wearable cardioverter-defibrillators (WCDs) may bridge the gap for patients temporarily at high SCD risk (post-myocarditis, early post-diagnosis, awaiting surgical repair) before definitive ICD decisions are made (Piepoli, 2019: 1463–1465).

Shared decision-making with the patient and family, incorporating realistic assessment of SCD risk versus device-related

complications, quality of life implications, and activity restrictions, is an ethical and practical cornerstone of CHD-SCD management (Greutmann & Tobler, 2012: 171–177). Expert consensus from both the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA) emphasizes multidisciplinary team decision-making at specialized ACHD centers (Stout, et al., 2019: e81–e192).

Special Populations and Emerging Therapies

Athletes with CHD

The management of competitive athletes with CHD who are at SCD risk requires careful application of eligibility recommendations. The 2015 ACC/AHA Task Force Criteria and the European Association of Preventive Cardiology (EAPC) guidelines provide condition-specific guidance (Sharma, Pelliccia, & Gati, 2021: 6–7). Athletes with repaired CHD and no residual hemodynamic lesions, no arrhythmias, and normal ventricular function may generally return to sport, whereas those with HCM, significant obstructive lesions, coronary anomalies with interarterial course, or channelopathies require individualized restriction. High-intensity sports are contraindicated in CPVT, LQTS1, and unrepaired ALCAPA regardless of treatment status (B. J. Maron, et al., 2007: 1643–1455).

Pregnancy and CHD

Women with CHD face increased SCD risk during pregnancy and the peripartum period due to the hemodynamic demands of gestation (30–50% increase in cardiac output, plasma volume expansion). The modified WHO classification of cardiovascular risk in pregnancy stratifies CHD patients from low (WHO I) to very high (WHO IV) risk (Regitz-Zagrosek, et al., 2018: 3165–3241). Patients with HCM, severe obstructive lesions, or prior ICD implantation require specialized preconception counseling, high-risk obstetric

care, and delivery planning at tertiary centers. ICD therapy during pregnancy remains safe, although lead dislodgement with uterine expansion and electromagnetic interference from monitoring equipment are theoretical concerns (Drenthen, et al., 2010: 2124–2132).

Emerging Pharmacological and Gene Therapies

Mavacamten represents a paradigm shift in HCM therapy by targeting the fundamental pathophysiology (excess myosin-actin cross-bridge cycling) rather than simply managing symptoms (Desai, et al., 2022: 95–108). Ongoing trials are evaluating cemdisertib (ATM inhibitor for fibrosis reduction) and gene silencing strategies (antisense oligonucleotides targeting mutant KCNQ1/KCNH2 alleles in LQTS) that may modify disease course rather than merely controlling symptoms or arrhythmias. For CPVT, adeno-associated virus (AAV)-mediated gene replacement therapy targeting RYR2 is in early preclinical stages and may offer future curative potential (Denegri, et al., 2014: 2673–2681).

Conclusion

Congenital heart diseases represent a diverse and clinically important group of conditions associated with significant SCD risk across the lifespan. A thorough understanding of disease-specific pathophysiology, risk markers, and management strategies is essential for the cardiologist managing these complex patients. Careful clinical evaluation – integrating symptom history, physical examination, ECG, echocardiography, and advanced imaging – forms the foundation of risk stratification. Treatment must be tailored to the individual, incorporating pharmacological therapy, timely surgical or catheter-based intervention to address hemodynamic substrate, and judicious use of ICD therapy informed by evidence-based guidelines and multidisciplinary consensus (Warnes, et al., 2008: e143–e263).

As the ACHD population continues to grow, longitudinal surveillance, specialized care in dedicated ACHD centers, and patient education remain cornerstone strategies for preventing premature death in this vulnerable population. Advances in cardiac imaging, genetic testing, and molecular therapies offer increasing hope for more precise risk stratification and potentially disease-modifying interventions in the years ahead (B. J. Maron, et al., 2014: 83–99).

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PRİMARY ELECTRİCAL DİSORDERS

BARIŞ AÇIKEL[1]

Long QT Syndrome

Congenital Long QT Syndrome (LQTS) is an inherited genetic channelopathy characterized by delayed myocardial repolarization, QT interval prolongation, and polymorphic ventricular tachycardia in a structurally normal heart, along with an increased risk of sudden cardiac death (Schwartz & Crotti, 2025; Schwartz et al., 1975). The disease was first described in 1957 by Jervell and Lange-Nielsen in a family with a history of congenital deafness, syncope attacks, QT prolongation on electrocardiography (ECG), and sudden death (Jervell & Lange-Nielsen, 1957). Shortly afterward, Romano (1963) and Ward (1964) reported similar cases not accompanied by deafness (Ward, 1964). Although the autosomal recessive form accompanied by deafness is called "Jervell and Lange-Nielsen syndrome" and the autosomal dominant form without deafness is called "Romano-Ward syndrome," these diseases have been referred to as "Long QT Syndrome" since 1975 (Schwartz et

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al., 1975). Its prevalence in the general population is estimated to be approximately 1:2000. (Schwartz et al., 2009).

Pathophysiology and Genetic Foundations

LQTS is primarily caused by mutations in genes encoding cardiac ion channels. While 17 different LQTS subtypes have been identified to date, three main genetic variants (LQT1, LQT2, and LQT3) are responsible for 75-90% of cases (Schwartz et al., 2009). The main forms of LQTS can be divided into the following categories:

Autosomal dominant LQTS (or Romano-Ward syndrome) involves LQT1-6 and LQT9-16 and is characterized by isolated prolongation of the QT interval.

-LQT1 (KCNQ1 Gene): This is the most common type (40-55% of cases). It causes a decrease (loss of function) in the slow-activated potassium repolarization current (IKs) in the cell membrane. Since this current is particularly activated by sympathetic activation (e.g., during exercise), in the presence of the mutation, the QT interval does not shorten sufficiently when the heart rate increases.

-LQT2 (KCNH2/hERG Gene): It accounts for 30-45% of cases. It leads to loss of function in the rapidly activated potassium current (IKr). This current is the most important component of the 3rd phase of the cardiac action potential.

-LQT3 (SCN5A Gene): It is responsible for approximately 5-10% of cases. By creating gain-of-function in the sodium channel, it increases late sodium influx into the cell (INa), which delays repolarization.

Autosomal dominant LQTS with extracardiac features includes:

- Andersen-Tawil syndrome (ATS or LQT7) is characterized by a long QT interval, prominent U-waves, facial dysmorphisms, and hyper/hypokalemic periodic paralysis. Approximately half of ATS cases are caused by loss-of-function mutations in the Kir2.1 potassium channel encoded by KCNJ2.

- Timothy syndrome (TS or LQT8) combines long QT interval, syndactyly, cardiac malformations, autism spectrum disorders, and facial dysmorphisms. The syndrome results from gain-of-function mutations in the L-type calcium channel alpha subunit encoded by CACNA1C.

Autosomal recessive LQTS include:

- Jervell and Lange-Nielsen syndrome is associated with congenital deafness due to an excessively long QT interval. It results from homozygous or compound heterozygous KCNQ1 or KCNE1 mutations.

- Triadin-associated LQTS represents an overlapping form of LQTS and catecholaminergic polymorphic ventricular tachycardia.

Clinical Findings and Triggers

The clinical spectrum ranges from individuals who remain completely asymptomatic throughout their lives to patients presenting with syncope, seizure-like convulsions, abortive cardiac arrest, or sudden cardiac death (Goldenberg, Zareba, et al., 2008; Moss et al., 1991). Syncope seizures may be accompanied by tonic-clonic movements, and therefore the diagnosis is often confused with epilepsy.

Triggers for cardiac events are genotype-specific:

• LQT1: The vast majority of events (68%) occur during exercise, particularly swimming, with increased sympathetic activity (Wilde et al., 1999).

• LQT2: Patients are highly sensitive to sudden and loud auditory stimuli such as telephone rings or alarm clocks, and events are often triggered by awakenings from rest or sleep due to these sounds. The risk is significantly increased in women during the postpartum period (Seth et al., 2007).

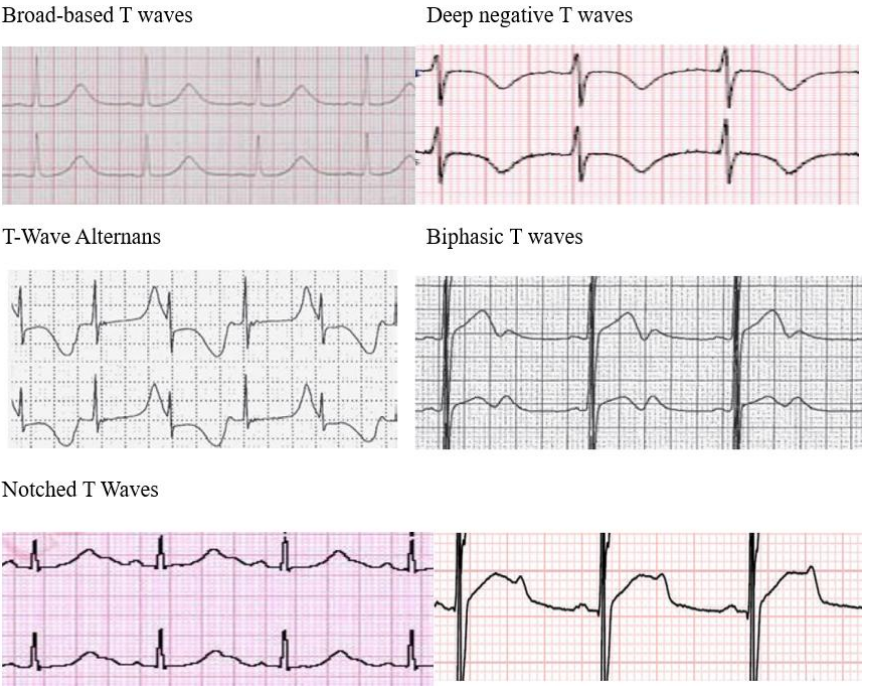
• LQT3: Fatal arrhythmias occur predominantly at slow heart rates, i.e., during rest and sleep (Goldenberg, Zareba, et al., 2008)

Diagnosis

The diagnosis of LQTS is based on a combination of detailed anamnesis and family history, physical examination, 12-lead ECG findings, calculation of the LQTS diagnostic score called the Schwartz score, and genetic testing.

ECG Findings and T-Wave Morphology: In a resting ECG, a QTc interval (Bazett formula) of ≥ 450 ms in men and ≥ 460 ms in women, in the absence of medications or other conditions affecting the QTc interval, increases the likelihood of LQTS. A QTc interval of ≥ 500 ms is indicative of high risk (Krahn et al., 2022). A borderline QTc interval is observed in 30% of patients (up to 470 ms in men and up to 480 ms in women) (Vink et al., 2018). Additionally, the QTc interval may be within the normal range in up to 40% of genotype-positive patients (Hofman et al., 2007). Therefore, further clinical evaluation is critical before diagnosing LQTS. T-wave morphology is helpful in diagnosis: broad-based T waves are seen in LQT1, low-amplitude and bifid T waves in LQT2, and late-onset peaked T waves following a long isoelectric ST segment are seen in LQT3 (Galić et al., 2021; Goldenberg, Zareba, et al., 2008). T-wave alternans, a significant indicator of electrical instability, can be observed in high-risk patients (Galić et al., 2021).

Figure 1: *ECG samples suggestive of long QT syndrome*



Exercise Stress Test and Holter Monitoring: Exercise stress tests are particularly valuable in patients with borderline QTc values. A QTc interval of milliseconds at the 4th minute of the post-exercise recovery phase is highly specific for LQTS (Krahn et al., 2022). Holter monitoring is used to detect nocturnal T-wave changes or bradyarrhythmias.

Genetic Tests: Confirming a diagnosis of high probability LQTS (QTc ≥ 500 ms, LQTS score ≥ 3.5), conducting family screening, establishing a genotype-specific risk profile for the disease, and planning personalized treatment is a standard approach.

Schwartz Score: The Schwartz criteria, one of the most valuable diagnostic tools for clinicians, scores ECG findings, clinical history, and family history. A total score of 0 to 1 indicates a low

probability; 1.5 to 3 points indicates a moderate probability; and 3.5 points or higher indicates a high probability diagnosis of LQTS (Krahn et al., 2022).

Table 1: *Diagnostic Criteria for LQTS (Schwratz score)*

	Points
ECG findings *	
QTc **	
• 450 - 459 msec, in male patients	1
• 460 - 479 msec	2
• ≥480msec	3
QTc ≥480 msec at 4 min of recovery from exercise stress test	1
Torsades de pointes***	2
T-wave alternans	1
Notched T wave in three leads	1
Low heart rate for age †	0,5
Clinical history	
Syncope***	
• Without stress	1
• With stress	2
Congenital deafness	0,5
Family history**	
≥1 Family member with confirmed LQTS	1
Unexplained SCD in immediate family member younger than 30 years of age ‡	0,5

*Patients who are not taking medication and do not have disorders that prolong the QT interval

**The heart rate-corrected QT interval (QTc) is calculated using the Bazett formula

***Torsades de pointes and syncope are mutually exclusive

† Resting heart rate below the 2nd percentile for age

‡ The same family member cannot be counted twice

Risk assessment

Several factors determine the risk of cardiac events in LQTS patients:

- QTc duration: As QTc length increases, the risk of cardiac events increases. A QTc > 500 ms is a major risk factor. (Priori et al., 2003).

-Age and gender interaction: Boys are at higher risk than girls. However, the risk reverses after puberty, and in adulthood, women have a higher risk of cardiac events and sudden death than men (Goldenberg, Moss, et al., 2008; Sauer et al., 2007).

-Syncope: A recent history of syncope or a previous abortive cardiac arrest is the strongest predictor of future fatal events. (Hobbs et al., 2006).

-Mutation Characteristics: Mutation localization in the KCNQ1 and KCNH2 genes (e.g., transmembrane region or pore region mutations) increases the risk of the event. (Moss et al., 2002).

Treatment and Management

LQTS management involves a combination of lifestyle changes, pharmacological treatments, and, when necessary, device/surgical treatments.

Lifestyle and Avoiding Triggers

All patients should absolutely avoid medications that prolong the QT interval (lists can be found at crediblemeds.org). Rapid correction of electrolyte imbalances (hypokalemia, etc.) and avoidance of genotype-specific triggers (such as swimming alone for LQT1, or having an alarm clock by the bedside for LQT2) are essential.

Beta-Blocker Therapy

Beta-blockers are the cornerstone and first-line treatment for LQTS management, including in asymptomatic patients (Al-Khatib et al., 2018). S By inhibiting the increase in sympathetic activity, they significantly reduce the risk of cardiac events. Large-scale studies have shown that not all beta-blockers are equally effective. While non-selective agents such as nadolol and propranolol (especially in LQT1 and LQT2) have very high efficacy, metoprolol, a cardioselective agent, has lower protective efficacy, especially in symptomatic patients, and has been shown to increase the risk of sudden breakthrough events (Chockalingam et al., 2012). Therefore, metoprolol should not be preferred in the treatment of LQTS.

Mexiletine and Other Drugs

Mexiletine is a class Ib sodium channel blocker that suppresses late sodium current. As a genotype-specific targeted therapy in LQT3 patients, it significantly reduces QTc duration and cardiac event rates. Recent data have shown that mexiletine treatment also successfully shortens QTc in some LQT2 patients (Schwartz et al., 1995).

Left Cardiac Sympathetic Denervation (LCSD)

This is a surgical procedure performed on patients who experience syncope despite medical treatment (full-dose beta-blockers), who cannot tolerate medication, or who experience recurrent ICD shocks (Schwartz et al., 2004). This procedure involves the removal of the lower half of the left stellate ganglion and the T2-T4 thoracic ganglia. By reducing the main norepinephrine release in the heart, the procedure results in a long-term reduction of over 90% in cardiac event rates (Dusi et al., 2022).

Implantable Cardioverter Defibrillator (ICD)

ICDs are used in patients with a history of abortive cardiac arrest (secondary prevention), or in those with recurrent syncope despite treatment with beta-blockers and LCSD, a QTc > 500 ms, or a very high-risk profile such as Jervell-Lange-Nielsen syndrome (Zareba et al., 2003). While ICDs can be life-saving, due to risks such as unnecessary shock, infection, and psychological trauma, they should only be considered in high-risk patients for whom optimized medical treatment has been insufficient and for whom there is an indication.

Short QT Syndrome

Short QT Syndrome (SQTS) is a rare, inherited primary arrhythmia syndrome characterized by a shorter than normal corrected QT (QTc) interval, atrial and ventricular arrhythmias in a structurally normal heart, and an increased risk of sudden cardiac death (SCD). It was first described in 2000 by Gussak et al., based on cases with a family history of short QT interval, atrial fibrillation, and sudden death (Gussak et al., 2000). The true prevalence in the population is estimated to be very low, approximately 2.7 per 100,000 (Guerrier et al., 2015).

Genetics and Pathophysiology

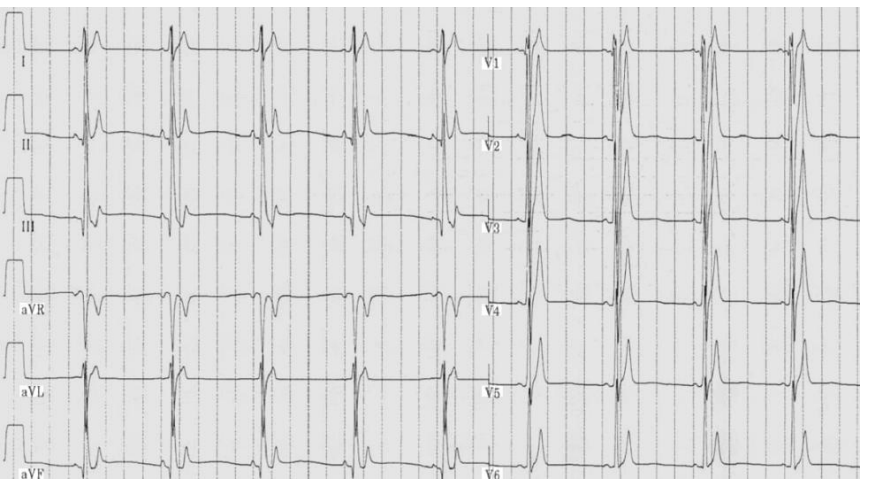
Short QT syndrome arises from a disruption of the currents that generate the cardiac action potential at the cellular level and usually exhibits autosomal dominant inheritance. Currently, 9 different genetic subtypes (SQT1-9) have been identified based on mutations in the genes encoding cardiac ion channels. Most cases are based on an increase in potassium repolarization currents or a decrease in sodium/calcium depolarization currents. This shortening of the action potential and refractory period increases electrical

heterogeneity and repolarization distribution between myocardial cells, creating a predisposition to reentrant arrhythmias.

Potassium Channel Mutations (SQT1, SQT2, SQT3): These are the most common causes of the syndrome and account for the vast majority of cases. Gain-of-function mutations in the KCNH2, KCNQ1, and KCNJ2 genes lead to increased potassium currents in IKr, IKs, and IK1, respectively. These mutations accelerate potassium outflow from the cell, thereby accelerating repolarization and shortening the ventricular action potential duration and refractory period.

Calcium Channel Mutations (SQT4, SQT5, SQT6): These are loss-of-function mutations in the CACNA1C, CACNB2, and CACNA2D1 genes, which encode L-type voltage-gated calcium channels. These mutations reduce calcium influx into the cell and often create a phenotype combined with Brugada syndrome (Antzelevitch et al., 2007).

Figure 2 *Twelve- lead ECGs of patients with SQTS1*



*Very short QTc interval of 250 ms, peaked T waves and PQ depression

Table 2: *List of genetic subtypes associated with short QT syndrome*

Subtype	Gen	Channel	Mechanism
SQTS 1	*KCNH2, HERG*	α-subunit IKr	Gain of function
SQTS 2	*KCNQ1, KvLQT1*	α-subunit IKs	Gain of function
SQTS 3	*KCNJ1, Kir2.1*	α-subunit IK1	Gain of function
SQTS 4	*CACNA1C*	α-subunit IL,Ca	Loss of function
SQTS 5	*CACNB2*	B2-subunit IL,Ca	Loss of function
SQTS 6	*CACNA2D1*	Δ1-subunit IL,Ca	Loss of function
SQTS 7	*SCN5A*	*I*Na (Canonical *α* Subunit)	Loss of function
SQTS 8	*SLC4A3*	Anion Exchanger AE3	Loss of function
SQTS 9	*SCN10A*	α-subunit *I*Na	Loss of function

Clinical Appearance

Patients exhibit a wide clinical spectrum ranging from completely asymptomatic to those experiencing recurrent syncope, palpitations, and sudden cardiac death (Gollob et al., 2011).

Although symptoms usually begin around the age of 20-30, they can occur in any age group (Giustetto et al., 2011). The most common symptom (34%) and the first clinical sign in patients was cardiac arrest (28%), the second most common symptom was syncope due to self-terminating ventricular fibrillation or tachycardia attacks (15-24%) (Giustetto et al., 2011). SQTS has a very strong association with paroxysmal atrial fibrillation, which occurs in young individuals and those without structural heart disease (Hong et al., 2005). The syndrome does not have a specific or uniform trigger; arrhythmic events can occur at rest, during exertion, or with triggers such as loud noises.

Electrocardiographic Features and Diagnosis

SQTS is diagnosed based on characteristic ECG findings, evaluation of the patient's symptoms, and family history. Specific symptoms such as palpitations and fainting, a family history of fainting, sudden death, or atrial fibrillation at a young age should be investigated during the medical history.

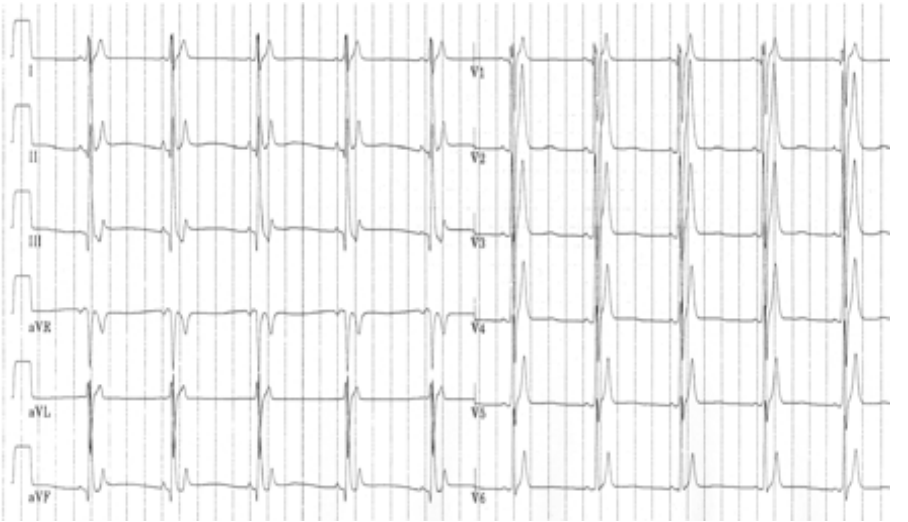
The key ECG features used in diagnosing SQTS are as follows:

Short QT/QTc Interval: A QTc interval of 370 ms or less should raise suspicion. However, in diagnosed patients, these values are usually ≤330-340 ms (Gollob et al., 2011).

Lack of Heart Rate Adaptation: In healthy individuals, the QT interval is significantly prolonged with a decrease in heart rate, but in SQTS patients, this dynamic adaptation mechanism is disrupted. At high heart rates, the calculated QTc may appear normal ("pseudonormal" QTc), but the QTc does not lengthen as the heart rate slows. In patients with congenital SQTS, the variation in the QT interval due to changes in heart rate is less pronounced (Pérez-Riera et al., 2024).

Characteristic T-wave: T waves are typically pointed, long, symmetrical, and narrow-based. Additionally, the "minus-plus T wave" which begins immediately after the QRS complex without a prominent ST segment and shows a negative initial reflection in some derivations, is a valuable ECG finding specific to the syndrome (Pérez Riera et al., 2005).

Figure 3: *A patient with the SQT1 variant*



*The minus-plus T wave signal without ST segment observed in lead III

Shortening of J-Tpeak Range: The time interval between the J-point and the T-wave peak (Tpeak) being less than 120 ms supports the diagnosis (Gollob et al., 2011).

PQ Segment Depression: PQ segment depressions in the inferior and anterior derivations, due to heterogeneous shortening of repolarization in the atria, are seen in a large proportion of patients (Tülümen et al., 2014).

Diagnostic Criteria

In the system developed by Gollob and colleagues, scoring is done based on ECG characteristics, clinical history, family history, and genetic findings (Gollob et al., 2011). According to this system, scores of ≥4 are classified as high probability, 3 as medium probability, and ≤2 as low probability SQTS.

Table 3: *Short QT Syndrome Diagnostic Scoring System*

Category	Diagnostic Criteria	Point
ECG	QTc < 370 msec	1
	QTc < 350 msec	2
	QTc < 330 msec	3
	J point – T peak range (Jp-Tp) < 120 ms	1
Clinical History	History of Sudden Cardiac Arrest	2
	Polymorphic VT or VF	2
	Unexplained Syncope	1
	Atrial Fibrillation (AF)	1
Family History	SQTS diagnosis in a first or second-degree relative	2
	Sudden death of a first or second-degree relative	1
	Sudden Infant Death Syndrome (SIDS)	1
Genetic*	Genotype Positive (Known mutation)	2
	Mutation of undetermined significance in the culprit gene	1

* A minimum score of 1 is required from the electrocardiography section, VT: ventricular tachycardia; VF: ventricular fibrillation.

Treatment and Management

Because SQTS carries a very high mortality risk, rapid risk stratification and treatment of patients is vital.

Implantable Cardiovascular Defibrillator (ICD): For patients with a history of cardiac arrest or documented ventricular arrhythmia/syncope, ICD implantation is the primary first-line treatment (Giustetto et al., 2011). Because the T waves in SQTS patients are narrow and high-amplitude, similar to the QRS complex, the ICD often mistakes T waves for R waves and performs a double

count (T-wave oversensing) (Schimpf et al., 2003). Careful programming is necessary to avoid this situation leading to painful, inappropriate shocks.

Pharmacological Treatment: It is used in very young children who cannot have an ICD implanted due to anatomical limitations, in adults who refuse ICD implantation, or to prevent recurrent inappropriate ICD shocks and atrial fibrillation attacks. In SQTS, pharmacological treatment's long-term efficacy has only been proven in SQTS 1 patients. Quinine/hydroquinidine is the only antiarrhythmic drug proven to be effective in managing SQTS by blocking numerous potassium channels, primarily IKr, but also IKs and IK1, thereby prolonging the QT cycle **(Wolpert et al., 2005)**. Other agents, such as sotalol, amiodarone, or flecainide, have generally been unsuccessful in prolonging the QT interval and preventing fibrillation induction (Giustetto et al., 2011).

J-Wave Syndromes

Brugada syndrome (BrS) and early repolarization syndrome (ERS) are currently studied under the concept of "J Wave Syndromes," which encompasses the pleiotropic expression of J-point abnormalities. Although BrS and ERS affect different regions on electrocardiography (ECG), they are caused by similar genetic disorders and cellular mechanisms (Antzelevitch et al., 2017).

Early Repolarization Syndrome

For many years, early repolarization (ER), characterized by an elevation of the junction between the QRS complex and the ST segment (J-poınt), was considered a normal variant. However, case-control studies conducted since 2008 have shown that this ECG pattern (particularly in the inferior and lateral leads) may be associated with an increased risk of idiopathic ventricular fibrillation and sudden cardiac death (Haïssaguerre et al., 2008; Tikkanen et al.,

2009). The prevalence of ER in the general population varies greatly, ranging from 2% to 31%, depending on the diagnostic criteria used and the population studied (Maury & Rollin, 2013). It is more common in men, young people, African Americans, and athletes who regularly participate in sports (Rollin et al., 2012). The incidence tends to decrease with age, especially in men (Noseworthy et al., 2011). According to the consensus paper published in 2015 (Macfarlane et al.), the presence of an ER pattern on an ECG requires the fulfillment of the following three criteria (Macfarlane et al., 2015);

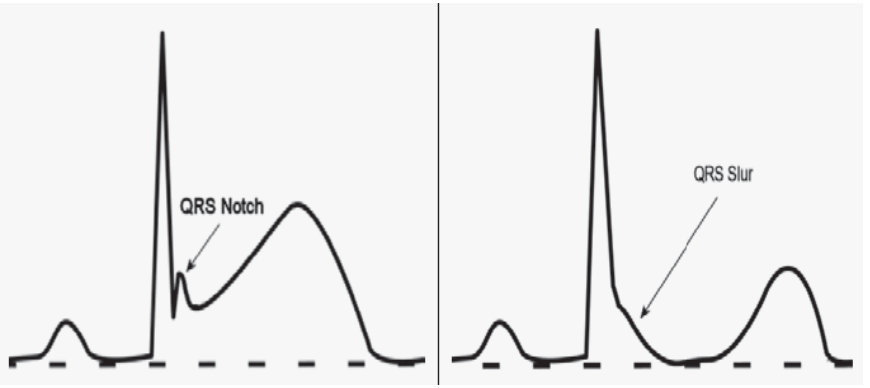
1- A prominent R wave should have a notch or slur at the end of the QRS complex on its descending limb

2- The peak of the notch or the starting point of the deceleration (Jp) must be ≥ 0.1 mV high in at least two consecutive derivations, excluding derivations V1 through V3.

3- The QRS duration should be less than 120 ms.

While it is now known that not all early repolarization is harmless, identifying individuals at risk of sudden cardiac death is critically important. Studies have shown that individuals with J-point elevation > 0.2 mV in inferior leads have a higher risk of cardiac death (adjusted relative risk 2.98) and arrhythmia-related death. This risk is a stronger predictor than other ECG risk markers such as prolonged QT interval or left ventricular hypertrophy (Tikkanen et al., 2009). The slope of the ST segment is also of vital importance in determining risk in patients. Studies show that a horizontal or descending ST segment is associated with a significant arrhythmic risk, whereas an ascending ST segment followed by a positive T wave is generally benign (Tikkanen et al., 2011).

Figure 4: *QRS Notching and Slurring*



Genetic Basis and Pathophysiology

Mutations in genes encoding ATP-sensitive potassium channels, which are densely located in the epicardial region of ventricular cardiomyocytes, play a role in its pathogenesis. In particular, S422L, a gain-of-function mutation in the KCNJ8 gene encoding the Kir6.1 alpha subunit of cardiac channels, has been identified as a novel pathogenicious substrate (Medeiros-Domingo et al., 2010). This mutation causes a significant increase in Kir6.1-current, ranging from 60% to 67%. This increase shortens the action potential duration in the epicardial region, exacerbating transmural repolarization heterogeneity and predisposing to premature repolarization waves in the inferior and right precordial derivations. The detection of the relevant KCNJ8-S422L mutation in patients exhibiting both Brugada syndrome and ERS phenotypes demonstrates the pleiotropic nature of this gene (Medeiros-Domingo et al., 2010).

Treatment

It is not surprising that ERS treatment is similar to BrS treatment, as the underlying mechanisms of the two syndromes are potentially similar. The only proven effective treatment strategy for

preventing sudden cardiac arrest in high-risk BrS and ERS patients is the ICD (Antzelevitch et al., 2017). Quinidine, phosphodiesterase III inhibitors, and isoproterenol have been shown to have a therapeutic effect in preventing or alleviating ERS-related arrhythmias. ICDs are indicated in patients with symptomatic (strong family history of sudden cardiac arrest, electrical storm or syncope, seizures (NAR), and sudden death at a young age (possibly of arrhythmic origin)) or asymptomatic but high-risk ECG patterns (prominent J waves, horizontal/descending ST segment, high dynamism) and a family history of unexplained sudden death at a young age. Quinidine, phosphodiesterase III inhibitors (cilostazol), and isoproterenol have been shown to have a therapeutic effect in preventing or alleviating ERS-related arrhythmias. (Haïssaguerre et al., 2009; Iguchi et al., 2013)

Brugada Syndrome

Brugada syndrome (BrS), first described by Pedro and Joseph Brugada in 1992, is a hereditary canalopathy that, despite not being a structural heart disease, is associated with "coved-type" ST segment elevation in the right chest leads (V1-V3) on the electrocardiogram (ECG) and an increased risk of sudden cardiac death (SCD) (Brugada & Brugada, 1992).

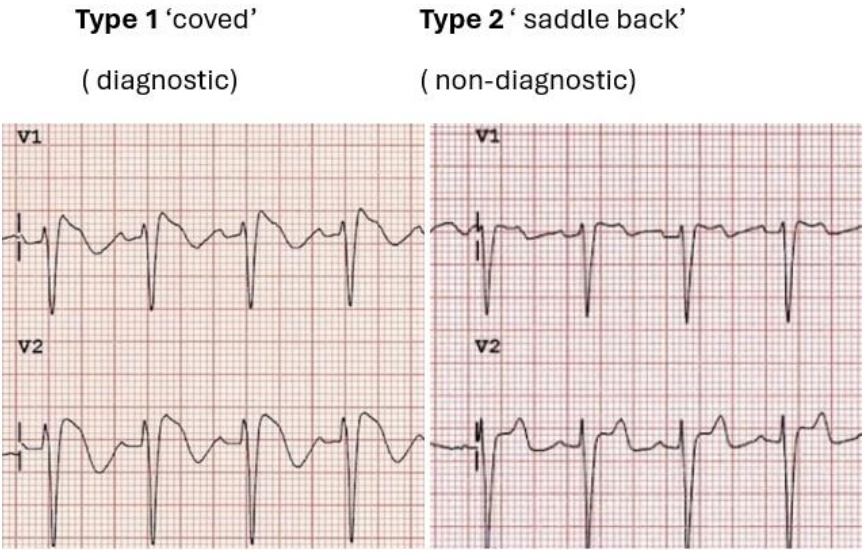
The prevalence of Brugada Syndrome is estimated to be 0.5 per 1000 worldwide; however, this figure is likely an underestimate of the true value due to the wide range of clinical presentations, from asymptomatic forms to sudden cardiac death. The disease shows significant geographical and gender variations; it is particularly more common in Southeast Asia, especially Thailand, and is significantly more frequent in men (Vutthikraivit et al., 2018).

Type 1 (“coved type”) This change is the only diagnostic pattern for BrS. An ST segment elevation of ≥2 mm is seen in at least one of the right precordial derivations (V1 to V3), followed by an r′

wave and a concave or flat ST segment. A negative and symmetrical T wave follows after the descending ST segment crosses the isoelectric line.

Type 2 'saddle back' This ECG anomaly is not diagnostic but suggests BrS. It is seen as an ST segment elevation of ≥0.5 mm (usually ≥2 mm in V2) in at least one of the right precordial derivations (V1 to V3), followed by a convex ST wave. The r' wave may or may not coincide with the J point, but has a slow downward slope. The ST segment is followed by a positive T wave in V2, while it has a variable morphology in V1.

***Figure 5**: Electrocardiographic Patterns in Brugada Syndrome*

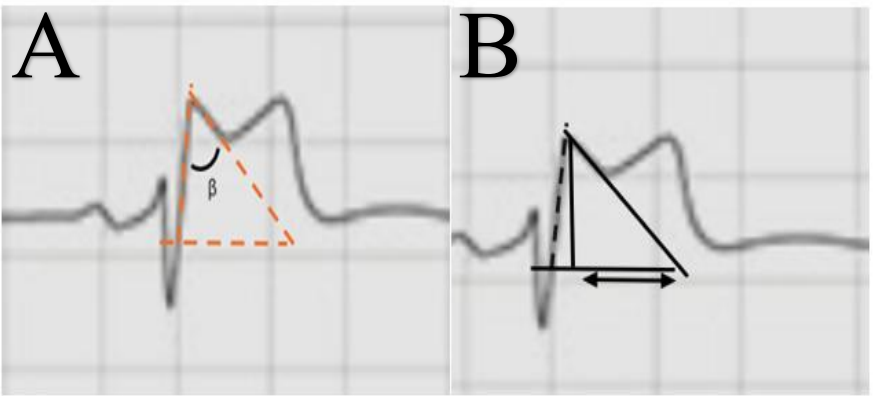


Several additional criteria have been proposed to facilitate the differentiation of type 2 ECGs, which highly demonstrate Brugada syndrome, from other Brugada-like patterns (e.g., athletes, pectus excavatum, and arrhythmic cardiomyopathy).

Angle β: A cutoff value of ≥ 58 degrees provided the best prediction values for conversion to type 1 BrS pattern (Chevallier et al., 2011).

Length of r'-wave base triangle 5 mm below the maximum rise point: A cutoff value of 4 mm (≥ 4 mm in BrS patients) demonstrated 96% specificity and 85% sensitivity (95% positive predictive value and 88% negative predictive value) in distinguishing the BrS ECG pattern in BrS patients from the ECG pattern in healthy individualst (Serra et al., 2014).

Figure 6: *Additional criteria for the diagnosis of Brugada electrocardiogram pattern type 2*



A;the β angle; B: the length of the base triangle

Genetic Basis and Pathophysiology

The disease typically exhibits an autosomal dominant inheritance pattern. Initially thought to be a monogenic and autosomal dominant disease resulting from a single gene mutation, BrS is now considered to be polygenic (or oligogenic), with genetic modifiers, environmental factors, and aging also playing a role. The primary gene definitively associated with Brugada syndrome, and responsible for 20-30% of cases, is the SCN5A gene, which encodes the cardiac sodium channel (NaV1.5) (Le Scouarnec et al., 2015). Current guidelines recommend screening the SCN5A gene as a primary component of clinical routine. The efficiency of DNA testing is significantly higher in familial Brugada cases (44%)

compared to isolated cases (21%) (Hofman et al., 2013). However, next-generation sequencing technologies have shown that genetic variants previously associated with BrS have a fairly high prevalence (10%) in the general population; this suggests that the variants are not always pathogenic and that some may be harmless polymorphisms (Risgaard et al., 2013)

Clinical Diagnosis and Risk Classification

The disease may be completely asymptomatic, or unexplained syncope, nocturnal respiratory irregularities, or sudden cardiac arrest due to polymorphic ventricular tachycardia/ventricular fibrillation may be the first symptom.

ECG and Provocation Tests: If clinical suspicion exists without a spontaneous type 1 ECG pattern (syncope, agonal breathing, aborted sudden death, or just a family history of BrS, or a suggestive but non-diagnostic ECG), pharmacological provocation tests should be performed with sodium channel blockers (intravenous ajmaline and flecainide).

Assessing the risk of arrhythmias in patients with Brugada syndrome is one of the most critical steps in current management.

Table 4: *Genetic Types and Mechanisms of Action Associated with Brugada Syndrome*

Gen	Protein / Ion Channel	Frequency	Mechanism of Action
SCN5A	Nav1.5 (Sodium channel subunit)	%20 - 30	Reduced sodium current (loss of function). This is the most commonly identified core gene universally.
SCN10A	Nav1.8 (Sodium channel subunit)	~%16.7	It reduces sodium current by modulating Nav1.5 expression.
SCN1B, SCN2B, SCN3B	Nav 1, 2, 3 (Sodium duct subunits)	< %1	Disruption of sodium channel activation/inactivation kinetics or surface expression
CACNA1C	Cav1.2 (Calcium channel 1C subunit)	%2 - 12	Decreased inward L-type calcium influx (may overlap with short QT syndrome)
CACNB2	Cav 2 (Calcium channel 2 subunit)	%2 - 12	Decreased calcium channel transport and function
KCND3	Kv4.3 (Potassium channel)	< %1	Increase in transient outward potassium current (Ito) (Gain of function)
KCNE3	MiRP2 (Potassium channel regulator)	< %1	Changes in channel complex stability and potassium current modulation
GPD1L	Glycerol-3-phosphate dehydrogenase 1-like protein	< %1	It indirectly reduces sodium influx by decreasing the cell membrane expression of the sodium channel (Nav1.5)
PKP2	Plakophilin-2 (Desmosomal protein)	Rare	Impaired interaction of Nav1.5 in the intercalary disc (phenotypic overlap with arrhythmogenic cardiomyopathy)

Clinical Factors: The presence of spontaneous Type 1 ECG, a history of previous syncope, and especially a history of abortive

sudden cardiac death (SCD) are the strongest prognostic indicators of worsening condition (Sieira et al., 2017).

Family History:A family history of sudden death has not been shown to significantly increase the future risk of major arrhythmic events in patients. However, a history of SCD in first-degree relatives under the age of 35 has been reported to slightly increase the risk (Sarkozy et al., 2011).

Programmed Ventricular Stimulation (PVS): During electrophysiological studies (EPS), arrhythmia inducibility has prognostic value. Analyses have shown that inducing VT/VF using one or two premature beats is statistically associated with an increased risk of cardiac events (Sroubek et al., 2016).

Risk Skoru: Risk Score: There are scoring models that combine multiple parameters in risk assessment. The scoring in this score developed by Sieira et al (Sieira et al., 2017) is as follows;

- Early familial history of SCD under age 35 (1 point)
- Inducibility in EPS (2 points)
- History of syncope (2 points)
- Sinus node dysfunction (3 points)
- History of abortive SCD (4 points)

Patients with a total score exceeding 2 have a statistically significantly higher probability of experiencing a cardiac event compared to the group with a lower score.

Management and Treatment Approaches

Implantable Cardiovascular Defibrillator (ICD): In high-risk patients, ICD implantation is a primary treatment method proven to improve survival. However, because these devices are implanted at a young age, they also carry significant risks. 18-20% of patients

receive inappropriate shocks, and device-related complications such as lead fractures, displacement, and infections occur in 15% to 22% of cases (Conte et al., 2015). When deciding on prophylactic ICD in asymptomatic patients, the risks of these complications and the potential benefits should be considered. In asymptomatic patients showing a spontaneous type 1 ECG pattern, EPS can be used to evaluate the need for ICD (Priori & Blomström-Lundqvist, 2015)

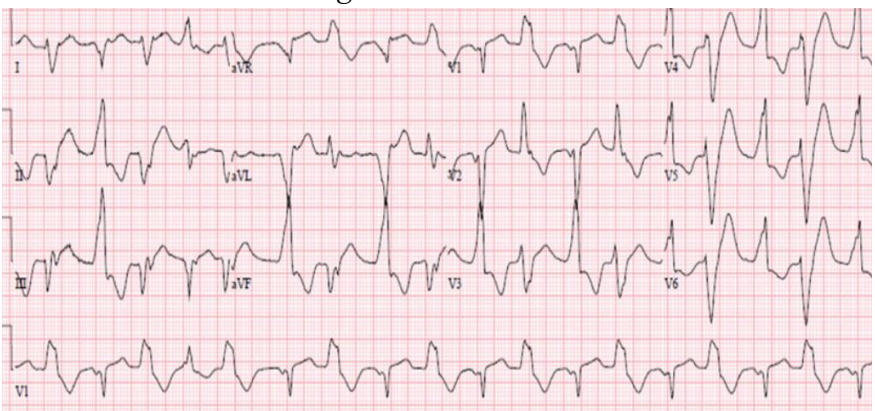
Pharmacological Treatment and Ablation: In addition to ICD therapy, or in patients who cannot/reject ICDs, quinidine, a Class 1A antiarrhythmic, has rendered inducible VF inducible in patients with baseline EPS. It has also been successfully used in electrical storms, in multiple ICD shocks, or as an alternative to ICDs in children (Belhassen et al., 2015; Shenthar et al., 2017). Apart from pharmacological treatment, ajmaline administration has been shown to identify, characterize, and treat the arrhythmic electrophysiological substrate in the RVOT, normalize the ECG, render patients inducible of ventricular arrhythmias, and prevent spontaneous arrhythmic events in symptomatic patients (Pappone et al., 2017; Rudic et al., 2016) . Managing extrinsic triggers is vital. Class 1 antiarrhythmics and some psychotropic drugs, alcohol consumption, and high-calorie meals can increase the risk of ventricular arrhythmias in Brugada patients (Postema et al., 2009). Additionally, since high fever can produce a BrS ECG pattern and trigger arrhythmias, patients are advised to control their fever using antipyretics (Dumaine et al., 1999).

Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare malignant inherited arrhythmia syndrome characterized by bidirectional or polymorphic ventricular arrhythmias that occur with exercise or intense emotional stress in individuals without structural heart disease and with a normal resting

ECG (Leenhardt et al., 1995). The first case was published in 1975, and it was subsequently described as a clinical syndrome in 21 cases in 1955. Its prevalence is estimated to be 1 in 10,000 (Leenhardt et al., 2012). Individuals are usually asymptomatic, but typically present with fainting or sudden cardiac arrest during childhood and young adulthood. In children, it is often misdiagnosed as epilepsy or vasovagal syncope, leading to delayed diagnosis. CPVT occurs equally in men and women, but men have a higher risk of cardiac event (Hayashi et al., 2009). 31% of untreated patients die by the age of 30 (Singh et al., 2019).

Figure 7: *Bidirectional ventricular tachycardia in a patient diagnosed with CPVT*



Genetic Basis and Pathophysiology

Mutations in genes responsible for calcium homeostasis in myocardial cells cause sympathetic stimulation to lead to abnormal Ca2+ release from the sarcoplasmic reticulum. This store overload-induced Ca2+ release (SOICR) creates a net inward flow through overactivation of the sodium-calcium exchanger (NCX), predisposing to delayed afterdepolarization and triggered ventricular ectopia (Kim et al., 2020). The most common mutations are RYR2 (cardiac ryanodine receptor 2) gene mutations, which account for

approximately 60-70% of cases and show autosomal dominant inheritance (CPVT1) (Leenhardt et al., 2012). Autosomal recessive mutations in the CASQ2 (cardiac calsequestrin 2) gene are responsible for 10-15% of cases and lead to a more severe clinical picture (CPVT2). In recent years, other genes that may cause disease, such as triadin (TRDN), calmodulin genes (CALM1, CALM2, CALM3) and Trans-2,3enoyl-CoA reductase-like protein (TECRL), have also been identified (Kim et al., 2020).

Diagnosis and Risk Strategic Planning

In patients with CPVT, increased adrenergic stimulation during exercise testing or isoproterenol infusion typically leads to a progression from sinus tachycardia to ventricular ectopia, followed by polymorphic premature ventricular contractions, and ultimately CPVT attacks. When the adrenergic trigger is removed, these arrhythmias regress and disappear in reverse order (Leenhardt et al., 1995). There are also "silent mutation carriers" in whom the pathological gene is detected but exercise tests are normal; however, this does not mean that these patients will not experience sudden, serious arrhythmic events (Hayashi et al., 2009).

In large studies analyzing risk factors, early diagnosis of the disease, avoidance of beta-blocker therapy, and a history of abortive cardiac arrest were identified as independent predictors of new cardiac and fatal events (Hayashi et al., 2009). In addition, index patients have a higher risk of syncope, cardiac arrest, and treatment failure compared to their carrier relatives (Roston et al., 2015). Patients with positive RyR2 mutations have been shown to experience syncope at a younger age compared to patients without detected mutations but with CPVT (Priori et al., 2002). Gender does not have a clear effect on clinical violence.

Pharmacological and Interventional Treatment Strategies

Lifestyle Changes: It is strongly recommended that all CPVT patients (including asymptomatic genotype-positive individuals) avoid competitive and high-intensity sports, strenuous physical activity, and environments that cause excessive emotional stress. Exercises such as swimming should always be done under supervision (Bergeman et al., 2023).

Beta-Blocker and Flekainid: Beta-blockers are recommended for all symptomatic and pathogenic asymptomatic CPVT mutation patients. Patients should be given beta-blockers that suppress sympathetic hyperactivity at the highest dose they can tolerate (Schneider et al., 2025). Non-selective beta-blockers (especially nadolol and propranolol) are significantly more effective than beta1-selective blockers and should be preferred (Sumitomo et al., 2003). However, complete protection may not be achieved with beta-blockers. Insufficient drug dosage and especially non-adherence to treatment are leading causes of sudden death and arrhythmias. Flecainide, a class Ic antiarrhythmic drug, has the ability to directly block RyR2 receptor-mediated sarcoplasmic reticulum calcium leakage and associated delayed after-depolarization (DADs). It has been shown to suppress exercise-induced ventricular arrhythmias when given in addition to beta-blocker therapy in patients experiencing recurrent syncope or PVT despite beta-blocker treatment (Watanabe et al., 2009).

Implantable Cardiovascular Defibrillator (ICD): ICD implantation is recommended for patients experiencing cardiac arrest, recurrent fainting, or PVT despite optimal medical treatment (Priori et al., 2013). However, despite the frequency of ICD use, the therapeutic benefits of ICDs have remained limited. The physical pain and anxiety caused by ICD shocks can exacerbate arrhythmias by causing a sudden release of catecholamines, leading to successive

shocks in the patient. At least one inappropriate shock was observed in 20.8% of CPVT patients with ICDs, and an arrhythmia storm occurred in 19.6% of these patients, with 1.4% of these patients dying (Roston et al., 2018). Furthermore, because patients are generally young, numerous generator replacements will be required throughout their lifetime, increasing the risk of complications such as infection, lead breakage or displacement, and pocket revisions. Therefore, the decision to implant an ICD should be made carefully, and device settings should be optimized to prevent inappropriate shocks.

Left Cardiac Sympathetic Denervation (LCSD): In high-risk patients who do not respond to drug therapy, it is an effective surgical method used before ICD placement or to stop ICD shocks (Priori et al., 2013). In surgery, removal of the lower half of the left stellate ganglion and the T2-T4 thoracic sympathetic chain halts regional norepinephrine release in the ventricular myocardium. In patients with persistent symptoms despite effective OMT, LCSD can reduce the rate of cardiac events by 92% and the frequency of ICD shocks by 93% (De Ferrari et al., 2015).

Idiopathic Ventricular Fibrillation

Idiopathic ventricular fibrillation (IVF) is a rare cause of sudden cardiac arrest (SCA). It accounts for approximately 5% to 7% of out-of-hospital cardiac arrests in seemingly healthy individuals (Wilde et al., 2022). Idiopathic ventricular fibrillation (IDF) is a diagnosis of exclusion used for cases of sudden cardiac arrest with documented ventricular fibrillation (VF) after ruling out known structural heart disease (myocarditis, cardiac sarcoidosis, arrhythmic right ventricular, hypertrophic and dilated cardiomyopathy, etc.), primary arrhythmia syndromes (Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), long-QT syndrome (LQTS), short-QT

syndrome, and early repolarization syndrome (ERS)), and respiratory, metabolic, and toxicological causes (Wilde et al., 2022). Particularly in recent years, the scope of this umbrella diagnosis has gradually narrowed with the definition of the spectrum of genetic heart diseases (GHD) that predispose to SCA and the emergence of molecular evidence of cardiac channelopathies through postmortem genetic analysis in unexplained sudden cardiac deaths in young people.

Mechanisms and Subtypes

It is currently suggested that IVF can be divided into two main phenotypes that are distinct but sometimes overlap in the same patient: Purkinje-related IVF and IVF associated with microstructural abnormalities (Arnaud et al., 2025).

Purkinje-derived IVF: In IVF patients, it has been found that the first beat initiating the arrhythmia originates from the Purkinje system in up to 93% of cases (Haïssaguerre et al., 2002). Historically, IVF has been known to be triggered mostly by short-coupled ventricular premature complexes leading to the "R-on-T" phenomenon. However, recent studies have shown that in approximately 15-17% of IVF patients, ventricular fibrillation may also be associated with long-coupled premature ventricular complexes that occur after the end of the T wave. These long-coupled PVKs have been found to originate from the left Purkinje system in an overwhelming majority (92%) (Surget et al., 2023).

IVF Associated with Microstructural Abnormalities: Electrophysiological mapping of IVF patients, who were considered structurally normal, revealed localized microstructural areas (usually epicardial) with slow conduction due to fibrosis, steatosis, or cellular pathologies (Haïssaguerre et al., 2002)

Diagnostic Assessment Algorithm

A complete and systematic clinical investigation is essential for diagnosing IVF. The current standard evaluation algorithm should include a detailed personal and family history, 12-lead ECG, blood tests, toxicology screening, echocardiography, coronary angiography, exercise stress test, long-term ECG monitoring, and cardiac magnetic resonance imaging (CMR). CMR plays a critical role in detecting underlying myocardial inflammation or fibrosis in cases with normal echocardiography. Following the exclusion of structural abnormalities, pharmacological provocation tests with sodium channel blockers (ajmaline or flecainide) are of great importance to reveal occult channelopathies (especially Brugada Syndrome) and Purkinje ectopies. The role of electrophysiology studies (EPS) is increasingly important in IVF cases. Further evidence of SCD caused by Wolf-Parkinson-White syndrome and other supraventricular tachycardias (SVT) has also been found (Brembilla-Perrot et al., 2006).

Genetic Basis and Tests

The presence of a positive family history of sudden cardiac death in some IVF patients indicates the existence of a genetic predisposition (Dekker et al., 2006). However, the diagnostic accuracy of routine genetic tests varies between 2% and 17% (Tfelt-Hansen et al., 2023). Approximately 30% of patients tested have variants of uncertain significance (VUS), which makes clinical interpretation extremely complex (Verheul et al., 2023). The main genes associated with IVF are: DPP6, CALM1, RYR2, DSP, TTN, FKTN, TRPM4, MYH7, ANK2, CACNA1C, DES and IRX3 (Arnaud et al., 2025).

Since the use of broad gene panels increases the rate of VUS without increasing the rate of finding pathogenic variants, it is important that genetic test results are carefully interpreted by a

multidisciplinary team of cardiologists and geneticists, and that intrafamily segregation analyses are performed.

Treatment and Management Strategies

In IVF patients, implantable cardioverter defibrillator (ICD) implantation is the standard and primary treatment method for secondary prevention (Zeppenfeld et al., 2022). Pharmacological treatment is limited; beta-blockers and calcium channel blockers are generally ineffective. However, quinidine and isoproterenol are effective in preventing recurrent VF attacks (Belhassen, 2024). Quinidine is indicated in cases of frequently recurrent ventricular fibrillation or in cases of rejection of ICD implantation.

Another option gaining increasing prominence in preventing ICD shocks and arrhythmia recurrences is catheter ablation. Ablation allows for the targeted elimination of Purkinje ectopies (often around the moderator band, pseudotendons, or papillary muscles) or epicardial/endocardial microstructural areas that initiate arrhythmias, and offers high long-term success rates (Duchateau et al., 2023).

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IDENTIFICATION OF INDIVIDUALS AT RISK FOR SUDDEN CARDIAC DEATH

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Introduction and Epidemiological Fundamentals

Sudden cardiac death (SCD) is defined as an unexpected natural death occurring within 1 hour of the onset of acute symptoms in individuals who appear clinically healthy or who have a stable, known cardiac pathology. Unwitnessed cases where the individual was seen in good health within the previous 24 hours are also included in this definition. SCD remains one of the most critical challenges in contemporary cardiovascular medicine. Epidemiologically, the burden of this condition is often expressed in the literature by the "Rule of 50s": SCD accounts for 50% of all cardiovascular-related deaths(Primorac et al., 2021); and in approximately 50% of cases, it presents as the first clinical manifestation of an underlying, concealed cardiac pathology (Li et al., 2024).

In the general population, the annual incidence of SCD ranges from 42 to 95 cases per 100,000 individuals (Deo & Albert,

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2012). This rate shows an exponential increase with age (Magi et al., 2017). While it is at very low levels of 1 to 5 per 100,000 during childhood (Magi et al., 2017), it exceeds 200 per 100,000 in the eighth decade of life (Basso et al., 2017). In individuals aged 35 and older, the primary etiology is coronary artery disease (CAD), accounting for approximately 80% of cases; ventricular fibrillation (VF) developing secondary to acute myocardial ischemia is the main mechanism of death in this demographic.

In contrast, the epidemiological picture is entirely different for young individuals under the age of 35 and active athletes. Since CAD is rare in this cohort, cardiomyopathies (heart muscle diseases) and primary electrical diseases (channelopathies) predominate (Abbas et al., 2023). Although traditional cardiovascular risk factors successfully predict overall morbidity at the population level, they are inadequate for identifying the precise risk of acute cardiac arrest at an individual level (Estes, 2007). Consequently, modern risk stratification approaches focus on the dynamic interaction of the cardiac substrate, transient arrhythmic triggers, and genetic modulators (Chugh et al., 2008; Obrová et al., 2021).

Family History, Genetic Predisposition, and Molecular Autopsy

A comprehensive family history is one of the strongest clinical predictors in determining SCD risk, especially for identifying hereditary cardiovascular diseases in younger populations. The risk of mortality and morbidity increases dramatically among the first-degree relatives of early-age SCD victims. If a family has a history of sudden death before age 35, the general cardiovascular disease risk (standardized incidence ratio, SIR) for first-degree relatives under 35 increases by 3.5 times. This risk escalates to extraordinary levels for specific pathologies, increasing approximately 6-fold for ischemic heart diseases, 18-fold for cardiomyopathies, and 19-fold for fatal ventricular arrhythmias.

Therefore, systematic clinical and genetic cascade screening for individuals with a family history of unexplained sudden death is designated as a Class I recommendation in current clinical guidelines.

Traditional autopsy methods are often insufficient to clarify the etiology of channelopathies, as these conditions do not present macroscopic or microscopic structural defects. Current data indicates that standard autopsies fail to detect an underlying pathology in approximately 40% of sudden unexplained deaths (SUD) in the young. In such scenarios, a "molecular autopsy"—which involves the post-mortem examination of the deceased's isolated DNA—is heavily utilized. Next-Generation Sequencing (NGS) technologies enable the accurate decoding of the genetic origins of fatal arrhythmias. This advanced approach facilitates pre-symptomatic diagnosis in at-risk, asymptomatic family members and prompts life-saving interventions, such as the prophylactic implantation of an implantable cardioverter-defibrillator (ICD).

Risk Stratification in Cardiomyopathies

Historically, the primary parameter used to determine the indication for a prophylactic ICD in cardiomyopathy patients was the left ventricular ejection fraction (LVEF). However, milestone studies conducted on non-ischemic patients with an LVEF $\leq$35% proved that relying solely on this mechanical parameter is largely insufficient (Oginosawa, 2022). Current European Society of Cardiology (ESC) guidelines have advanced far beyond isolated LVEF assessment, firmly positioning genetic testing and the detection of myocardial fibrosis (scar tissue) via Cardiovascular Magnetic Resonance (CMR) imaging at the core of the risk assessment process.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is characterized by asymmetric myocardial hypertrophy and cellular disarray caused by genetic mutations. To accurately evaluate the necessity of a prophylactic ICD, the HCM Risk-SCD Calculator was developed in 2014(Jordà & García-Álvarez, 2018). This Bayesian statistical model integrates seven core clinical parameters: age, maximum left ventricular wall thickness, left atrial diameter, maximum LVOT gradient, family history of SCD, unexplained syncope, and episodes of non-sustained VT (NSVT). Based on the algorithm's output, a 5-year absolute SCD risk of <4% indicates low risk, 4–6% indicates intermediate risk (Class IIb), and ≥6% indicates high risk (Class IIa). Furthermore, 2024 meta-analyses confirmed that late gadolinium enhancement (LGE) detected on CMR increases SCD risk approximately 5-fold. An LGE extent exceeding ≥10% of the left ventricular mass acts as a major risk modifier (Todiere et al., 2019).

Dilated Cardiomyopathy and Cardiac Sarcoidosis

The 2022 ESC Guidelines significantly expanded ICD indications for dilated cardiomyopathy (DCM) patients to address the fundamental limitations of the LVEF-only system. For a DCM patient with a reduced LVEF between 35% and 50% to qualify for prophylactic ICD implantation, at least two of the following four risk factors must be present: unexplained syncope, LGE on CMR, inducible sustained monomorphic VT during an Electrophysiological Study (EPS), or the presence of high-risk pathogenic gene mutations. In patients diagnosed with cardiac sarcoidosis, an LGE extent exceeding ≥9.9% of the total left ventricular mass is a strong, independent indication for an ICD, as it increases the 5-year sudden death risk to 21.5% (Pöyhönen et al., 2024).

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetic disease linked to desmosomal protein mutations, causing progressive fibrofatty replacement of the myocardium. The "Exercise Paradox" is highly prominent in this condition; engaging in competitive sports profoundly increases mechanical wall stress, simultaneously accelerating phenotypic disease progression and triggering lethal arrhythmias (Ruwald et al., 2015; Zorzi et al., 2018). The ARVC 5-Year Risk Calculator (v3.0) quantitatively evaluates the percentage risk of a first major arrhythmic event by processing age at diagnosis, sex, recent cardiac syncope, number of T-wave inversions (TWI), 24-hour PVC burden, and right ventricular ejection fraction (RVEF).

Primary Electrical Diseases

Channelopathies are arrhythmic syndromes where the heart is structurally and macroscopically normal, but cellular-level ion channel mutations (sodium, potassium, or calcium) cause severe myocardial repolarization or depolarization abnormalities.

Long QT Syndrome (LQTS): Characterized by QTc interval prolongation on the ECG. Arrhythmic triggers vary distinctly by genotype: exercise (especially swimming) in LQT1, sudden auditory stimuli and emotional stress in LQT2, and sleep or profound bradycardia in LQT3. The 1-2-3 LQTS Risk Calculator used in clinical risk stratification analyzes QTc duration, genotype, sex, history of syncope, and beta-blocker therapy status (Wang et al., 2022).

Brugada Syndrome (BrS): Characterized by a coved ST elevation in the right precordial leads. Risk stratification in asymptomatic patients remains challenging. Today, multiparametric models like the Sieira Score and the PAT Score—which integrate

clinical data, family history, and EPS results—are utilized to predict major arrhythmic events (Farkowski, 2022).

CPVT and Short QT Syndrome (SQTS): In CPVT patients (who present a normal resting ECG but develop polymorphic/bidirectional VT under adrenergic stress) and SQTS patients (QTc ≤320 ms), a history of aborted cardiac arrest or therapy-resistant syncope constitutes an absolute Class I indication for an ICD (Mazzanti et al., 2017; Shah et al., 2021).

Screening Approaches and Emergency Response in Athletes

The most common etiologies of SCD in young athletes under 35 are HCM, sudden arrhythmic death syndrome (SADS), ARVC, anomalous coronary artery origins, and commotio cordis. Pre-participation screening (PPS) strategies designed to mitigate these risks vary considerably by geographic region.

European, American, and Turkish Screening Models

European (Italian) Model: Supported by the ESC and the International Olympic Committee (IOC), this legally mandated model in Italy includes a medical history, a physical examination, and a mandatory 12-lead resting ECG. Since up to 80% of at-risk athletes are completely asymptomatic, the ECG can detect electrical abnormalities years prior to phenotypic expression (Basu & Malhotra, 2018; Ujeyl & Niederseer, 2023). This approach has reduced young athlete SCD incidence in Italy by 89% (Magnusson et al., 2020; Wheeler, 2010).

American Model: Due to cost-effectiveness concerns and the risk of false-positive ECG interpretations, the AHA does not mandate routine ECGs in mass athletic screenings (Dhutia & MacLachlan, 2018; Schmehil et al., 2017). Instead, it utilizes a 14-Element Pre-participation Screening Tool (querying exertional symptoms, family history, and physical findings) (Plassche et al.,

2025; Schmehil et al., 2017). ECG is performed only if clinical abnormalities are identified (Schmehil et al., 2017).

Turkish Model and Current Practices: In Turkey, pre-participation screenings for competitive athletes are primarily conducted in primary healthcare facilities (Savran et al., 2019, 2021). Standardized forms inquiring about personal symptoms and family history are required for licensing (Yaman et al., 2005). However, a universal system mandating a 12-lead ECG is not yet fully established (Savran et al., 2021). Cardiology experts recommend the routine integration of the ECG and echocardiography (ECHO) into screening algorithms to prevent the oversight of insidious heart diseases, alongside the creation of a national guideline.

ECG Interpretation Criteria: The **2017 International Criteria for ECG Interpretation** differentiate benign physiological adaptations ("athlete's heart") from actual pathological findings, successfully reducing unnecessary advanced testing and false-positive rates to 3%.

On-Field Emergency Response

Because no screening method offers absolute protection, the proactive implementation of Emergency Action Plans (EAP) and the strategic placement of automated external defibrillators (AED) in strategic, easily accessible locations are of vital importance. Immediate bystander cardiopulmonary resuscitation (CPR) and early electrical shock (defibrillation) within the first 3 to 5 minutes can increase survival rates up to 70%.

Future Perspectives and New Biomarkers

In future SCD risk stratification, relying solely on LVEF or classical ECG morphology will not be considered scientifically sufficient (Liew, 2015; Xie et al., 2022). Advanced imaging

modalities that examine cardiac tissue composition at a microscopic level, such as T1 mapping and extracellular volume (ECV) analysis via CMR, represent a major breakthrough in risk prediction.

In the realm of multi-omics technologies, polygenic risk scores (PRS) are being actively developed to integrate millions of genetic variants (single nucleotide polymorphisms, SNPs), accurately mapping a patient's exact genetic risk burden. Additionally, the combined analysis of high-sensitivity Troponin T, NT-proBNP, CRP, and serum fatty acid levels shows significant promise for mapping SCD risk as a combined reflection of both genetic predisposition and myocardial inflammatory or metabolic stress (Gladding et al., 2021; Osman et al., 2019). Furthermore, wearable technologies (e.g., smartwatches) are rapidly entering clinical practice, offering continuous dynamic rhythm monitoring for subclinical detection of lethal arrhythmias (Adasuriya & Haldar, 2022; Galgut et al., 2022).

Clinical Red Flags and Prodromal Symptoms

Sudden cardiac death (SCD) is often perceived as a dramatic event occurring without prior warning; however, extensive epidemiological evidence robustly indicates that in approximately 50% of cases, the body emits "prodromal" (warning) signals hours, days, or weeks before the fatal collapse (Chugh, 2017). In prospective population-based studies, SCD victims experienced warning symptoms—primarily chest pain and shortness of breath—in the four weeks preceding the event (Marijon et al., 2013). Significantly, 93% of these symptoms recurred within the 24 hours immediately prior to the cardiac arrest (Marijon et al., 2015). When emergency medical services (EMS) were contacted upon symptom onset, the survival rate increased dramatically from 6.0% to 32.1%, highlighting that recognizing these flags is a matter of life and death. The most critical warning signs that must not be overlooked include.

Exertional and Cardiogenic Syncope

Differentiating the exact etiology of syncope (vasovagal, orthostatic, or cardiogenic) is the critical first step in determining SCD risk. Unlike common and benign vasovagal syncope, cardiogenic syncope is a major red flag for SCD and indicates a highly unstable underlying structural or electrical pathology (Koene et al., 2017). Key clinical features that distinguish true cardiac syncope include:

Occurrence During Exertion: Abrupt loss of consciousness occurring precisely during the peak of physical exercise or competitive sports is a significant clinical predictor of HCM, coronary artery anomalies, or channelopathies (Katyal et al., 2023; Tiziano et al., 2016).

Lack of Posture Change and Prodrome: Syncope occurring in the supine position or without any autonomic warning signs (sweating, nausea, pallor, visual disturbances) immediately raises a high suspicion of a cardiac arrhythmia and requires urgent advanced investigation (Reed, 2018; Stewart et al., 2023).

Unexplained Seizures and Epilepsy Differential Diagnosis

When a cardiac arrest or fatal rhythm disorder occurs, the abrupt cessation of cerebral blood flow leads to acute cerebral hypoxia, which can rapidly cause physical convulsions and incontinence that mimic epileptic seizures.

Risk of Epilepsy Misdiagnosis: Secondary convulsions in channelopathies like Long QT Syndrome (specifically LQT2 mutations) and CPVT are frequently misdiagnosed as epilepsy (Johnson et al., 2008; Kang et al., 2021). Studies have identified that a "seizure phenotype" is ascribed to up to 29% of LQTS patients (Massey et al., 2014). While these patients unnecessarily consume

anti-epileptic drugs (AEDs) for years, they remain entirely unprotected against the truly fatal risk of SCD.

Clinical Differentiating Features: In cardiogenic seizures, the duration of unconsciousness is limited to seconds, and post-episode recovery is quite rapid compared to true epilepsy, which follows a prolonged postictal confusion period. Furthermore, cardiogenic seizures do not respond to anti-epileptic therapy (Dumont et al., 2024; Patel et al., 2017).

Disproportionate Exertional Dyspnea and Cardiac Chest Pain

Cardiac-origin symptoms are the most frequently reported warnings leading up to an event in SCD victims (Abbas et al., 2023).

Pathological fatigue: Excessive fatigue, sudden breathlessness, and a feeling of pressure or tightness in the chest suggesting ischemia during physical activity that is disproportionate to the individual's current conditioning capacity or training history may serve as an early harbinger of myocardial ischemia, anomalous aortic origin of a coronary artery (AAOCA), or hypertrophic cardiomyopathy.

Symptoms Confused with Asthma: Exercise-induced shortness of breath in young athletes is frequently misdiagnosed as "exercise-induced asthma" (bronchoconstriction) or laryngeal obstruction (EILO) and is erroneously dismissed with inhaler treatments. A sensation of severe choking accompanied by chest pain at peak exertion that does not respond to classic asthma treatments must absolutely be investigated for coronary artery anomalies or structural heart diseases.

Unexplained Palpitations and Nocturnal Symptoms

Tachycardic and highly irregular heartbeats starting suddenly (paroxysmal) at rest, without any exercise, fever, or prominent stress factor, are profoundly dangerous. Particularly if accompanied by

dizziness, presyncope, or excessive cold sweating, it is considered a major indicator of ventricular tachycardia (VT). Furthermore, nocturnal agonal breathing (agonal respirations during sleep) is a specific pathognomonic red flag for Brugada Syndrome and LQT3. These sounds often represent self-terminating polymorphic VT or VF episodes occurring during the night when vagal tone is dominant.

Familial Red Flags

Since cardiac channelopathies and cardiomyopathies generally possess strong autosomal dominant (familial inheritance) genetic traits (Magi et al., 2017), a careful and detailed pedigree analysis is one of the most cost-effective and critical screening methods (Magi et al., 2017). The presence of any of the following specific situations in the family history constitutes major warning signs necessitating urgent cardiovascular screening for the individual.

Premature Unexpected Losses: A history of unexplained sudden death, SIDS, or early disability due to severe heart disease in first or second-degree relatives before the age of 50.

Suspicious Accidents: Unexplained drowning incidents despite knowing how to swim well (especially for LQTS Type 1 syndrome) or unexplained single-vehicle traffic accidents where the driver was alone.

Association with Hearing Loss: Cases of syncope accompanied by a family history of congenital sensorineural deafness suggest Jervell and Lange-Nielsen Syndrome, which carries a very high risk of SCD.

Conclusion

The identification of individuals at risk for SCD has successfully transitioned from static, one-dimensional approaches of the past into a dynamic, Bayesian, and multiparametric system based

on the patient's age, genotype, myocardial tissue characterization, and specific clinical phenotype (Magi et al., 2017). The recently updated 2022–2024 international cardiology guidelines (ESC, AHA/ACC) have conclusively moved past the strict "LVEF ≤35%" paradigm for prophylactic ICD placement, assigning a primary role to CMR-based LGE presence and specific pathogenic gene mutations.

Mathematical risk calculators tailored for diseases like HCM, ARVC, and Brugada Syndrome (e.g., HCM Risk-SCD, ARVC Risk Calculator v3.0, PAT Score) currently provide clinicians with an evidence-based roadmap for timing critical interventions, such as ICD implantation and sympathetic denervation. These tools utilize statistics from large patient cohorts to predict individualized risk. However, it must be emphasized that these scores are dynamic and require periodic updates as clinical conditions change.

The integration of artificial intelligence into ECG interpretation (AI-ECG) and polygenic risk scores (PRS) represents the next frontier in SCD prevention. These technologies offer the potential to map "occult risk burdens" by identifying microscopic repolarization abnormalities that escape human observation, thereby maximizing cost-effectiveness and sensitivity in mass screenings. Ultimately, the most effective strategy against SCD combines technological advancements with community awareness of clinical red flags and rigorous family-based screening. Each unexpected SCD case must prompt a meticulous post-mortem evaluation and molecular autopsy, as this remains the most vital strategic link in protecting surviving genetic heirs from future tragedies.

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DIAGNOSTIC EVALUATION OF SUDDEN CARDIAC DEATH

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Introduction

The World Health Organization defines **sudden cardiac death (SCD)** as a natural death resulting from cardiac causes that occurs within one hour of the onset of acute symptoms in witnessed cases, or within 24 hours in unwitnessed cases (Jacobs, et al., 2004: 233–249).

Since approximately 80% of sudden deaths occur at home and nearly 40% are unwitnessed, accurately determining the interval between symptom onset and death is extremely challenging. This considerably complicates the clinical diagnostic process and renders the clinical classification difficult to establish (de Vreede-Swagemakers, et al., 1997: 1500–1505).

Cardiovascular collapse refers to the sudden impairment of effective blood flow due to cardiac or peripheral factors, whereas

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sudden cardiac arrest (SCA) denotes the abrupt cessation of the heart's pumping function.

Approximately half of all deaths attributable to heart disease occur in the form of sudden cardiac arrest. **Atherosclerotic cardiovascular disease** accounts for nearly 80% of all cases of sudden cardiac death. In adults over the age of 40, the most common cause is atherosclerotic cardiovascular disease, whereas in individuals under 40, structural heart diseases and electrical channelopathies are the predominant causes (Chugh, et al., 2004: 1268–1275).

In patients presenting with sudden cardiac death, the initial recorded rhythm is ventricular fibrillation in approximately 80% of cases. Unfortunately, in nearly 50% of sudden cardiac deaths, the first manifestation is sudden cardiac arrest itself (Pereyra, et al., 1983: 974–988).

The cornerstone of managing sudden cardiac death is the rapid identification of its underlying causes, with the primary objectives being prevention and the identification of patients at risk.

Clinical Assessment and Diagnostic Approach

Detailed Medical History and Symptom Inquiry

The cornerstone of the clinical evaluation of a patient at risk for sudden cardiac death (SCD) or who has survived cardiac arrest is a thoroughly obtained, detailed medical history. In the assessment of cardiovascular diseases and arrhythmias, a comprehensive history and symptom inquiry constitute the most critical initial step, leading to diagnosis in approximately 50% of cases (Brignole, et al., 2018: 1883–1948). Structural heart diseases (such as cardiomyopathies) and, in particular, electrical channelopathies (e.g., Brugada syndrome, Long QT syndrome) often present with episodic symptoms that occur in attacks. Therefore, the patient’s apparently

asymptomatic state in an outpatient setting should not mislead the clinician when investigating these conditions. The nature of the symptoms, their onset and resolution, and any triggering factors should be examined in detail (Zeppenfeld, et al., 2022: 3997–4126).

Syncope and Presyncope (Fainting and Near-Fainting)

Syncope is a transient loss of consciousness characterized by a rapid onset, short duration, and spontaneous recovery, resulting from cerebral hypoperfusion.

The patient's history of syncope constitutes the most critical step in determining the etiology of transient loss of consciousness, performing risk stratification, and, in particular, excluding life-threatening cardiac causes, as summarized in Table 1.

During the cardiological evaluation, the following key parameters should be thoroughly assessed when obtaining a history of syncope.

Prodromal Symptoms and Triggers

Vasovagal (Reflex) Syncope: These episodes typically begin in response to specific triggers such as prolonged standing, exposure to blood, pain, or extreme heat. Prior to the loss of consciousness, patients often report signs of autonomic hyperactivity that may last for several minutes. Symptoms such as visual dimming, severe nausea, cold sweating, facial pallor, tinnitus, and a sensation of warmth generally indicate vasovagal (reflex) syncope.

Arrhythmic (Cardiogenic) Syncope: Hemodynamic instability occurs due to the sudden cessation of cardiac output caused by an arrhythmia. Consequently, the prodromal phase is either absent or lasts only a few seconds. The absence of any warning symptoms or a very brief prodrome (less than 10 seconds) increases the risk of arrhythmic syncope.

***Table 1**: Clinical Differentiation Between Neurocardiogenic (Vasovagal) Syncope and Cardiogenic (Arrhythmic) Syncope*

Clinical Feature / Parameter	Neurocardiogenic (Vasovagal) Syncope	Cardiogenic (Arrhythmic / High-Risk) Syncope
Onset and Prodrome (Early Symptoms)	Gradual onset. Preceded by minutes-long autonomic symptoms, such as visual dimming, nausea, cold sweating, and pallor.	Sudden onset. No preceding symptoms, or prodrome lasts only a few seconds ("as if the electricity suddenly went out" sensation).
Position and Activity	Typically occurs after prolonged standing or while seated.	May occur in the supine position or during intense exertion/sports.
History of Physical Injury / Trauma	Rare, as protective reflexes are activated (the patient typically has the opportunity to brace themselves before collapsing).	Common. Sudden collapse may result in face-first falls, head trauma, eyebrow lacerations, or dental injuries.
Associated Cardiac Symptoms	Palpitations are rare, and the pulse is generally slow (bradycardia).	Sudden-onset severe palpitations and dizziness immediately preceding syncope are common.
Specific Triggers	Exposure to blood, severe pain, extreme heat, or emotional stress.	Swimming or diving (LQT1, CPVT), sudden loud noises (LQT2), febrile illness, or rest/sleep (Brugada, LQT3).
Differentiation from Epilepsy (Seizures)	Muscle contractions are rare. Recovery after syncope is relatively rapid, although fatigue may persist.	Contractions occur after the loss of consciousness (due to hypoxia). Once the cardiac rhythm is restored, the patient regains full awareness within seconds, and postictal confusion (prolonged sleepiness) is absent.
Family History	The family history typically includes benign fainting episodes.	Family history often reveals sudden death at a young age (<50 years), unexplained accidents, or a history of pacemaker/ICD implantation.

This table was created by synthesizing the diagnostic criteria from the 2018 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Syncope and the 2022 ESC Guidelines on Ventricular Arrhythmias.**Abbreviations**: LQT1; Long QT Syndrome Type 1, LQT2; Long QT Syndrome Type 2, LQT3; Long QT Syndrome Type 3, CPVT; Catecholaminergic Polymorphic Ventricular Tachycardia, ICD; Implantable Cardioverter Defibrillator

Position and Activity Status

Vasovagal syncope almost always occurs while the patient is standing or sitting. Syncope that develops upon standing is indicative of orthostatic hypotension.

Syncope occurring while supine or seated represents a high-risk scenario and suggests an arrhythmic etiology. Syncope that develops in the supine position or during exertion should, until proven otherwise, be considered of malignant arrhythmic or obstructive cardiac origin (e.g., hypertrophic cardiomyopathy, severe aortic stenosis) (Brignole, et al., 2018: 1883–1948).

History of Physical Injury and Trauma

In benign syncope, the presence of prodromal symptoms (such as visual dimming, nausea, and cold sweating) usually allows a gradual onset and provides the patient time to sit or take protective measures, thereby reducing the likelihood of major trauma.

In arrhythmic (cardiogenic) syncope, the sudden onset of loss of consciousness prevents protective reflexes from being activated. The occurrence of major trauma—such as the patient falling forcefully face-first or sustaining head injury—dramatically increases the likelihood that the syncope is of cardiogenic origin (Zeppenfeld, et al., 2022: 3997–4126).

Findings During the Episode (Witness Accounts)

Since patients are often unable to recall the event, observations provided by witnesses are of critical importance.

Skin Color: A “ashen” or “pale” appearance typically suggests reflex syncope, whereas cyanosis indicates more serious cardiac events.

Duration and Movements: The duration of loss of consciousness should be assessed, as true syncope typically lasts only a few seconds. Muscle contractions observed during syncope (convulsive syncope) can be mistaken for epileptic seizures; however, in syncope, these movements are of shorter duration and are not preceded by an aura. A significant proportion of patients experiencing cardiogenic syncope present to outpatient clinics with an incorrect diagnosis of “epilepsy.” Sudden interruption of cerebral blood flow (hypoxia) can lead to secondary generalized myoclonic jerks.

Differential Diagnosis: In epileptic seizures, muscle contractions typically begin simultaneously with the loss of consciousness, urinary or fecal incontinence is common, and a postictal period of minutes to hours—including sleepiness and confusion (postictal confusion)—is often observed. In contrast, in cardiac syncope, these contractions occur after the loss of consciousness, are brief, and resolve within seconds as the heart returns to its normal rhythm, with the patient fully aware of their surroundings and orientation preserved.

In a young patient experiencing seizures that are resistant to antiepileptic medications, triggered by exertion, or accompanied by a sensation of “severe palpitations” rather than a typical aura prior to loss of consciousness, the primary suspicion should be cardiologic rather than neurologic, with channelopathies or cardiomyopathies being the most likely considerations (Yamashita, et al., 1998: 146–150).

Associated Symptoms (Particularly Palpitations)

The sudden onset of severe palpitations, beginning seconds before syncope and accompanied by dizziness, represents one of the strongest indicators of a ventricular tachycardia episode (sustained or non-sustained VT).

Post-episode fatigue, weakness, and nausea lasting for several hours are commonly observed in vasovagal syncope. In contrast, prolonged confusion (mental clouding) and tongue biting are more indicative of an epileptic seizure.

Personal and Family History Assessment

Medical History: The presence of a known structural heart disease (such as heart failure, reduced ejection fraction, or a prior myocardial infarction) predicts a cardiac cause of syncope with approximately 95% sensitivity (Mott, et al., 2001: 1700–1706).

Medication History: The use of antihypertensives, diuretics, antiarrhythmics, and drugs that prolong the QT interval should be carefully assessed.

Family History: A family history of sudden cardiac death, drowning, or unexplained traffic accidents at a young age (<50 years) represents a strong risk factor for inherited ion channelopathies, such as Long QT syndrome or Brugada syndrome (Tokeji, et al., 2017: 85–90).

Specific Triggers for Genetic Channelopathies

If syncope occurs in a structurally normal heart, the patient's history can directly guide the clinician toward specific genetic mutations.

Swimming, Diving, or Competitive Physical Exertion: These activities are known triggers for Long QT Syndrome Type 1

(LQT1) and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT).

Auditory Stimuli (Alarm Clock, Telephone Ring, Sudden Loud Noise): These triggers are associated with Long QT Syndrome Type 2 (LQT2).

Rest, Nighttime Sleep, or Febrile Illness: These conditions are recognized triggers for Brugada Syndrome and Long QT Syndrome Type 3 (LQT3) (Priori, et al., 2015: 2793–2867; Zeppenfeld, et al., 2022: 3997–4126).

Palpitations

Palpitations refer to the patient's perception of their heartbeats in a disturbing or uncomfortable manner and represent a very common clinical complaint. While benign palpitations due to anxiety, sinus tachycardia, or premature contractions (extrasystoles) are highly prevalent in the general population, in patients at risk for sudden cardiac death (SCD), palpitations may serve as a critical warning sign of life-threatening ventricular tachycardia (VT).

Rate and Rhythm

Regular and Rapid: Suggestive of paroxysmal supraventricular tachycardia (PSVT) or ventricular tachycardia (VT).

Irregular and Rapid: Increases the likelihood of atrial fibrillation (AF) or atrial flutter with variable conduction.

Palpitations / Skipped Beats: Descriptions such as "my heart stops and then restarts" or "it skips a beat" typically indicate atrial or ventricular premature contractions (extrasystoles) (Josephson & Wellens, 1990: 411–442).

Onset and Termination

Sudden Onset and Termination: A palpitation that starts and stops abruptly ("as if a switch were flipped") is typically observed in reentrant arrhythmias such as AVNRT or AVRT.

Gradual Onset (Warm-Up / Cool-Down): Palpitations that gradually accelerate and then gradually subside are indicative of sinus tachycardia or focal atrial tachycardia (Al-Khatib, et al., 2018: e272–e391).

Triggering Factors and Position

Exercise and Stress: Increased sympathetic stimulation can trigger many arrhythmias; however, palpitations accompanied by syncope during exercise should raise suspicion for life-threatening ventricular tachycardia (VT) or channelopathies such as CPVT.

Positional Changes: Rising abruptly from a squatting position can trigger AVNRT. Palpitations felt when lying on the left side or in the supine position are generally due to the heart's closer proximity to the chest wall, which makes normal beats more perceptible.

Vagal Maneuvers: If the patient's palpitations terminate with straining (Valsalva maneuver), carotid sinus massage, or immersion of the face in cold water, this suggests a reentrant supraventricular tachycardia (AVNRT/AVRT) (Bunch, et al., 2004: 1236–1240).

Associated Symptoms (Red Flags)

During a palpitatory episode, if the patient experiences severe dizziness, visual dimming (presyncope), cold sweating, chest pain, or shortness of breath, this indicates a dramatic reduction in cardiac output.

A tachyarrhythmia resulting in hemodynamic compromise should, unless proven otherwise, be regarded as either ventricular tachycardia (VT) or a supraventricular arrhythmia with a rate sufficiently elevated to impair left ventricular function, and the patient should be considered to belong to a high-risk category (Al-Khatib, et al., 2018: e272–e391).

“The ‘Frog Sign’: The patient’s perception of rapid and regular pulsations in the neck during tachycardia is considered a pathognomonic finding for atrioventricular nodal reentrant tachycardia (AVNRT). This phenomenon arises from the simultaneous contraction of the atria and ventricles, causing blood to strike the closed tricuspid valve and be reflected back into the jugular veins.

Syncope or Dizziness: The occurrence of fainting concomitant with tachycardia suggests a hemodynamically significant arrhythmia—particularly ventricular tachycardia (VT)—or the presence of structural heart disease (Goldreyer, Kastor, & Kershbaum, 1976: 783–789; Leitch, et al., 1992: 1064–1071).

Chest Pain and Dyspnea: These symptoms may indicate underlying conditions such as ischemia, heart failure, or acute pulmonary embolism.

Polyuria: Frequent urination following tachycardia may occur in supraventricular tachycardias (SVTs) due to atrial natriuretic peptide (ANP) release secondary to atrial stretch (Porter, et al., 2004: 393–396).

Habits and Medication History

Substance Use: Sympathomimetic substances such as excessive caffeine (from coffee or tea), alcohol (associated with ‘Holiday Heart’ syndrome/atrial fibrillation), tobacco, and cocaine can trigger arrhythmias.

Medications: Certain antiarrhythmics, drugs that prolong the QT interval, and weight-loss medications may exhibit proarrhythmic effects.

Mad Honey (Chestnut Honey): Consumed particularly in the Black Sea region, this type of honey can induce significant bradyarrhythmias and, in some cases, palpitations secondary to escape rhythms (Aliyev, et al., 2009: 954–956).

Chest Pain and Dyspnea

In the cardiovascular system assessment, chest pain and dyspnea are among the most critical symptoms for the detection of life-threatening conditions, particularly acute coronary syndromes (ACS), heart failure, and pulmonary embolism. A thorough evaluation of these symptoms forms the basis for differential diagnosis and for determining the patient's risk level.

Assessment of Chest Pain

Although chest pain is the most common symptom of acute coronary syndromes (ACS), its characteristics and associated findings vary depending on the underlying etiology.

Ischemic Pain (Typical Angina Pectoris): It is typically described as a sensation of pressure, burning, tightness, or a feeling of 'a heavy weight on the chest' behind the sternum. The pain may radiate to the left arm, neck, or jaw. Classic features include provocation by exertion, cold exposure, or heavy meals, and relief within 5–10 minutes with rest or sublingual nitrates. This presentation usually indicates atherosclerotic coronary artery disease, the most common cause of acute coronary syndromes (ACS).

Chest Pain Due to Cardiomyopathies (Non-Atherosclerotic): In young patients with hypertrophic cardiomyopathy (HCM), severe exertional angina may occur despite completely normal epicardial

coronary arteries. This is attributed to the increased oxygen demand of the excessively thickened myocardium and microvascular dysfunction in the small vessels supplying this tissue. Exertional chest pain in a young athlete or individual constitutes a definite 'red flag' for acute coronary syndromes (ACS) (Ommen, et al., 2024: e1239–e1311).

Position-Dependent or Pleuritic Pain: Stabbing-type pain that increases with deep inspiration, coughing, or changes in position is generally of non-cardiac origin, such as pericarditis, pleuritis, or musculoskeletal causes. However, a history of myocarditis should not be overlooked, as it carries an associated arrhythmic risk.

Triggers and Relieving Factors: Physical activity, emotional stress, exposure to cold, or heavy meals can precipitate stable angina, whereas rest or administration of nitroglycerin alleviates the pain. In pericarditis, pain typically intensifies when lying supine and is relieved by leaning forward (Shishehbor, 2008: xiv, 338 p. : ill.).

Assessment of Dyspnea

Dyspnea is the earliest and most sensitive symptom of heart failure and valvular diseases. It serves as a key indicator of reduced cardiac pumping capacity (heart failure) or the onset of pulmonary congestion due to fluid accumulation. Heart failure developing on the background of dilated cardiomyopathy (DCM) or advanced-stage hypertrophic cardiomyopathy (HCM) exponentially increases the risk of arrhythmic death (Arbelo, et al., 2023: 3503–3626).

Exertional Dyspnea: This refers to shortness of breath triggered by physical activity and indicates the heart's inability to meet increased metabolic demands.

Orthopnea: Shortness of breath that occurs when lying supine and resolves upon assuming a sitting position. It is a highly specific finding in advanced heart failure.

Paroxysmal Nocturnal Dyspnea (PND): The sudden onset of shortness of breath that awakens the patient a few hours after sleep.

Bentopnea: Shortness of breath that worsens when leaning forward (e.g., while tying shoes), indicative of elevated intracardiac filling pressures.

Accompanying Findings: The presence of pleuritic pain and cyanosis alongside sudden-onset dyspnea should raise suspicion for pulmonary embolism (Heidenreich, et al., 2022: e895–e1032).

Arrhythmia-Equivalent (Sudden-Onset) Dyspnea: Episodes of unexplained dyspnea that begin abruptly within seconds, without physical exertion, and are accompanied by a sensation of severe palpitations, may indicate attacks of supraventricular or ventricular tachycardia associated with a sudden and marked increase in heart rate, potentially leading to hemodynamic compromise (Zeppenfeld, et al., 2022: 3997–4126).

Angina Equivalents and Red Flags

Some patients—particularly women, the elderly, and individuals with diabetes—may present with symptoms known as ‘angina equivalents’ rather than typical chest pain.

Symptoms: Patients may exhibit dyspnea, extreme fatigue, malaise, nausea, diaphoresis, or syncope without the presence of chest pain.

High-Risk Indicators: The presence of cold sweating, hypotension, a newly detected murmur, or crackles in the lungs accompanying chest pain or dyspnea signifies a critical condition and suggests acute decompensation or a large myocardial infarction (Gulati, et al., 2021: e368–e454).

Family History and Pedigree Analysis

A large proportion of sudden cardiac death cases, particularly among individuals under 35 years of age, are attributable to cardiomyopathies and primary electrical disorders (channelopathies) with a genetic (inherited) basis. As many of these conditions exhibit autosomal dominant inheritance, obtaining a detailed family history is crucial for diagnosis (Arbelo, et al., 2023: 3503–3626; Zeppenfeld, et al., 2022: 3997–4126).

Standard outpatient questions such as ‘Is there a history of heart disease in the family?’ or ‘Has anyone in the family experienced a heart attack?’ are insufficient for detecting genetic arrhythmia syndromes. Physicians should pursue ‘hidden and unexplained’ deaths through targeted questioning and construct a structured pedigree spanning at least three generations.

Three-Generation Pedigree Analysis

A comprehensive pedigree, utilizing standard symbols, should be constructed to determine the genetic risk of the patient (index case).

Scope: The pedigree should include the index case’s first-degree relatives (parents, siblings, children), second-degree relatives (grandparents, uncles, aunts), and, if possible, third-degree relatives.

Detail of Inquiry: Information should be recorded not only for living relatives but also for deceased family members, including their age at death and the definite or probable cause of death.

Identification: When constructing the pedigree, affected individuals, those who have experienced acute coronary syndromes (ACS), and apparently healthy but potentially at-risk individuals should be clearly indicated (Wever & Robles de Medina, 2004: 1137–1144).

History of Early and Unexplained Death

Sudden deaths occurring in a family before the age of 50 years (or 40 years according to certain guidelines and syndromes) that remain unexplained after autopsy constitute a major red flag.

Unexplained deaths occurring during sleep should raise suspicion for Brugada syndrome or Long QT Syndrome Type 3 (LQT3).

Deaths occurring during exertion or sports increase the suspicion for hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), or catecholaminergic polymorphic ventricular tachycardia (CPVT) (Ommen, et al., 2024: e1239–e1311).

Investigation of Masked Cardiac Deaths

The greatest challenge with channelopathies and cardiomyopathies is that previous deaths in the family may have been recorded with incorrect diagnoses.

Drowning Cases: Has any family member, despite being a proficient swimmer, died unexpectedly by drowning? This is particularly characteristic of Long QT Syndrome Type 1 (LQT1) and catecholaminergic polymorphic ventricular tachycardia (CPVT), as the cold shock and exertion associated with entering the water can trigger a fatal arrhythmia.

Suspicious Traffic Accidents: Accidents involving a single vehicle that suddenly veers off a straight road or collides with a tree or wall. A fatal cardiogenic syncope occurring at the wheel may have been recorded simply as a ‘traffic accident’.

Unexplained Infant/Child Deaths: A family history of sudden infant death syndrome (SIDS) or unexplained recurrent miscarriages

may indicate severe forms of channelopathies, such as Long QT Syndrome (Zeppenfeld, et al., 2022: 3997–4126).

Patients with Refractory Epilepsy: The presence of family members diagnosed with epilepsy who are unresponsive to treatment or who have died during a seizure may actually reflect a cardiac rhythm disorder rather than a neurological condition, with convulsions resulting from cerebral hypoxia.

Known Cardiac Diseases

A family history of diagnosed hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), or Marfan syndrome should be investigated. It is essential to inquire whether any relative has had a pacemaker or implantable cardioverter-defibrillator (ICD) inserted, regardless of whether the underlying cause is known. Relatives who underwent heart transplantation at a young age or developed unexplained heart failure may indicate familial variants of dilated cardiomyopathy (DCM) (Arbelo, et al., 2023: 3503–3626).

Clinical Screening of Family Members

First-Degree Relatives: Even if no cause is identified in the index case, all first-degree relatives should be offered clinical screening.

First-Line Tests: The initial phase of screening should include a detailed physical examination, a 12-lead electrocardiogram (ECG), and echocardiography (ECHO). ECHO is essential for excluding structural diseases such as hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM).

Repeat Screening: Since hereditary diseases, particularly hypertrophic cardiomyopathy (HCM), may manifest with age (age-dependent penetrance), children and young adults with initially

normal results should undergo clinical reevaluation every 1–2 years, while adults should be reassessed every 3–5 years.

Genetic Testing and Cascade Screening

Genetic analysis is a powerful tool for clarifying uncertain findings within the family pedigree.

Testing in the Index Case: Pathogenic mutations should first be sought in an affected (phenotype-positive) family member or in a deceased individual through molecular autopsy.

Cascade Screening: When a disease-causing mutation is identified in the index case, all other family members should be screened specifically for this mutation.

Management: Individuals who do not carry the mutation (‘genotype-negative’) may be discharged from follow-up, whereas mutation carriers without symptoms (‘genotype-positive, phenotype-negative’) should be closely monitored and advised to avoid high-risk medications and situations.

Physical Examination

Assessment of Vital Signs

Blood Pressure: Blood pressure should be measured in both arms. In patients with a history of syncope, orthostatic blood pressure should be assessed at the 3rd and 5th minutes after standing. A systolic blood pressure below 90 mmHg is considered a high-risk indicator.

Pulse and Temperature: Pulse rate, rhythm, and volume (graded on a 0–3 scale) should be assessed. The presence of fever may raise suspicion for myocarditis or infective endocarditis (0–3 Scale for Pulse: 0 indicates an impalpable pulse, 1+ a diminished pulse, 2+ a normal and easily palpable pulse, and 3+ a bounding pulse, e.g., stronger than normal) (Griffin, et al., 2026).

Cardiac Examination (Palpation and Auscultation)

Precordial Palpation: Lateral or leftward displacement of the apical impulse suggests dilated cardiomyopathy or heart failure (Lok & Lau, 1996: 231–236).

Heart Sounds

S3 (Third Heart Sound): An important finding indicative of increased left ventricular end-diastolic pressure and heart failure.

S4 (Fourth Heart Sound): Heard in conditions associated with decreased ventricular compliance, such as hypertrophy or ischemia (Neville, et al., 2007: 205–213).

Murmurs and Clicks

Systolic Murmurs: A murmur that increases with the Valsalva maneuver on the left side of the sternum suggests hypertrophic obstructive cardiomyopathy (HOCM). Its intensity increases when the patient performs the Valsalva maneuver or stands suddenly (reducing venous return to the heart) and decreases with squatting. This dynamic change is a characteristic sign of left ventricular outflow tract obstruction. A late systolic murmur accompanied by a click favors mitral valve prolapse. A newly developed harsh pansystolic murmur may indicate post-myocardial infarction ventricular septal rupture (VSR) (Ommen, et al., 2024: e1239–e1311).

Diastolic Murmurs: Essential for the diagnosis of valvular diseases such as aortic regurgitation or mitral stenosis.

Systemic and Peripheral Findings

Lung Auscultation: Inspiratory crackles (rales) are indicative of pulmonary congestion and left heart failure.

Edema and Ascites: Pitting edema in the legs, ascites, and hepatomegaly are indicative of right heart failure.

Peripheral Pulses: Femoral pulses should be assessed to rule out aortic coarctation, and the presence of a radio-femoral delay should be investigated. Extremity pulses should also be palpated to evaluate for peripheral arterial disease.

Non-Invasive Electrical Assessment

12-Lead Resting Electrocardiogram (ECG)

The 12-lead resting electrocardiogram (ECG) is the most fundamental and rapid diagnostic tool used in the evaluation of individuals who survive sudden cardiac arrest and for predicting the risk of sudden cardiac death (SCD). Following the return of spontaneous circulation (ROSC), an ECG should be obtained and interpreted in all adult patients as soon as possible to determine the underlying cause. A standard ECG not only reflects the instantaneous electrical rhythm of the heart but also provides a comprehensive map of arrhythmogenic substrates, ranging from cellular-level ion channel dysfunctions (channelopathies) to macroscopically visible myocardial scars (fibrosis).

Acute and Chronic Ischemic Changes

Coronary artery disease is responsible for approximately 80% of sudden cardiac death (SCD) cases.

STEMI and Ischemia: ST-segment elevation (STEMI) or depression in two or more contiguous leads, T-wave inversion, and a ‘tombstone’ morphology indicate acute coronary occlusion. However, it should be noted that ECGs obtained within the first 8 minutes after ROSC may yield a high rate of false-positive STEMI, and repeat ECGs may be necessary after 30 minutes (Aufderheide, et al., 2021: 45–52).

Pathological Q Waves: Indicate a prior silent or clinically evident myocardial infarction. This scar tissue serves as a substrate for life-threatening arrhythmias such as ventricular tachycardia (VT) and ventricular fibrillation (VF).

aVR Lead: ST-segment elevation ≥0.5 mm in lead aVR is associated with an increased risk of left main coronary artery or triple-vessel disease (Byrne, et al., 2023: 3720–3826).

Inherited Electrical Channelopathies

They are the most common causes of sudden cardiac death (SCD) in young individuals without structural heart disease.

Long QT Syndrome (LQTS): A condition characterized by prolongation of the electrical recovery (repolarization) phase of the myocardium. It predisposes to intracellular calcium overload, which can trigger the life-threatening arrhythmia known as *torsades de pointes*. The QT interval should be corrected for heart rate (Bazett formula: QTc = QT / √RR) and calculated carefully. A QTc >470 ms in men and >480 ms in women is considered abnormal, whereas a QTc >500 ms represents a major risk indicator (red flag) for sudden cardiac death (SCD).

Short QT Syndrome (SQTS): A condition characterized by an abnormally shortened corrected QT (QTc) interval (<360 ms, and in some cases <330 ms). The ST segment is typically markedly abbreviated or may be virtually absent.

Brugada Syndrome (Type 1 Pattern): Characterized by a ≥2 mm coved-type ST-segment elevation in the right precordial leads (V1–V2), followed by a negative T wave. This pattern is associated with an increased risk of malignant polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF), particularly during sleep or at rest.

Early Repolarization Pattern: Characterized by notching or slurring at the end of the QRS complex (J point), often accompanied by >1 mm elevation, particularly in the inferior and lateral leads. Although it may represent a benign finding commonly observed in the general population, it can also appear as a high-risk variant—referred to as Early Repolarization Syndrome—in patients with a history of idiopathic ventricular fibrillation (VF) (Zeppenfeld, et al., 2022: 3997–4126).

Structural Heart Diseases and Cardiomyopathies

Left Ventricular Hypertrophy (LVH) and the 'Strain' Pattern: High QRS voltage accompanied by asymmetric ST-segment depression and T-wave inversion in the lateral leads (V5, V6, I, and aVL), known as the 'strain' pattern, is a classic finding in severe hypertensive heart disease, aortic stenosis, or hypertrophic cardiomyopathy (HCM). In apical HCM, the presence of giant negative T waves is highly characteristic.

Findings of Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC): T-wave inversion in the right precordial leads (V1–V3) and the presence of epsilon waves—small electrical deflections occurring at the end of the QRS complex and the onset of the ST segment—represent the characteristic electrocardiographic manifestations of fibro-fatty replacement of the right ventricular myocardium in ARVC (Arbelo, et al., 2023: 3503–3626).

Dilated Cardiomyopathy (DCM): Left bundle branch block (LBBB), non-specific intraventricular conduction delays, and prolonged QTc intervals may be observed.

Fragmented QRS (fQRS): Defined by the presence of multiple notches or spikes within the QRS complex. In a healthy heart, electrical conduction proceeds smoothly along a uniform pathway; however, when islands of myocardial fibrosis (scar tissue)

are present, conduction is forced to travel around these barriers in a 'zig-zag' manner. Fragmented QRS represents a simple yet reliable 12-lead ECG marker of myocardial scarring and an increased risk of sudden cardiac death (SCD).

Pre-Excitation Syndromes

Wolff-Parkinson-White (WPW) Syndrome: Diagnosed by a short PR interval (<120 ms), a slurred delta wave at the onset of the QRS complex, and a widened QRS complex. When atrial fibrillation occurs, rapid ventricular conduction via the accessory pathway can lead to ventricular fibrillation (VF) and sudden death.

Ambulatory ECG (Holter Monitoring)

The 12-lead resting ECG provides only a brief, 10-second snapshot of the heart's electrical activity. However, life-threatening arrhythmias are often triggered by fluctuations in autonomic nervous system activity (sympathetic/parasympathetic imbalance), daily physical activities, or sleep stages. To capture these dynamic changes, Holter monitoring for at least 24–48 hours, and up to 7 days when indicated, is essential (Zeppenfeld, et al., 2022: 3997–4126).

Premature Ventricular Complex (PVC) Burden and Morphology

"Premature Ventricular Complexes (PVCs) may occasionally be observed even in healthy individuals. However, a high PVC burden—defined as constituting more than 10–15% of total daily heartbeats—can chronically overload the left ventricle, leading to dilation and the development of 'PVC-induced cardiomyopathy' (heart failure). Additionally, whether PVCs are monomorphic (single morphology) or polymorphic (multiple morphologies, suggestive of myocardial scarring/fibrosis) is diagnostically important.

In arrhythmogenic right ventricular dysplasia (ARVD), a daily PVC burden exceeding 1,000 is associated with increased risk. Conversely, the absence of ventricular extrasystoles indicates a low risk for sudden cardiac death (SCD).

'R on T' Phenomenon (Short Coupling Interval): Occurs when a premature ventricular complex (PVC) coincides with the peak of the preceding T wave, the heart's most electrically vulnerable (refractory) phase. This phenomenon is one of the most well-known and dangerous triggers of ventricular fibrillation (VF).

Non-Sustained Ventricular Tachycardia (NSVT)

Non-Sustained Ventricular Tachycardia (NSVT): Defined as three or more consecutive wide QRS ventricular beats lasting less than 30 seconds and terminating spontaneously. NSVT episodes detected in patients with a left ventricular ejection fraction (LVEF) <40% or those with hypertrophic cardiomyopathy (HCM) constitute a major 'red flag' supporting the consideration for implantation of an implantable cardioverter-defibrillator (ICD) (Arbelo, et al., 2023: 3503–3626; Ommen, et al., 2024: e1239–e1311).

İmplante Edilebilir Loop Kaydediciler (ILR- Implantable Loop Recorder)

Cilt altına, sol göğüs bölgesine lokal anestezi ile 5 dakikada enjekte edilen, küçük USB bellek boyutunda cihazlardır. 3 yıla kadar 7/24 kesintisiz ritim takibi yaparlar. Açıklanamayan, tekrarlayan senkopları olan ve ailesinde ani kardiyak ölüm öyküsü bulunan hastalarda ölümcül bir ritim bozukluğunun yakalanmasında güncel kılavuzların "altın standart" kabul ettiği tanı aracıdır (Brignole, et al., 2018: 1883–1948).

Exercise (Stress) Testing

Exercise testing is a noninvasive diagnostic method used to increase cardiac workload, thereby creating a supply-demand mismatch in coronary blood flow to detect resulting ischemia or arrhythmias. Exercise represents the most physiological means of increasing myocardial oxygen demand. Although primarily employed in clinical practice for the assessment of coronary artery disease (ischemia), exercise testing also holds invaluable value in arrhythmia risk stratification as a 'provocative' electrical test. Increased heart rate and catecholamine (adrenaline) release during exercise can unmask latent electrical abnormalities in the heart.

Ischemic Heart Disease

In patients with chest pain, exercise testing serves as the primary tool for diagnosing coronary artery disease (CAD) and assessing the severity of ischemia. During exercise, ST-segment depression (indicative of ischemia) or, less commonly, ST-segment elevation (indicative of severe transmural ischemia or infarction) may be observed (Gulati, et al., 2021: e368–e454).

Inherited Arrhythmia Syndromes

Diagnosis of Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT): Patients with CPVT typically have completely normal resting ECGs and echocardiograms. The only definitive diagnostic method for this insidious condition is exercise testing. When heart rate reaches 110–120 bpm during exercise, the sudden onset of ventricular tachycardia with continuously alternating beat directions—termed *bidirectional VT*—is pathognomonic for CPVT, providing a definitive diagnosis.

Assessment of QTc Adaptation: In healthy individuals, the QT interval physiologically shortens as heart rate increases during exercise. In patients with Long QT Syndrome Type 1 (LQT1),

however, the QT interval fails to shorten adequately with increasing heart rate (paradoxical repolarization prolongation). This phenomenon explains the heightened risk of developing *Torsades de Pointes* (TdP) during exertion (Zeppenfeld, et al., 2022: 3997–4126).

Non-Invasive Structural Imaging Modalities

In the vast majority of sudden cardiac death (SCD) cases, structural abnormalities of the heart serve as the primary substrate triggering the electrical storm (arrhythmia). Echocardiography is the first-line and most fundamental tool available to detect these structural abnormalities.

Echocardiography (ECHO)

Echocardiography is the gold-standard first-line imaging modality that uses sound waves (ultrasound) to provide real-time, dynamic, three-dimensional visualization of the heart. It is radiation-free and can be easily performed at the bedside.

Left Ventricular Ejection Fraction (LVEF)

Left ventricular ejection fraction (LVEF) refers to the percentage of blood within the left ventricle (the heart's main pumping chamber) that is ejected into the systemic circulation with each heartbeat. In healthy individuals, this value typically ranges from 50% to 70%.

In sudden cardiac death (SCD) risk assessment, LVEF has long been the most powerful and classical parameter. A history of myocardial infarction (ischemia) or dilated cardiomyopathy leading to an LVEF ≤35% dramatically increases the risk of ventricular fibrillation (VF) and sudden death.

Current guidelines recommend that patients with an LVEF <35% and symptomatic heart failure should receive an implantable cardioverter-defibrillator (ICD) as a Class I (definite) indication,

aimed at preventing arrhythmias and sudden death (Zeppenfeld, et al., 2022: 3997–4126).

Advanced Echocardiographic Techniques: Global Longitudinal Strain (GLS)

Conventional ejection fraction (LVEF) measures only volumetric changes of the heart and may overlook microscopic myocardial damage in its early stages. The recently developed 'strain echocardiography' assesses the longitudinal contractile function of the myocardium at the cellular level, expressed as global longitudinal strain (GLS). Even when LVEF appears normal (e.g., ~55%), an impaired GLS value (e.g., absolute value <15%) may serve as an early indicator of subclinical heart failure or myocardial fibrosis (scarring) (Arbelo, et al., 2023: 3503–3626).

Diagnosis of Structural Heart Diseases

Hypertrophic Cardiomyopathy (HCM)

Hypertrophic cardiomyopathy (HCM) is characterized by unexplained, asymmetric thickening of the cardiac walls, particularly the interventricular septum. On echocardiography, a wall thickness ≥15 mm (or ≥13 mm in the presence of a family history) is diagnostic. A maximal wall thickness ≥30 mm indicates a high risk for sudden cardiac death (SCD). Additionally, echocardiography with color Doppler can readily identify any obstruction in the left ventricular outflow tract (Ommen, et al., 2024: e1239–e1311).

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC/ARVD)

Echocardiography is used to assess global dilation of the right ventricle, regional wall motion abnormalities (akinesia,

dyskinesia), and structural changes within the so-called ‘triangle of dysplasia’.

Dilated Cardiomyopathy (DCM)

Dilated cardiomyopathy (DCM) is characterized by excessive enlargement of the cardiac chambers and thinning of the ventricular walls, resulting in impaired contractile function. In DCM, the weakened and stretched myocardium provides a substrate for life-threatening arrhythmias.

Valvular Heart Diseases and High-Risk Variants

Severe aortic stenosis can increase left ventricular pressure and cause subendocardial ischemia, potentially leading to sudden cardiac death (SCD) during exertion. Additionally, although mitral valve prolapse (MVP) is common and generally considered benign, a rare but high-risk subtype—‘malignant MVP’—exists. Echocardiography revealing annular disjunction and excessive leaflet motion with each heartbeat should raise concern for its potential to trigger ventricular arrhythmias (Zeppenfeld, et al., 2022: 3997–4126).

Approach in Acute Settings and Post-Arrest (ROSC)

Identification of Reversible Causes: Echocardiography performed after return of spontaneous circulation (ROSC) can rapidly identify reversible conditions such as pericardial tamponade, right ventricular dilation suggestive of pulmonary embolism, and hypovolemia.

Mechanical Complications: Echocardiography is the gold-standard tool for diagnosing life-threatening mechanical complications following myocardial infarction, such as ventricular septal rupture (VSR), papillary muscle rupture, and free wall rüptüre (Byrne, et al., 2023: 3720–3826).

Provocative and Advanced Echocardiographic Techniques

Stress Echocardiography: Exercise (ESE) or dobutamine (DSE) stress echocardiography is used to detect ischemia in suspected coronary artery disease, assess myocardial viability, and provoke latent left ventricular outflow tract (LVOT) obstruction in hypertrophic cardiomyopathy (HCM).

Transesophageal Echocardiography (TEE): Provides superior resolution when transthoracic imaging is inadequate, and is particularly useful for detecting aortic dissection, infective endocarditis, and intracardiac thrombi—especially within the left atrial appendage.

Cardiac Magnetic Resonance (CMR)

In the diagnostic approach to sudden cardiac death (SCD), cardiac magnetic resonance (CMR) plays a central role due to its ability to perform tissue characterization and visualize structural abnormalities with high resolution. CMR is considered the 'gold-standard' imaging modality in cases where echocardiography (ECHO) is insufficient or when specific cardiac conditions require definitive assessment (Di Marco, et al., 2017: 28–38; Zeppenfeld, et al., 2022: 3997–4126).

Cardiac MRI in the Etiological Diagnosis of Sudden Cardiac Death

Ischemic vs. Non-ischemic Differentiation: The pattern of late gadolinium enhancement (LGE) allows differentiation between damage consistent with a coronary artery distribution (ischemic) and mid-wall or subepicardial involvement (non-ischemic/ inflammatory).

Myocarditis and Takotsubo Cardiomyopathy: CMR is crucial for distinguishing acute myocarditis—characterized by edema and late gadolinium enhancement (LGE)—from Takotsubo

cardiomyopathy, which mimics myocarditis but lacks LGE (Hanbali, Alrajeh, & Rasheed, 2015: 91–92).

Detection of Subclinical Scar: CMR can identify 'silent' myocardial scars in patients with coronary artery disease that are not evident on ECG or echocardiography (Kwong, et al., 2006: 2733–2743).

Diagnosis and Risk Stratification in Cardiomyopathies

CMR is the most powerful tool for identifying the phenotypes of cardiomyopathies at risk for sudden cardiac death (SCD) and for performing risk stratification.

Hypertrophic Cardiomyopathy (HCM): CMR can detect apical or lateral hypertrophy that may be missed on echocardiography. A late gadolinium enhancement (LGE) burden exceeding 15% of left ventricular mass is considered an independent marker of sudden cardiac death (SCD) risk and serves as a key adjudicator in decisions regarding implantable cardioverter-defibrillator (ICD) implantation (Fu, et al., 2014: 1159–1168).

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC/ARVD): CMR is the gold-standard modality for detecting fibrofatty replacement of the right ventricle, aneurysms, and regional wall motion abnormalities (Corrado, et al., 2020: 1414–1429).

Dilated Cardiomyopathy (DCM): CMR can demonstrate myocardial fibrosis through late gadolinium enhancement (LGE), allowing prediction of sudden cardiac death (SCD) risk independently of ejection fraction (EF).

Infiltrative and Inflammatory Diseases

Cardiac Sarcoidosis: Even when LVEF is normal, this disease can lead to sudden death. CMR enables diagnosis and risk assessment through patchy late gadolinium enhancement (LGE)

patterns. It is characterized by extensive subendocardial or transmural LGE, which is critical for prognostic evaluation (Coleman, et al., 2017: 411–420).

Myocarditis: One of the insidious causes of sudden cardiac death (SCD) in young individuals is the permanent damage left by prior myocarditis, such as epicardial scars. Even when the heart appears completely normal on echocardiography, these lesions can be detected only by CMR.

Arrhythmic Mitral Valve Prolapse (AMVP)

CMR can identify mitral annular disjunction (MAD) and fibrosis in the papillary muscles of patients with mitral valve prolapse, allowing assessment of their risk for malignant arrhythmias.

Invasive Diagnostic Modalities

In individuals at risk for sudden cardiac death (SCD) or those who have survived a cardiac arrest, invasive diagnostic modalities are employed to establish the underlying cause and guide treatment planning, including pharmacologic therapy, device implantation, or surgical intervention.

Coronary Angiography

Since approximately 80% of sudden cardiac death (SCD) cases are attributable to coronary artery disease, coronary angiography represents a critical component of the diagnostic approach. Impaired myocardial perfusion (ischemia) is the strongest trigger for initiating electrical storms.

Catheter-Based Angiography

Coronary angiography is the ‘gold-standard’ invasive diagnostic modality used to visualize anatomical stenoses, plaque

ruptures, or complete occlusions in the coronary arteries. Current guidelines (Class I) recommend performing coronary angiography in all patients over 35 years of age who experience unexplained cardiogenic syncope, demonstrate ischemic findings on exercise testing, or have had an episode of ventricular tachycardia (VT), to rule out underlying obstructive coronary artery disease (Zeppenfeld, et al., 2022: 3997–4126).

Coronary Anomalies

In individuals under 35 years of age, particularly athletes, angiography is not performed to assess atherosclerosis but to detect congenital lethal anomalies, such as anomalous origin of a coronary artery from the wrong sinus or myocardial bridging, where the artery is compressed between cardiac muscle fibers during exertion.

Electrophysiological Study (EPS)

An electrophysiological study (EPS) is a procedure in which the heart's electrical system is mapped from within. During EPS, a technique called 'programmed ventricular stimulation' delivers extra electrical impulses to the heart to test whether a potentially lethal arrhythmia (ventricular tachycardia [VT] or ventricular fibrillation [VF]) can be induced. However, EPS is not performed in every patient at risk for sudden cardiac death (SCD); it has specific indications.

EPS in Ischemic Heart Disease Patients: Electrophysiological study is particularly valuable in patients with a prior myocardial infarction (MI), borderline left ventricular ejection fraction (LVEF 35–40%), and unexplained syncope. If a potentially lethal ventricular tachycardia (VT) can be induced under controlled laboratory conditions during EPS, this confirms the patient as high-risk and warrants immediate implantation of an implantable

cardioverter-defibrillator (ICD) (Zeppenfeld, et al., 2022: 3997–4126).

EPS in Channelopathies (Brugada Syndrome): In asymptomatic individuals with a Type 1 Brugada pattern on resting ECG, EPS may be performed to assess the risk of sudden cardiac death (SCD). Induction of an arrhythmia during the study reveals previously hidden risk.

EPS in Wolff-Parkinson-White (WPW) Syndrome: EPS plays a fundamental and critical role both in diagnosis and risk stratification, as well as in guiding definitive (curative) therapy (Brugada, et al., 2020: 655–720).

Studies have shown that in conditions such as hypertrophic cardiomyopathy (HCM), Long QT Syndrome, or catecholaminergic polymorphic ventricular tachycardia (CPVT), attempting to induce arrhythmias via EPS has no clinical value, and the results do not reliably reflect the patient's true risk. In these patients, diagnosis and risk assessment should be based entirely on ECG, Holter monitoring, CMR, and clinical history (Ommen, et al., 2024: e1239–e1311).

Laboratory Tests and Biochemical Markers (Biomarkers)

Markers of Myocardial Wall Stress

B-type Natriuretic Peptide (BNP) and NT-proBNP: These hormones are released into the circulation by cardiac myocytes in response to increased volume or pressure load (wall stress). Elevated NT-proBNP levels in left ventricular dysfunction, heart failure, or hypertrophic cardiomyopathy (HCM) serve as one of the most powerful independent indicators of myocardial stress and, consequently, electrical instability (arrhythmic risk) (Zeppenfeld, et al., 2022: 3997–4126).

In patients with heart failure, even when LVEF is <35%, low NT-proBNP levels indicate a relatively stable electrical status,

whereas persistently elevated levels signify a substantially increased risk of ventricular fibrillation (VF).

Markers of Subclinical Myocardial Injury

High-Sensitivity Troponins (hs-TnT and hs-TnI): Unlike the massive elevations seen in acute myocardial infarction, persistent low-level elevations in troponin in stable patients at risk for sudden cardiac death (SCD)—particularly those with ischemic or dilated cardiomyopathies—serve as critical warning signals. This 'leakage'-type elevation reflects ongoing microscopic cardiomyocyte death (necrosis/apoptosis). Each lost cell is replaced by fibrous tissue (scar), which then provides an ideal substrate for lethal macro re-entrant ventricular tachycardias (VT) (McDonagh, et al., 2023: 3627–3639).

Markers of Fibrosis and Cardiac Remodeling

Myocardial fibrosis represents the most important anatomical substrate for arrhythmias. In recent years, 'profibrotic' biomarkers detectable in the blood have gained prominence, even before a visible scar (LGE) appears on CMR:

Galectin-3 (Gal-3): A protein secreted by activated macrophages that stimulates collagen production (scarring) in the heart. Elevated Gal-3 levels indicate ongoing active myocardial fibrosis and an increased risk of sudden cardiac death (SCD)..

Soluble ST2 (sST2): A specific marker of myocardial stress and tissue fibrosis. Unlike NT-proBNP, sST2 is less influenced by patient age, body mass index (BMI), or renal function, making it a highly valuable prognostic biomarker.

Electrolyte Balance and Systemic Inflammation

Inflammation: Chronic elevations in inflammatory markers, such as high-sensitivity C-reactive protein (hs-CRP), can impair the

function of ion channels in myocardial cell membranes—particularly sodium and potassium channels (channel dysfunction). This may prolong the QT interval and increase cellular excitability.

Electrolytes and the Renal Axis: Early-stage renal dysfunction, characterized by increased urinary albumin excretion (microalbuminuria) or reduced glomerular filtration rate (eGFR), reflects systemic vascular damage and is associated with a marked increase in sudden cardiac death (SCD) incidence. Chronic low levels of potassium (hypokalemia) and magnesium (hypomagnesemia), in particular, disrupt repolarization and act as direct triggers for Torsades de Pointes.

Genetic Testing

In sudden cardiac death (SCD) risk assessment, radiologic and electrical tests reveal the current state of the heart, whereas genetic testing explains why this condition has arisen at the cellular and hereditary level. In particular, in unexplained cardiac arrest cases under the age of 40, there is a high likelihood that the underlying cause is a genetically inherited cardiomyopathy or channelopathy. Therefore, genetic testing is not only directed at the patient but also serves as a cornerstone of preventive cardiology, aiming to protect at-risk family members.

Clinical Genetic Screening and Variant Interpretation

Genetic testing is performed in survivors who are clinically suspected of having a genetic arrhythmia syndrome (e.g., Long QT Syndrome, Brugada Syndrome, or HCM)—referred to as the index case or proband. Today, this is typically conducted by analyzing DNA obtained from blood or saliva using next-generation sequencing (NGS) techniques.

Pathogenic / Likely Pathogenic Variants: Mutations that are definitively or highly likely to cause disease. This result confirms

the diagnosis and provides a clear indication for screening other family members.

Benign Variants: Genetic variations that are common in the general population and do not cause disease..

Variants of Uncertain Significance (VUS): This represents the gray zone that challenges clinicians the most. A genetic variation is identified, but it has not yet been scientifically proven to cause disease. The presence of a VUS alone is insufficient to make clinical decisions (e.g., ICD implantation) or to justify screening of family members.

Cascade Screening Strategy: Upon the identification of a pathogenic variant in the index patient, the systematic, stepwise evaluation of at-risk relatives is termed cascade screening. The genetic testing modalities utilized in the etiology of sudden cardiac death (SCD) are outlined in Table 2 (McDonagh, et al., 2023: 3627–3639; Spilsberg, et al., 2024: e0016524; Zeppenfeld, et al., 2022: 3997–4126).

***Table 2**: Genetic Tests in the Etiology of Sudden Cardiac Death*

Clinical Phenotype (Disease)	**Type of Genetic Panel Used**	**Most Frequently Identified (Major) Causative Genes**	**Clinical Impact of the Pathogenic Mutation**
Hypertrophic Cardiomyopathy (HCM)	Sarcomeric Gene Panel	***MYBP3*** ***MYH7*** *TNNT2* *TNNI3*	Alters the structure of contractile proteins (sarcomeres) in cardiac myocytes, leading to hypertrophy, cellular disarray, and fibrosis.
Arrhythmogenic Right Ventricular	Desmosomal Gene Panel	***PKP2*** ***DSP*** ***DSG2*** *DSC2* *JUP*	Causes disruption of the intercellular junctions (desmosomes), leading to cell death and replacement

Cardiomyopathy (ARVC)			of myocardial tissue with fat and scar tissue.
Dilated Cardiomyopathy (DCM) and Arrhythmogenic Dilated Cardiomyopathy	Extended Cardiomyopathy Panel	***TTN*** *(Titin)*, ***LMNA***, *FLNC, RBM20*	Mutations in **LMNA (Lamin A/C)** and **FLNC** are particularly notable for causing life-threatening arrhythmias and conduction blocks long before the development of overt pump failure (Arrhythmogenic DCM).
Long QT Syndrome (LQTS)	Ion Channel (Channelopathy) Panel	***KCNQ1*** *(LQT1)* ***KCNH2*** *(LQT2)* ***SCN5A*** *(LQT3)*	Disrupts the function of potassium (K^+) or sodium (Na^+) channels, prolonging cardiac repolarization and triggering Torsades de Pointes.
Brugada Syndrome	Ion Channel (Channelopathy) Panel	***SCN5A***	Causes a loss-of-function in sodium (Na^+) channels, leading to electrical instability in the right ventricular outflow tract and resulting in polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF).
Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)	Calcium Regulation Panel	***RyR2***, *CASQ2*	Causes uncontrolled calcium (Ca^{2+}) leakage from the sarcoplasmic reticulum into the cytoplasm. Ventricular fibrillation (VF) can be triggered immediately by adrenergic discharge (exercise/stress).

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PRIMARY AND SECONDARY PREVENTION IN SUDDEN CARDIAC DEATH

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Sudden cardiac death (SCD) remains one of the most formidable challenges in contemporary cardiology, accounting for a significant proportion of cardiovascular mortality worldwide (Wong, et al., 2019: 6–14). Despite notable advancements in resuscitative medicine, the survival rate following out-of-hospital cardiac arrest remains alarmingly low, highlighting the paramount importance of robust prevention paradigms (Myerburg, 2001: 369–381). This comprehensive book chapter elucidates the fundamental distinction between primary prevention—interventions deployed in at-risk individuals without a prior history of life-threatening arrhythmias—and secondary prevention, which addresses survivors of sudden cardiac arrest (Zeppenfeld, et al., 2022: 3997–4126). We extensively review the clinical indications, technological evolution, and evidence-based applications of individual therapeutic modalities (Al-Khatib, et al., 2018: e272–e391). Special emphasis is given to implantable cardioverter-defibrillators (ICDs), the cornerstone of SCD attenuation, alongside optimizing pharmacological regimens

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leveraging current guideline-directed medical therapy (Bardy, et al., 2005: 225–237). Finally, navigating the complexities of long-term follow-up necessitates a multidisciplinary approach incorporating remote physiological monitoring, psychosocial evaluation, and genetic counseling (Hindricks, et al., 2014: 583–590).

Introduction to Sudden Cardiac Death

Sudden cardiac death (SCD) is defined as an unexpected death due to a cardiac cause that occurs within one hour of symptom onset in witnessed cases, or within 24 hours of the patient last being seen alive and symptom-free in unwitnessed cases (Zeppenfeld, et al., 2022: 3997–4126). The predominant electrophysiological mechanisms underlining SCD are ventricular fibrillation (VF) and sustained ventricular tachycardia (VT), rapidly degenerating into hemodynamic collapse and cerebral anoxia (Zipes, et al., 2006: e385–484).

Epidemiological registries indicate that SCD is responsible for approximately 50% of all cardiovascular deaths, claiming millions of lives globally each year (Wong, et al., 2019: 6–14). Given the dismal survival rate of out-of-hospital cardiac arrest (OHCA)—generally reported at less than 10% on a global scale—the focal point of modern electrophysiology remains heavily weighted toward preventative strategies (Dankiewicz, et al., 2021: 2283–2294). Prevention is dichotomized into primary and secondary arms, each governed by specific risk-stratification parameters and differing patient phenotypes (Al-Khatib, et al., 2018: e272–e391).

Primary Prevention Strategies

Primary prevention refers to the prophylactic deployment of therapeutic measures in individuals who are deemed to be at an elevated risk of experiencing sudden cardiac arrest, but who have not yet exhibited sustained ventricular arrhythmias (Zeppenfeld, et al.,

2022: 3997–4126). Risk stratification for primary prevention predominantly hinges on left ventricular ejection fraction (LVEF), symptomatology classified by the New York Heart Association (NYHA) functional class, and the underlying ischemic or non-ischemic etiology (Al-Khatib, et al., 2018: e272–e391).

Ischemic Cardiomyopathy (ICM)

Coronary artery disease accounts for roughly 75-80% of all SCD cases (Wong, et al., 2019: 6–14). The pathogenesis involves a complex interplay between acute myocardial ischemia, which promotes triggered activity, and chronic myocardial scar tissue, which serves as an anatomical substrate for macro-reentrant ventricular tachycardia (Myerburg, 2001: 369–381).

LVEF Criteria: Extensive randomized controlled trials, notably MADIT-II and SCD-HeFT, have unequivocally demonstrated the mortality benefit of primary prevention ICDs in patients with ischemic cardiomyopathy (Moss, et al., 2002: 877–883).

Current Guideline Recommendations: A primary prevention ICD is indicated in patients with ischemic etiology, an LVEF of 35% or less, and NYHA class II or III symptoms, subjected to at least three months of optimal guideline-directed medical therapy (GDMT) (Zeppenfeld, et al., 2022: 3997–4126).

Temporal Constraints: ICD implantation is generally contraindicated within the first 40 days following an acute myocardial infarction (AMI) or within 90 days following coronary revascularization, as myocardial recovery may occur (Hohnloser, et al., 2004: 2481–2488).

Non-Ischemic Dilated Cardiomyopathy (NICM)

The pathogenesis of non-ischemic dilated cardiomyopathy encompasses a broad spectrum of etiologies, including viral

myocarditis, cardiotoxic exposure, autoimmune processes, and genetic mutations (Wilde, et al., 2022: e1–e60).

Evidence Evolution: The SCD-HeFT trial initially established the efficacy of ICDs in NICM patients [5]. However, the DANISH trial generated widespread debate by demonstrating that while ICDs significantly reduced the rate of sudden cardiac death in NICM patients, they did not lead to a statistically significant decrease in overall all-cause mortality, particularly in older demographics (Kober, et al., 2016: 1221–1230).

Risk Evaluation Formulation: Currently, clinical selection for NICM emphasizes younger patient age, prominent late gadolinium enhancement (LGE) on Cardiac Magnetic Resonance (CMR) imaging representing mid-wall fibrosis, and known highly arrhythmogenic genetic mutations (Zeppenfeld, et al., 2022: 3997–4126).

Inherited Arrhythmia Syndromes (Channelopathies)

In structurally normal hearts, SCD is frequently precipitated by genetic ion channelopathies (Wilde, et al., 2022: e1–e60).

Long QT Syndrome (LQTS): This is a repolarization abnormality leading to Torsades de Pointes, for which primary prevention includes rigorous beta-blocker therapy, specifically non-selective agents like nadolol (Al-Khatib, et al., 2018: e272–e391).

Brugada Syndrome: This disease is characterized by coved-type ST-segment elevation in right precordial leads, and patients exhibiting spontaneous Brugada type 1 patterns with syncope often require ICD prophylaxis (Zeppenfeld, et al., 2022: 3997–4126).

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT): This fatal syndrome is triggered by adrenergic stress, and left cardiac sympathetic denervation (LCSD) alongside beta-blockers serves as the foundational primary

prevention modality (Wilde, et al., 2022: e1–e60). The principal inherited arrhythmia syndromes associated with sudden cardiac death and their respective primary prevention strategies are summarized in Table 1.

Table 1: Inherited Arrhythmia Syndromes (Channelopathies)

Syndrome	**Electrophysiological & Phenotypic Characteristics**	**Primary Prevention & Management**
Long QT Syndrome (LQTS)	A repolarization abnormality leading to Torsades de Pointes.	Rigorous beta-blocker therapy utilizing non-selective agents, specifically nadolol.
Brugada Syndrome	Characterized by coved-type ST-segment elevation in the right precordial leads.	ICD prophylaxis is indicated for patients exhibiting spontaneous Brugada type 1 patterns with syncope.
Catecholaminergic Polymorphic VT (CPVT)	A fatal syndrome directly triggered by adrenergic stress.	Left cardiac sympathetic denervation (LCSD) combined with beta-blockers constitutes the foundational modality.

Hypertrophic Cardiomyopathy (HCM)

In hypertrophic cardiomyopathy, mechanical disarray of myofibrils, microvascular ischemia, and extensive fibrosis provide the primary arrhythmic substrate (O'Mahony, et al., 2014: 2010–2020). Given the unreliability of LVEF as a marker in HCM, primary prevention relies on a multifactorial clinical calculator (Zeppenfeld,

et al., 2022: 3997–4126). The ESC HCM Risk-SCD mathematical formula is often utilized to estimate 5-year risk (O'Mahony, et al., 2014: 2010–2020). The mathematical expression estimating the probability of sudden cardiac death at 5 years is formulated as:

$$P_{SCD}=1-S_0(t)^{\exp(\text{Prognostik indeks})}$$

This prognostic index incorporates parameters such as maximal left ventricular wall thickness, left atrial diameter, maximal left ventricular outflow tract (LVOT) gradient, family history of SCD, non-sustained VT, and unexplained syncope. An estimated risk of 6% or greater generally mandates an active ICD discussion (O'Mahony, et al., 2014: 2010–2020; Zeppenfeld, et al., 2022: 3997–4126).

Principles of Secondary Prevention

Secondary prevention entails the ultimate medical, structural, and device-based management of patients who have survived an episode of sudden cardiac arrest due to VF or hemodynamically unstable VT (Al-Khatib, et al., 2018: e272–e391). These specific patients inherently possess a profoundly elevated risk of arrhythmic recurrence (Zipes, et al., 2006: e385–484). The conceptual distinctions between primary and secondary prevention paradigms in sudden cardiac death are summarized in Table 2.

Initial Resuscitation and Neurological Preservation

The cornerstone of secondary prevention begins immediately after the return of spontaneous circulation (ROSC) (Dankiewicz, et al., 2021: 2283–2294).

Targeted Temperature Management (TTM): Aggressively avoiding hyperpyrexia remains a critical secondary prevention measure to mitigate anoxic brain injury following a cardiac arrest (Dankiewicz, et al., 2021: 2283–2294).

Hemodynamic Optimization: Maintaining mean arterial pressure targets ensures adequate cerebral perfusion and prevents secondary ischemic insults resulting from prolonged cardiogenic shock (Myerburg, 2001: 369–381).

Table 2: Fundamental Paradigms in Sudden Cardiac Death Prevention

Clinical Paradigm	Patient Phenotype & Indication	Primary Therapeutic Objective
Primary Prevention	Prophylactic deployment in at-risk individuals who have not yet exhibited sustained ventricular arrhythmias.	To mitigate the elevated risk of an initial sudden cardiac arrest event through risk stratification.
Secondary Prevention	Addresses survivors of sudden cardiac arrest precipitated by ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia (VT).	To prevent arrhythmic recurrence in a cohort that inherently possesses a profoundly elevated risk.

Evaluation of Reversible Causes

Before committing a patient to lifelong implanted hardware or rigorous antiarrhythmic therapy, the clinician must exhaustively seek out and rectify transient, reversible triggers of the arrest (Al-Khatib, et al., 2018: e272–e391).

Acute Coronary Syndrome (ACS): The most frequent reversible cause of VF is acute transmural myocardial ischemia, which is resolved via emergent coronary angiography and subsequent percutaneous coronary intervention (PCI) (Zeppenfeld, et al., 2022: 3997–4126).

Electrolyte Derangements: Severe hypokalemia or hypomagnesemia can directly precipitate ventricular arrhythmias and must be aggressively corrected (Zipes, et al., 2006: e385–484).

Proarrhythmic Medications: A thorough pharmacological reconciliation is pivotal to identify and discontinue agents known to chronically prolong the QTc interval (Al-Khatib, et al., 2018: e272–e391).

Structural and Electrophysiological Interrogation

Once acute triggers are evaluated, a comprehensive assessment of the myocardial architecture is mandatory to dictate further secondary therapy (Zeppenfeld, et al., 2022: 3997–4126).

Echocardiography & CMR: These non-invasive modalities are vital for delineating scar volume, identifying aneurysms, and assessing global biventricular function (Myerburg, 2001: 369–381).

Electrophysiological Study (EPS): In secondary prevention of sustained monomorphic VT, an EP study can pinpoint the precise location of the reentrant circuit for targeted radiofrequency catheter ablation (Al-Khatib, et al., 2018: e272–e391).

Implantable Cardioverter-Defibrillator (ICD) Therapy

The advent of the implantable cardioverter-defibrillator represents the most profound paradigm shift in SCD mitigation in the last four decades (Zipes, et al., 2006: e385–484). ICDs unequivocally demonstrate superiority over sole antiarrhythmic pharmacotherapy for both primary and secondary prevention endpoints (Bardy, et al., 2005: 225–237). The principal device-based therapeutic modalities currently used for SCD prevention are summarized in Table 3.

Table 3: Device-Based Therapeutics for SCD Attenuation

Modality	Structural & Functional Architecture	Clinical Advantages & Constraints
Transvenous ICD	Subcutaneously implanted pulse generator linked to intravascular leads navigated into the right ventricular apex.	Delivers high-energy biphasic shocks for VF and high-frequency anti-tachycardia pacing (ATP) to terminate macro-reentrant monomorphic VT.
Subcutaneous ICD (S-ICD)	Entirely subcutaneous system situating the shock coil tunneled alongside the sternum.	Circumvents transvenous lead morbidities ; however, its extrathoracic positioning precludes the delivery of ATP for monomorphic VT.
Wearable Cardioverter-Defibrillator (WCD)	External, transient, non-invasive bridging device.	Utilized primarily in critical transitional periods, such as the initial 40 days post-myocardial infarction or following the explantation of an infected permanent ICD.

The Transvenous ICD Structure and Function

The traditional transvenous ICD consists of a subcutaneously implanted pulse generator housing the battery and capacitor, linked to leads navigated into the right ventricular apex (Moss, et al., 2002: 877–883).

Anti-Tachycardia Pacing (ATP): High-frequency pacing bursts are designed to functionally interrupt and terminate macro-reentrant monomorphic VT before the patient loses consciousness, thereby diminishing the burden of painful shocks (Moss, et al., 2012: 2275–2283).

High-Energy Defibrillation: This entails the delivery of a direct-current biphasic shock to depolarize critical myocardial mass during VF, allowing the sinoatrial node to safely resume intrinsic chronotropic control (Zeppenfeld, et al., 2022: 3997–4126).

Subcutaneous ICDs (S-ICD)

To circumvent the well-documented morbidities affiliated with transvenous leads, the entirely subcutaneous ICD (S-ICD) was developed (Knops, et al., 2020: 526–536).

Clinical Advantages: The S-ICD system avoids intravascular placement entirely, situating the shock coil tunneled alongside the sternum (Knops, et al., 2020: 526–536).

Limitations: The PRAETORIAN trial corroborated the non-inferiority of S-ICDs regarding severe complications, though the extrathoracic positioning means it cannot deliver anti-tachycardia pacing (ATP) for monomorphic VT (Knops, et al., 2020: 526–536).

Wearable Cardioverter-Defibrillators (WCD)

The Wearable Cardioverter-Defibrillator serves as a transient, non-invasive bridge to decision-making or permanent therapy in high-risk patients (Olgin, et al., 2018: 1205–1215).

Indications: The VEST trial demonstrated that WCDs are utilized primarily in critical transitional periods, such as the initial 40 days post-myocardial infarction or following the explantation of an infected permanent ICD (Olgin, et al., 2018: 1205–1215).

Device Programming

Inappropriate shocks significantly impair patient quality of life and are associated with paradoxically increased mortality indices. Modern strategy necessitates advanced programming to mitigate this issue. The MADIT-RIT trial proved that prolonged detection algorithms and higher heart rate thresholds safely permit

spontaneous arrhythmia termination without inappropriately delivering high-voltage therapy (Moss, et al., 2012: 2275–2283; Sears & Conti, 2002: 488–493).

Pharmacological Treatment

While device therapy provides the definitive life-saving shock, optimal pharmacological intervention serves a critical dual purpose (Connolly, et al., 2006: 165–171). Medications lower the arrhythmogenic substrate to prevent the initiating event and optimize overall cardiac hemodynamics (Al-Khatib, et al., 2018: e272–e391). The principal pharmacological classes used for arrhythmia suppression and their clinical applications are summarized in Table 4.

Foundational Heart Failure Therapy (GDMT)

For patients with heart failure with reduced ejection fraction (HFrEF), foundational therapies distinctly reduce the incidence of SCD entirely independent of their favorable effects on myocardial remodeling (Zeppenfeld, et al., 2022: 3997–4126).

Beta-Blockers: Carvedilol and metoprolol block surging sympathetic excess, limiting cyclic-AMP mediated intracellular calcium overload, and elevating the overall fibrillation threshold (Al-Khatib, et al., 2018: e272–e391).

MRAs: Spironolactone and eplerenone curb aldosterone-driven myocardial fibrosis, directly suppressing the formation of anatomical arrhythmogenic substrates (Zeppenfeld, et al., 2022: 3997–4126).

Table 4: Pharmacological Optimization and Arrhythmia Suppression

Pharmacological Class	Mechanism of Action & Hemodynamic Impact	Clinical Application & Associated Trials
Beta-Blockers (Carvedilol, Metoprolol)	Block surging sympathetic excess, limit cyclic-AMP mediated intracellular calcium overload, and elevate the fibrillation threshold.	Foundational therapy for HFrEF; reduces SCD incidence independent of favorable myocardial remodeling effects.
Mineralocorticoid Receptor Antagonists (MRAs)	Curb aldosterone-driven myocardial fibrosis.	Directly suppress the formation of anatomical arrhythmogenic substrates.
Amiodarone	Highly efficacious pharmacological agent for suppressing both VT and VF in patients with structural heart disease.	Drastically reduces ICD shock burden when paired with a beta-blocker (OPTIC trial), despite long-term pulmonary and thyroid toxicities.
Lidocaine & Mexiletine	Fast sodium channel blockers.	Serve excellently in the acute suppression of recurrent post-MI VT storms when administered intravenously.

ARNI: The landmark PARADIGM-HF trial illustrated that sacubitril/valsartan successfully generated a notable relative risk reduction in the absolute occurrence of sudden cardiac death compared to enalapril (J. J. McMurray, et al., 2014: 993–1004).

SGLT2 Inhibitors: The DAPA-HF trial showed that dapagliflozin serves as a foundational pillar displaying marked

mortality and arrhythmia benefits via multiple pleiotropic pathways (J. J. V. McMurray, et al., 2019: 1995–2008).

Antiarrhythmic Drugs (AADs)

True antiarrhythmic agents are primarily reserved as adjunctive therapies in patients who maintain a high burden of symptomatic ventricular arrhythmias despite maximal GDMT and successful ICD implantation (Connolly, et al., 2006: 165–171).

Amiodarone: This remains the most efficacious pharmacological agent for suppressing both VT and VF in patients with structural heart disease [5]. The OPTIC trial confirmed that amiodarone paired with a beta-blocker drastically reduces ICD shock burden, albeit with known long-term pulmonary and thyroid toxicities (Connolly, et al., 2006: 165–171).

Sotalol: Possessing both potent non-selective beta-blocking action and primary potassium channel blockade, sotalol is heavily utilized for regulating ICD shock burdens (Zeppenfeld, et al., 2022: 3997–4126).

Lidocaine and Mexiletine: These fast sodium channel blockers serve excellently in acute suppression of recurrent post-MI VT storms when administered intravenously (Al-Khatib, et al., 2018: e272–e391).

Long-term Follow-up and Care Horizons

The successful implementation of primary or secondary preventative strategies transitions the patient from an acute risk state to a chronic, device-managed paradigm (Hindricks, et al., 2014: 583–590). This chronic phase requires rigorous and methodical surveillance over decades (Zeppenfeld, et al., 2022: 3997–4126).

Device Interrogation and Remote Patient Monitoring (RPM)

The contemporary standard of care mandates the utilization of remote physiological monitoring for all ICD recipients (Hindricks, et al., 2014: 583–590).

Mechanics: The IN-TIME trial established that transceivers placed in the patient's residence communicate wirelessly with the ICD, uploading comprehensive device diagnostics to a secure server (Hindricks, et al., 2014: 583–590).

Benefits: RPM drastically reduces the latency between an asymptomatic arrhythmic event and clinical intervention, decreasing heart failure readmissions safely (Hindricks, et al., 2014: 583–590).

Sequential Re-stratification of Heart Failure

Longitudinal follow-up mandates routine echocardiographic assessments to gauge actual trajectories of targeted left ventricular remodeling (Zeppenfeld, et al., 2022: 3997–4126). If a patient experiences robust reverse-remodeling exceeding the initial 35% threshold, decisions regarding generator replacement upon ultimate battery depletion must be meticulously individualized (Al-Khatib, et al., 2018: e272–e391).

Psychosocial Ramifications and Mental Health

Navigating the existence of an implanted defibrillator profoundly alters a patient’s emotional and psychological landscape (Sears & Conti, 2002: 488–493).

ICD Shocks and PTSD: Patients who endure multiple ICD shocks frequently develop substantial anxiety, anticipatory panic disorders, and clinical Post-Traumatic Stress Disorder (Sears & Conti, 2002: 488–493).

Intervention: Long-term clinical pathways must integrate systematic psychological screening, offering cognitive-behavioral

therapy alongside aggressive shock reduction protocols (Sears & Conti, 2002: 488–493).

Genetic Counseling and Cascade Screening

For sudden cardiac death cases occurring in structurally ambiguous phenotypes or highly distinct inherited channelopathies, long-term care fundamentally extends far beyond the singular patient (Wilde, et al., 2022: e1–e60).

Proband Identification: When a genetic origin is established in the primary survivor, the framework officially mandates intensive clinical evaluation and genetic cascade screening directed at all first-degree relatives (Wilde, et al., 2022: e1–e60).

Preemptive Prevention: This rigorously allows for the extremely early identification of asymptomatic mutation carriers in the family tree, initiating primary prevention tactics long before the a sudden cardiac arrest can manifest (Wilde, et al., 2022: e1–e60).

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SUDDEN CARDIAC ARREST: CLINICAL PRESENTATION AND EMERGENCY MANAGEMENT

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Introduction

Sudden cardiac arrest (SCA) is a clinical condition characterized by the abrupt and unexpected cessation of effective cardiac mechanical activity, which, if not promptly treated, results in irreversible brain injury or death within minutes. Current guidelines, particularly the international recommendations published in 2025, provide comprehensive updates in both technical and organizational aspects of resuscitation science by systematically synthesizing evidence accumulated over the past five years to improve survival outcomes (Wigginton, et al., 2025: S538–S577). Within this framework, the management of cardiac arrest should not be considered merely as a mechanical intervention involving chest compressions and defibrillation; rather, it should be approached as a comprehensive system of care that encompasses pre-event risk reduction strategies, in-hospital treatment, post-arrest intensive care

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management, and long-term neurological rehabilitation (Del Rios, et al., 2025: S284–S312).

Although survival rates vary across regions worldwide, the incidence of cardiac arrest remains high. Particularly in cases of out-of-hospital cardiac arrest, survival is strongly associated with the organization of emergency medical systems and the capability for early intervention. Contemporary resuscitation guidelines aim to improve survival by optimizing the steps within the chain of survival, standardizing terminology to enhance interdisciplinary communication, and promoting community-based intervention strategies that encourage every individual to potentially act as a lay rescuer (Cao, et al., 2025: S578–S672).

Modern resuscitation science continues to evolve with the integration of biotechnology, digital health, and data science applications. Advanced interventions such as artificial intelligence–assisted early warning systems, real-time feedback mechanisms, and extracorporeal cardiopulmonary resuscitation (ECPR) applied in selected patient populations have gradually expanded the limits of conventional resuscitation strategies. Despite these technological advancements, the most critical determinants of survival remain the rapid recognition of cardiac arrest, uninterrupted high-quality chest compressions, timely defibrillation, and the effective implementation of multidisciplinary post-arrest care (Dezfulian, et al., 2025: S353–S384).

Out-of-Hospital and In-Hospital Cardiac Arrest

Current resuscitation guidelines classify cardiac arrest cases into two main categories based on the setting in which they occur and the resources available within the healthcare system: out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA). This distinction not only defines the physical location of the event but also represents a key determinant of response time, team

organization, treatment strategies, and overall survival outcomes (Alkuwari, et al., 2025: 112368).

Epidemiological data demonstrate that the global incidence of cardiac arrest remains substantially high, and survival rates vary significantly depending on the environment where the event occurs. In out-of-hospital cardiac arrest, survival rates are generally low, with hospital discharge rates in many countries remaining around 10%. In contrast, survival rates following in-hospital cardiac arrest can reach 20–25% in adult populations, largely due to advantages such as continuous monitoring, a higher likelihood of witnessed arrest, and rapid access to advanced life support interventions. Even higher survival rates have been reported in pediatric populations. These differences reflect the combined influence of multiple variables, including early recognition, initial rhythm, comorbidities, the quality of resuscitation, and the organization of healthcare systems (Elmer, et al., 2025: S323–S352).

In the management of out-of-hospital cardiac arrest, the most important determinant of survival is the early initiation of high-quality cardiopulmonary resuscitation (CPR) at the scene. Since the majority of these events occur in private residences, resuscitative efforts are often initiated by individuals without formal medical training. Consequently, contemporary strategies emphasize strengthening community-based response capacity. Early chest compressions performed by bystanders and the widespread availability and use of automated external defibrillators (AEDs) significantly improve survival outcomes. Additionally, the ability of emergency dispatch centers to rapidly recognize cardiac arrest and provide telephone-assisted CPR instructions plays a critical role, particularly when rescuers lack prior training. Current recommendations prioritize the delivery of continuous high-quality resuscitation at the scene rather than early transport before adequate stabilization. This strategy aims to minimize the deterioration in

compression quality that may occur during transport and to enhance overall team safety (Del Rios, et al., 2025: S284–S312).

In contrast, the fundamental paradigm in the management of in-hospital cardiac arrest extends beyond responding to an arrest; it also focuses on preventing cardiac arrest and detecting clinical deterioration at an early stage. Because many hospitalized patients are continuously monitored, physiological changes can often be detected before the onset of cardiac arrest. In this context, early warning scoring systems and rapid response teams activated based on these scores have emerged as effective tools in reducing the incidence of cardiac arrest. Regular multidisciplinary assessment of high-risk patients and proactive management of clinical deterioration contribute significantly to lowering IHCA incidence. Once cardiac arrest occurs, the rapid mobilization of a trained code team and clearly defined roles among team members represent key determinants of resuscitation quality (Del Rios, et al., 2025: S284–S312).

Contemporary resuscitation strategies increasingly view OHCA and IHCA not as separate processes but as components of an integrated system of care. The universal chain of survival model includes the following steps: preparedness, prevention, early recognition, activation of the emergency response system, high-quality CPR, rapid defibrillation, advanced life support, post-arrest care, and long-term recovery. In particular, the growing emphasis on post-arrest care and rehabilitation after hospital discharge highlights that cardiac arrest should not solely be regarded as an acute event but rather as a clinical syndrome with long-term consequences (Berg, et al., 2020: S580–S604).

In conclusion, although the setting in which cardiac arrest occurs is a critical determinant of survival, the fundamental factors associated with successful outcomes in both environments remain

early recognition, continuous high-quality chest compressions, and timely defibrillation in appropriate patients. While in-hospital systems primarily rely on early warning mechanisms and coordinated professional teams, out-of-hospital systems place greater emphasis on community training and AED accessibility; modern resuscitation science aims to integrate these two areas into a comprehensive system of care to improve survival outcomes (Panchal, et al., 2020: S366–S468).

Warning Symptoms Before Cardiac Arrest

Although sudden cardiac arrest is traditionally defined as an abrupt and unpredictable clinical event, recent epidemiological data and the 2025 resuscitation guidelines indicate that in a significant proportion of cases, prodromal symptoms may occur hours or even weeks before the arrest event. These findings suggest that cardiac arrest may not always represent a completely sudden phenomenon but rather involve a detectable pre-arrest phase that can be identified clinically (Thevathasan, et al., 2025).

Current studies indicate that more than 50% of patients who experience cardiac arrest report at least one notable symptom within the 24 hours preceding the event. The type and presentation of symptoms vary significantly among individuals, and their distribution has been shown to differ markedly between the sexes (Zheng, et al., 2022: 7738–7748).

In female patients, the most prominent and predictive symptom is dyspnea. Women experiencing sudden and unexpected shortness of breath have been shown to have approximately a three-fold increased risk of impending cardiac arrest. In contrast, the most commonly reported and strongly associated symptom in male patients is chest pain, which has been associated with approximately a two-fold increase in the risk of cardiac arrest. Other symptoms

frequently reported in men include dyspnea and diaphoresis, both of which are recognized as prodromal manifestations.

When the distribution of prodromal symptoms in the general population is examined, the five most common symptoms have been reported as follows: shortness of breath (48.7%), chest pain (18.3%), loss of consciousness or syncope (15.2%), focal neurological deficit or stroke-like symptoms (4.3%), and vomiting (4.0%). This distribution indicates that respiratory and cardiovascular symptoms predominate during the pre-arrest phase (Sohail, et al., 2023: e43732).

Agonal breathing and seizure-like movements observed immediately before or during the early minutes of cardiac arrest may also lead to delays in diagnosis.

Agonal breathing is an abnormal breathing pattern observed in approximately 40% of cases during the early phase of cardiac arrest, characterized by irregular, infrequent, and gasping inspiratory efforts. In clinical practice, this pattern is frequently misinterpreted as normal breathing. Current guidelines emphasize that agonal breathing does not represent effective ventilation and should be interpreted as a sign of cardiac arrest. In such situations, basic life support should be initiated immediately.

Seizure-like movements may also occur at the onset of cardiac arrest, particularly in younger patients. These episodes often manifest as brief tonic-clonic-like motor activity and may be mistaken for primary epileptic seizures, frequently resulting in delayed initiation of resuscitation (Kleinman, et al., 2025: S448–S478).

The clinical recognition of prodromal symptoms and the timely activation of the emergency response system have a significant impact on survival outcomes. Studies have shown that survival rates reach approximately 32.1% in patients who contact

emergency services before or during the early phase of the event, whereas survival decreases to approximately 6% among patients who ignore symptoms or delay seeking help. This dramatic difference highlights the critical role of community-based education programs and early help-seeking behavior in strengthening the first link of the chain of survival (Kleinman, et al., 2025: S448–S478).

Overall, the management of cardiac arrest has evolved beyond the traditional approach that focuses solely on post-arrest resuscitative interventions. Modern strategies increasingly emphasize the systematic recognition of prodromal symptoms and risk stratification, reflecting a more comprehensive understanding of the disease process. Accurate identification of the prodromal phase and reducing the symptom-to-intervention time interval represent key objectives of modern resuscitation science and play a decisive role in improving survival outcomes.

Initial Cardiac Rhythms

The first cardiac rhythm recorded during sudden cardiac arrest plays a crucial role in both understanding the underlying pathophysiology and determining the acute treatment algorithm. Current literature and the 2025 resuscitation guidelines classify arrest rhythms into two primary categories based on therapeutic approach: shockable rhythms and non-shockable rhythms. This distinction not only guides the intervention strategy but also directly influences both short- and long-term prognosis (Jordan, et al., 2025; Ricketts, Goyal, & Ahmed, 2025).

Shockable rhythms include ventricular fibrillation (VF) and pulseless ventricular tachycardia (pVT). Ventricular fibrillation, which represents chaotic, rapid, and electrically disorganized activity within the ventricular myocardium, is hemodynamically ineffective. Pulseless ventricular tachycardia, although more electrically organized, is similarly unable to produce effective

cardiac output due to the absence of a palpable pulse. These rhythms most commonly develop in the setting of coronary artery disease, often triggered by plaque rupture or primary electrical instability. In particular, ventricular arrhythmias associated with acute coronary syndromes account for a significant proportion of sudden cardiac arrest cases (Ricketts, Goyal, & Ahmed, 2025).

Patients presenting with shockable rhythms who receive early intervention have the highest probability of survival among all cardiac arrest subgroups. When early defibrillation can be performed, survival rates may reach approximately 40%. This observation highlights the clinical importance of rapid recognition and immediate intervention (Chan, et al., 2008: 9–17).

In the management of cardiac arrest, the priority is immediate defibrillation combined with ongoing cardiopulmonary resuscitation (CPR). Research indicates that each minute of defibrillation delay reduces the probability of successful shock delivery and survival by approximately 7–10%. Therefore, the early shock principle constitutes a central therapeutic priority in the treatment of shockable rhythms (Stieglis, et al., 2025: 235–244).

Non-shockable rhythms include asystole and pulseless electrical activity (PEA). These rhythms are generally associated with severe myocardial damage, prolonged arrest duration, or non-cardiac etiologies (Jordan, Lopez, & Morrisonponce, 2025).

Asystole represents the complete absence of both electrical and mechanical cardiac activity, typically reflecting the terminal phase of the arrest. The prognosis for patients presenting with asystole is extremely poor, with reported hospital discharge rates of approximately 2–3% (McNally, et al., 2011: 1–19).

In pulseless electrical activity (PEA), the cardiac monitor shows organized electrical activity, but effective cardiac output and a palpable pulse are absent. This condition is often associated with

reversible underlying causes. Management, therefore, focuses on the rapid identification and treatment of the potential etiologies known as the Hs and Ts, including hypovolemia, hypoxia, acidosis, hypo- or hyperkalemia, hypothermia, cardiac tamponade, tension pneumothorax, toxins, and other reversible conditions (Panchal, et al., 2018: e740–e749).

In non-shockable rhythms, the primary treatment strategy consists of continuous high-quality CPR combined with early pharmacologic intervention. Epinephrine administration is recommended as early as possible, preferably within the first minutes of arrest (Kleinman, et al., 2025: S448–S478). The distribution of the initial rhythm varies significantly depending on the clinical environment where the arrest takes place.

In cases of out-of-hospital cardiac arrest (OHCA), delayed recognition of arrest and prolonged time to defibrillation lead to over 80% of patients presenting with non-shockable rhythms such as asystole or PEA. Among these, asystole is the most frequently recorded initial rhythm (Leow, et al., 2025: 1656–1666).

In contrast, in-hospital cardiac arrest (IHCA) is often detected earlier due to continuous patient monitoring and early warning systems within the hospital environment. As a result, the proportion of shockable rhythms is significantly higher compared to OHCA. Large-scale studies have demonstrated that approximately 25–30% of IHCA cases present with an initial shockable rhythm, further emphasizing the critical role of early recognition in determining prognosis (Chang, et al., 2025: 41).

Diagnosis of Cardiac Arrest

The early and accurate recognition of cardiac arrest represents one of the most critical steps determining the effectiveness of resuscitation and the likelihood of neurologically

favorable survival. The 2025 resuscitation guidelines aim to simplify the diagnostic process to reduce intervention delays and recommend the '3-C' model (Check–Call–CPR/AED) as a practical approach. This model emphasizes the importance of rapid clinical assessment at the scene while simultaneously activating the emergency response system (Thevathasan, et al., 2025).

The diagnosis of cardiac arrest is established clinically based on three main findings: unresponsiveness, absence of normal breathing, and absence of a palpable pulse. The patient's failure to respond to verbal or painful stimuli indicates critical reduction in cerebral perfusion. This is typically accompanied by the absence of breathing or the presence of ineffective, irregular, or abnormal respiratory patterns. The inability to palpate a pulse in the central arteries indicates cessation of effective mechanical circulation. The combined evaluation of these findings enables rapid and accurate decision-making, particularly in out-of-hospital settings (Jordan, Lopez, & Morrisonponce, 2025).

One of the most common diagnostic errors involves the misinterpretation of agonal breathing as normal respiration. Agonal breathing, which may occur in the early phase of cardiac arrest, is characterized by infrequent, irregular, gasping, or snoring-like breaths. From a pathophysiological perspective, this pattern reflects terminal respiratory efforts originating from the brainstem and does not provide effective ventilation. Therefore, agonal breathing should not be interpreted as a sign of life. Current guidelines recommend that cardiopulmonary resuscitation should be initiated immediately when agonal breathing is present (Riou, et al., 2018: 92–98).

Time is a critical determinant in cardiac arrest management. For this reason, modern Basic Life Support (BLS) algorithms have abandoned the traditional “look-listen-feel” approach and replaced it with a more rapid observational assessment strategy. For lay rescuers

without medical training, pulse checks are not recommended due to the risk of delaying intervention. Instead, chest compressions should be initiated immediately in an unresponsive individual who is not breathing normally.

Healthcare professionals, however, may perform pulse assessment in adults (carotid artery) or infants (brachial artery), but this evaluation should not exceed 10 seconds. If a pulse is not definitively detected within 10 seconds, or if there is uncertainty regarding the presence of a pulse, the patient should be treated as if in cardiac arrest and chest compressions should be initiated immediately. This approach aims to minimize delays caused by incorrect or prolonged pulse assessment (Jordan, et al., 2025).

At the onset of cardiac arrest, brief tonic or myoclonic movements may occur as a result of cerebral hypoperfusion. These movements are frequently mistaken for primary epileptic seizures. Once the convulsive activity subsides, the patient's respiratory and circulatory status must be reassessed immediately.

In pediatric patients, cardiac arrest most often develops secondary to hypoxic causes, typically following progressive respiratory failure. In this population, behavioral changes or unresponsiveness, abnormal respiratory patterns, and cyanosis should be considered early warning signs (Michels, et al., 2026).

In summary, an unresponsive patient who is not breathing normally (including the presence of agonal breathing) should be considered to be in cardiac arrest until proven otherwise. Early recognition and rapid activation of the emergency response system are essential. Immediate initiation of cardiopulmonary resuscitation and automated external defibrillator (AED) application forms the cornerstone of the chain of survival; simplifying the diagnostic process and reducing decision-making time are key objectives of modern practice.

Basic Life Support

Basic Life Support (BLS) represents the most critical and time-sensitive component of resuscitation, aiming to maintain cerebral and coronary perfusion in individuals experiencing cardiac arrest until professional medical teams arrive at the scene. The current 2025 American Heart Association (AHA) and European Resuscitation Council (ERC) guidelines approach resuscitation not merely as a technical procedure but also as part of a comprehensive system of care. Within this framework, strong emphasis is placed on the integration of early recognition, rapid activation of emergency services, high-quality cardiopulmonary resuscitation (CPR), and early defibrillation. This approach aims to optimize every link in the chain of survival (Dezfulian, et al., 2025: S353–S384).

The success of resuscitation primarily depends on the rapid and accurate recognition of cardiac arrest. In an unresponsive individual who is not breathing normally (or exhibits agonal breathing), lay rescuers are advised to immediately initiate chest compressions without delaying for pulse assessment. Healthcare providers may perform pulse checks; however, this evaluation should not exceed 10 seconds. If a pulse is not definitively detected within this time frame or if uncertainty remains, cardiac arrest should be assumed and chest compressions should begin immediately. Simultaneously, the emergency response system should be activated (Del Rios, et al., 2025: S284–S312).

High-quality chest compressions form the foundation of effective BLS. In adult patients, the recommended compression rate is 100–120 compressions per minute, with a compression depth of at least 5 cm but not exceeding 6 cm. Complete chest recoil after each compression is essential, as it facilitates diastolic filling and thereby maintains coronary perfusion pressure. Interruptions in chest compressions for rhythm analysis or defibrillation should be

minimized and not exceed 10 seconds whenever possible. Compressions should be performed on a firm surface, with the rescuer's shoulders positioned directly above the patient's sternum to maximize mechanical efficiency (Hwang, et al., 2016: 1491–1498).

In adult resuscitation, the compression-to-ventilation ratio of 30:2 should be maintained until an advanced airway is established. Each ventilation should last approximately 1 second and produce visible chest rise. Excessive ventilation should be avoided because increased intrathoracic pressure reduces venous return, which subsequently decreases cardiac output and cerebral perfusion. The standard technique for opening the airway is the head-tilt-chin-lift maneuver. However, in patients with suspected cervical spine injury, the jaw-thrust maneuver should be preferred (as illustrated in Figure 1) to minimize movement of the cervical spine (Idris, et al., 2023: 1847–1856).

Timely defibrillation is one of the most critical determinants of survival, particularly in patients presenting with shockable rhythms such as ventricular fibrillation and pulseless ventricular tachycardia. Each minute of delay in defibrillation significantly decreases survival probability. Therefore, the early and appropriate use of automated external defibrillators (AEDs) is of paramount importance. After a shock is delivered, chest compressions should be immediately resumed without performing a pulse check, as this approach helps maintain adequate perfusion pressure (Anderson, et al., 2025: 30–36).

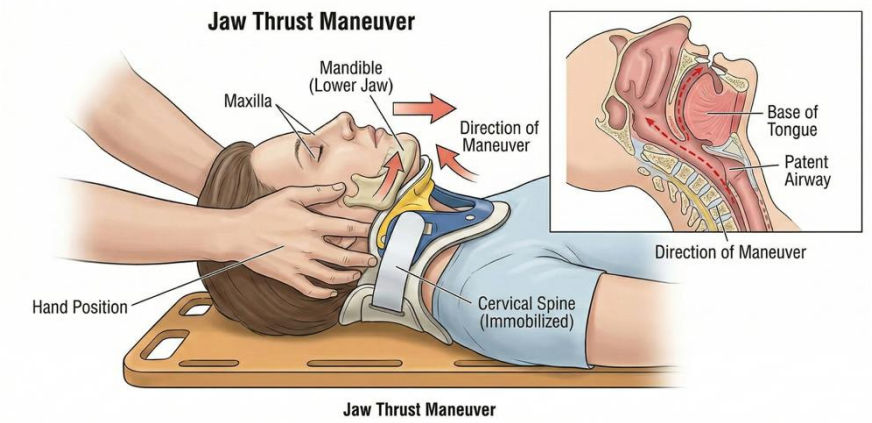

Figure 1: The jaw-thrust technique in patients with cervical trauma.

In pediatric patients, cardiac arrest most frequently results from respiratory causes, making ventilatory support especially important. The recommended compression depth is at least one-third of the anterior–posterior diameter of the chest, which is approximately 4 cm in infants; however, the two-thumb-encircling-hands technique is recommended when two rescuers are present, whereas the heel-of-the-hand technique may be used by a single rescuer.

In cases of foreign body airway obstruction, both adults and pediatric patients should be managed using a sequence of back blows followed by abdominal thrusts (Heimlich maneuver) when appropriate (Cao, et al., 2025: S578–S672).

Advanced Cardiac Life Support

Advanced Cardiac Life Support (ACLS) is the stage of resuscitation following basic life support and includes rhythm monitoring, treatment, advanced airway management, pharmacologic interventions, and systematic evaluation of reversible causes. The primary objectives at this stage are to achieve return of

spontaneous circulation (ROSC), minimize target organ injury, and improve neurologically meaningful survival.

Establishing vascular access is critical for the timely and effective administration of pharmacologic therapy. Current guidelines recommend intravenous (IV) access as the preferred route for medication delivery. Large randomized studies suggest that obtaining IV access as the initial approach may be associated with higher rates of ROSC compared to intraosseous (IO) access. Nevertheless, intraosseous access remains an effective and acceptable alternative when IV access cannot be rapidly or safely established. Administration of medications through the endotracheal route is no longer recommended in modern resuscitation algorithms due to pharmacokinetic uncertainty and reduced bioavailability (Vadeyar, et al., 2023: 109951).

The timing of drug administration during resuscitation differs depending on whether the arrest rhythm is shockable or non-shockable rhythm. Epinephrine should be administered at a dose of 1 mg IV or IO every 3-5 minutes in all cardiac arrest rhythms. In non-shockable rhythms (asystole and pulseless electrical activity), early administration of epinephrine—preferably within the first 3 minutes of arrest—is considered critical for improving survival and neurological outcomes (Zhong, et al., 2023: 24).

In shockable rhythms (ventricular fibrillation and pulseless ventricular tachycardia), the priority remains early defibrillation, and epinephrine should be administered only after initial defibrillation attempts have failed. In cases of refractory ventricular fibrillation or pulseless ventricular tachycardia, antiarrhythmic agents such as amiodarone or lidocaine are recommended. Amiodarone is typically administered as a 300 mg IV bolus, followed by an additional 150 mg dose if necessary. Lidocaine may be used as an alternative, with an initial dose of 1-1.5 mg/kg, followed by additional doses of 0.5-

0.75 mg/kg if required (Kudenchuk, et al., 2016: 1711–1722; White, Hankins, & Bugliosi, 1998: 145–151).

Rhythm management and defibrillation strategies constitute the central elements of ACLS. For ventricular fibrillation and pulseless ventricular tachycardia, the recommended energy level for biphasic defibrillators should follow the manufacturer's recommendations; if these are unknown, the maximum available energy should be used. In synchronized cardioversion for atrial fibrillation or atrial flutter, higher initial energies (at least 200 J biphasic) are recommended because they increase the likelihood of successful cardioversion with the first shock (Stiell, et al., 2007: 1511–1517).

In cases of refractory ventricular fibrillation unresponsive to standard shocks, alternative strategies such as double sequential defibrillation or vector change have been proposed. However, current evidence remains limited; these techniques should be considered primarily within research settings rather than routine clinical practice. Polymorphic ventricular tachycardia should be treated as a hemodynamically unstable rhythm and requires immediate defibrillation (Deakin, et al., 2002: 812–813).

For hemodynamically unstable symptomatic bradycardia, the recommended atropine dose has been updated to 1 mg IV. If pharmacologic therapy is ineffective, temporary transvenous pacing should be considered (Chadda, et al., 1977: 503–510).

Advanced airway management should be performed in a manner that minimizes interruptions in chest compressions. The choice between supraglottic airway devices and endotracheal intubation depends largely on the provider's experience and local success rates. Once an advanced airway is established, capnography monitoring becomes standard practice (Rivers, et al., 1993: 878–883).

Capnography has two important purposes: confirming correct endotracheal tube placement and monitoring the quality of cardiopulmonary resuscitation. During CPR, an end-tidal carbon dioxide ($ETCO_2$) value of 20 mmHg or higher generally indicates adequate perfusion and a higher probability of ROSC. Conversely, the head-up technique proposed to improve cerebral perfusion is not currently recommended in routine clinical practice due to insufficient evidence (Nassal, et al., 2024: e2419274).

Systematic evaluation of reversible causes represents an integral component of ACLS. Rapid identification and treatment of conditions such as hypoxia, hypovolemia, hyperkalemia, hypothermia, toxic exposures, and pulmonary embolism may significantly improve survival outcomes (Reynolds, et al., 2022: 54–63). Additionally, in cases of suspected opioid overdose, administration of naloxone is recommended as an adjunct to standard resuscitation algorithms (McClellan, et al., 2018: 90–95).

In summary, according to the 2025 guidelines, Advanced Cardiac Life Support is based on the following: early and appropriately timed epinephrine administration; prioritization of intravenous access; effective defibrillation at adequate energy levels; capnography-guided quality monitoring; and systematic management of reversible causes.

Defibrillation

Defibrillation is a fundamental resuscitative intervention that terminates chaotic electrical activity in the ventricular myocardium through the delivery of a high-energy electrical shock, thereby allowing the heart's natural pacemaker centers—primarily the sinoatrial node—to re-establish organized electrical control (Ricketts, Goyal, & Ahmed, 2025). The 2025 resuscitation guidelines emphasize that early defibrillation in shockable rhythms, particularly ventricular fibrillation (VF) and pulseless ventricular

tachycardia (pVT), is the most powerful independent determinant of survival (Wigginton, et al., 2025: S538–S577).

Before defibrillation can be performed, the patient must first be connected to a monitor and the cardiac rhythm must be accurately analyzed. Ventricular fibrillation is characterized by irregular and chaotic electrical activity within the ventricles that prevents effective mechanical contraction, resulting in the absence of cardiac output and a palpable pulse. Pulseless ventricular tachycardia, although more electrically organized, similarly fails to generate effective circulation because of extremely rapid ventricular activity. In the absence of timely defibrillation, both rhythms may rapidly deteriorate into asystole (Ricketts, Goyal, & Ahmed, 2025).

Time is a critical determinant of successful defibrillation. Each minute of delay in delivering a shock significantly reduces the probability of survival. Defibrillation performed within the first few minutes following cardiac arrest has a substantially higher likelihood of restoring a perfusing rhythm. Consequently, the widespread availability and rapid use of automated external defibrillators (AEDs) constitute a central strategy in the management of out-of-hospital cardiac arrest. The concept of “zero tolerance for delay” emphasizes immediate rhythm analysis followed by prompt shock delivery (Swor, et al., 1995: 780–784).

The energy level used for defibrillation depends on the waveform characteristics of the device. For biphasic defibrillators, the initial energy should follow the manufacturer’s recommended settings (typically 120–200 J). If the recommended energy level is unknown, the maximum available energy should be used. In cases of hemodynamically unstable atrial fibrillation or atrial flutter, synchronized cardioversion is indicated, and beginning with at least 200 J of biphasic energy increases the likelihood of successful conversion with the first shock. For monophasic defibrillators, a

standard energy level of 360 J is recommended for all shocks (Tang, et al., 2025: e257411).

In pediatric patients, energy dose should be calculated according to body weight. The recommended energy for the first shock is 2–4 J/kg, while subsequent shocks should be delivered at 4 J/kg (maximum 10 J/kg or adult maximum dose if necessary) (Lavignasse, et al., 2021: 291–292).

The effectiveness of defibrillation depends not only on the delivered energy but also on its integration into continuous chest compressions. Interruptions in compressions before and after shock delivery should be minimized and not exceed 10 seconds; immediately after shock delivery, chest compressions should be resumed without performing rhythm or pulse checks, as maintaining perfusion pressure is essential for improving post-shock outcomes (Dezfulian, et al., 2025: S353–S384).

Defibrillator pads should typically be placed in an anterolateral configuration, with one pad positioned on the right upper parasternal region and the other on the left mid-axillary region. Alternatively, an anteroposterior configuration may be used. In female patients, unnecessary delays should be avoided during pad placement; rather than removing all clothing, pads should be positioned appropriately to allow rapid continuation of resuscitation efforts. Superficial metallic accessories on the body generally do not constitute a contraindication to defibrillation unless they directly interfere with pad placement (Lupton, et al., 2024: e2431673).

Return of Spontaneous Circulation and Early Post-Resuscitation Care

Return of spontaneous circulation (ROSC) represents a critical milestone in the management of cardiac arrest; however, it does not signify the end of the clinical process. Instead, it marks the

beginning of a complex pathophysiological condition known as the post-cardiac arrest syndrome. This syndrome is characterized by a combination of global ischemia–reperfusion injury, myocardial dysfunction, systemic inflammatory response, and persistent underlying etiological factors. The 2025 resuscitation guidelines consider post-resuscitation care an integral component of the chain of survival, aiming to limit neurological injury, optimize organ perfusion, and rapidly identify and treat the underlying cause (Hirsch, et al., 2025: S673–S718).

From a terminological perspective, the restoration of circulation achieved through mechanical support is referred to as "return of circulation" (ROC), whereas the spontaneous reappearance of effective cardiac mechanical activity is defined as "return of spontaneous circulation" (ROSC). Following ROSC, patients should be systematically evaluated using an ABCDE approach. Airway patency must be secured; adequate oxygenation and ventilation must be ensured; circulatory parameters must be stabilized; and neurological status must be closely monitored. Importantly, the resuscitation process should not be considered complete at this stage (Hirsch, et al., 2025: S673–S718).

Hemodynamic stability is of paramount importance during the post-arrest period. Hypotension is directly associated with poor neurological outcomes and increased mortality. Therefore, maintaining a mean arterial pressure (MAP) of at least 65 mmHg is recommended. When necessary, fluid resuscitation and vasopressor therapy should be initiated to achieve this target MAP (Lamontagne, et al., 2020: 938–949).

Oxygenation should be carefully titrated. While the initial administration of high-concentration oxygen is appropriate during early stabilization, once this is achieved, the arterial oxygen saturation should be targeted within the range of 92–98% to avoid

potential oxidative injury associated with hyperoxia. Ventilation strategies should aim to maintain normocapnia (PaCO2 35–45 mmHg), and hyperventilation should be avoided. Hypocapnia may lead to cerebral vasoconstriction and reduced cerebral perfusion, thereby potentially worsening neurological injury (Lamontagne, et al., 2020: 938–949).

Targeted Temperature Management (TTM) is a key component of neuroprotection following cardiac arrest. In adult patients who remain unresponsive to verbal commands after ROSC, body temperature should be maintained at a constant temperature between 32°C and 37.5°C, and current guidelines recommend that temperature control should be maintained for at least 36 hours. The primary aim of this strategy is to prevent fever and mitigate reperfusion injury; active normothermia is also considered an acceptable approach within this framework (Granfeldt, et al., 2023: 109928).

Following ROSC, etiological evaluation should be conducted systematically. A 12-lead electrocardiogram (ECG) should be obtained in all adult patients to assess for evidence of acute coronary syndrome. Early coronary angiography is recommended in patients with an initial shockable rhythm, ST-segment elevation, or when a cardiac etiology is strongly suspected (Kern, et al., 2015: 1031–1040).

To determine the underlying cause of cardiac arrest and identify potential complications related to resuscitation, additional diagnostic imaging may be considered. Computed tomography (CT) imaging from head to pelvis, and point-of-care cardiac ultrasound (POCUS) can be valuable tools in selected patients. These modalities are particularly useful in rapidly excluding alternative etiologies such as pulmonary embolism, aortic dissection, or intracranial pathology (Magon, et al., 2024).

The process of neuroprognostication should not be rushed. In the early post-arrest period, the effects of sedative medications, metabolic disturbances, and targeted temperature management may reduce the reliability of neurological assessment. Therefore, definitive evaluation should generally be postponed for at least 72 hours after the event, and an additional 72 hours after the return to normothermia if TTM has been applied.

A multimodal approach is recommended for neurological prognostication, including clinical neurological examination, electroencephalography (EEG), somatosensory evoked potentials, and biochemical biomarkers. Biomarkers such as neuron-specific enolase (NSE) and neurofilament light chain (NfL) may provide valuable information regarding the extent of hypoxic-ischemic brain injury (Czimmeck, et al., 2023: 109964; Wahlster, et al., 2023: 676–687).

Post-resuscitation care extends beyond acute physiological stabilization. Survivors of cardiac arrest frequently experience cognitive impairment, depression, anxiety, and symptoms consistent with post-traumatic stress disorder. Similarly, caregivers may experience a substantial psychosocial burden. Therefore, structured psychosocial assessment prior to hospital discharge and referral to multidisciplinary rehabilitation programs are recommended.

Ultimately, the goal of post-resuscitation care is not only to ensure survival but also to maximize functional recovery and long-term quality of life (Yaow, et al., 2022: 82–91).

In summary, while the restoration of spontaneous circulation represents a successful stage in resuscitation, optimal clinical outcomes can only be achieved through a systematic, evidence-based, and multidisciplinary early post-resuscitation care strategy. Hemodynamic optimization, controlled oxygenation and ventilation, targeted temperature management, early etiological evaluation, and

careful neuroprognostication constitute the fundamental components of this process.

Termination of Resuscitation

Termination of resuscitation (TOR) represents one of the most complex and ethically sensitive decision-making areas encountered by clinicians during cardiopulmonary resuscitation (CPR). The primary objective of this decision is to avoid futile resuscitation efforts in situations where the likelihood of survival is absent or extremely low, while ensuring that resuscitative efforts continue in patients who may still have the potential for recovery. This approach aims both to maximize patient benefit and to promote the efficient use of emergency medical system resources. The 2025 resuscitation guidelines, particularly in the context of out-of-hospital cardiac arrest (OHCA), have further systematized the decision-making process for termination of resuscitation by redefining TOR rules according to the level of training and capability of emergency medical services personnel and clarifying their appropriate application (Wigginton, et al., 2025: S538–S577).

To standardize clinical decision-making and reduce the risk of inappropriate termination, clinicians should use validated termination of resuscitation rules. These rules are generally categorized into three main approaches. The Basic Life Support (BLS) TOR rule was developed for application by BLS-level healthcare providers in out-of-hospital cardiac arrest situations in which advanced life support (ALS) resources are not available or are expected to be significantly delayed. In contrast, the Advanced Life Support (ALS) TOR rule is designed to guide resuscitation termination decisions made by teams capable of providing ALS-level interventions at the scene. The third approach, known as the Universal TOR rule, was developed for tiered emergency medical systems in which both BLS and ALS teams operate together. Despite

these differences, the core criteria underlying these TOR rules are largely similar. These include: cardiac arrest not witnessed by emergency medical services personnel, no defibrillation delivered prior to transport, and failure to achieve return of spontaneous circulation during resuscitation efforts (Wigginton, et al., 2025: S538–S577).

Physiological parameters may also contribute to the decision-making process when considering termination of resuscitation. In this context, end-tidal carbon dioxide ($ETCO_2$) measurement is recognized as a parameter reflecting the effectiveness of circulation during resuscitation and provides prognostic information; however, the current guidelines emphasize that $ETCO_2$ values alone should not be used as the sole criterion for terminating resuscitation.

In intubated patients receiving advanced life support, the inability to maintain an $ETCO_2$ level above 10 mmHg after at least 20 minutes of resuscitation, as measured using waveform capnography, may be considered as part of a multifactorial clinical assessment in evaluating the termination of resuscitation. Conversely, in adult patients without an advanced airway, there is insufficient evidence to support using a specific $ETCO_2$ threshold measured during CPR as a reliable criterion for terminating resuscitation. Therefore, $ETCO_2$ measurements in this patient population should be interpreted with caution (Crickmer, et al., 2021: 76–81; Wayne, Levine, & Miller, 1995: 762–767).

Importantly, the applicability of TOR rules does not extend to all patient populations. Current evidence suggests that these rules have not been sufficiently validated for drug overdose-related cardiac arrest, trauma-related cardiac arrest, or in-hospital cardiac arrest (IHCA). Consequently, direct application of TOR rules in these scenarios is not recommended. Instead, decisions should be individualized based on patient-specific clinical characteristics, the

underlying etiology of the arrest, and the dynamic findings observed during the resuscitation process.

In conclusion, although standardized TOR rules provide valuable guidance in the resuscitation decision-making process, the termination of resuscitation should always involve a comprehensive clinical assessment integrating clinical judgment, patient-specific factors, and ethical considerations.

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POST-SUDDEN CARDIAC DEATH EVALUATION, POST-MORTEM EXAMINATION, FAMILY SCREENING, AND THE GENETIC APPROACH

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Sudden cardiac death (SCD) should be approached differently across the various stages of life. Although SCD is a very rare event during infancy, childhood, and adolescence, it typically results in death within minutes. The most common causes include malformations of the heart and great vessels, as well as cardiac arrhythmias. In young and middle-aged adults, myocarditis, cardiomyopathies, and rhythm disorders are more frequent causes of death. In older adults, acute myocardial infarction appears to be the leading cause and is often regarded as the first manifestation of coronary artery disease (Madhavan, et al., 2011: 93–102). For this reason, forensic autopsy is required more often in cases of sudden death occurring in younger individuals than in those occurring in older adults.

Cardiovascular diseases are estimated to cause approximately 17 million deaths worldwide each year, and nearly

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25% of these deaths are thought to be attributable to SCD (Basso, et al., 2017: 691–705). Autopsy represents both the first and the final opportunity to establish an accurate diagnosis in cases of SCD. Macroscopic examination of the heart and the collection of histological samples are routine components of the autopsy; however, the investigation should not be limited to these procedures alone. When indicated, toxicological, microbiological, biochemical, and molecular analyses should also be performed.

Determination of the Cause of Sudden Cardiac Death and Autopsy

In the 2017 guidelines on the evaluation of SCD issued by the Association for European Cardiovascular Pathology, the role of the forensic autopsy was defined as follows (Basso, et al., 2017: 691–705):

to determine whether SCD is attributable to a cardiac disorder or to other causes of sudden death

to establish the nature of the underlying cardiac disease and to clarify whether the mechanism of death is arrhythmic or mechanical

to assess whether the condition responsible for SCD is hereditary and, accordingly, to determine the need for screening and genetic counselling among close relatives

to investigate the possible involvement of toxins or illicit substances, trauma, and other non-natural causes

to evaluate the potential role of third parties in the death

Identifying the underlying cause of SCD can be challenging. For this reason, a careful and methodical procedure is required. The first step in the diagnostic approach is the collection of a detailed medical history. Information obtained from the deceased individual's family members and primary care physician may be particularly

valuable. Age, sex, occupation, lifestyle factors—especially alcohol consumption and smoking habits—and exercise patterns should be carefully assessed. The location and circumstances of death, such as whether it occurred at rest, during sleep or during physical exertion, as well as the presence of eyewitnesses, may help clarify the cause of death. Past medical history, available medical records, prescribed and over-the-counter medications, and family history should also be reviewed. When available, electrocardiographic recordings obtained during resuscitation and troponin measurements may provide additional insight into the cause of SCD.

The autopsy begins with an external examination. Body weight, height, and waist circumference should be measured, and body mass index should be calculated. The body habitus, hair, and skeletal system should be assessed for any abnormalities. All external and internal injuries must be examined in detail, with particular attention to findings associated with cardiovascular disease, such as digital clubbing, xanthelasma, and xanthomas. The presence of implanted pacemakers and other electrical devices should also be investigated. Devices such as smartwatches and mobile phones capable of recording cardiac rhythm may provide valuable information regarding potential arrhythmias. Evaluation of these devices by a cardiologist before the autopsy may yield evidence relevant to causes of death that cannot be demonstrated morphologically, particularly rhythm disorders (Strik, et al., 2024: 174–180). If implantable cardioverter defibrillators are present, they should be deactivated before the autopsy for safety reasons.

In the standard macroscopic examination of the heart, the pericardium and pericardial cavity should be carefully evaluated. The anatomy of the great vessels should be assessed, and the pulmonary arteries should be examined to exclude thromboembolism. When congenital heart disease is suspected, removal of the heart and lungs en bloc may represent an appropriate

approach. If aortic dissection is suspected, the aorta should be examined meticulously from the ascending aorta to the iliac bifurcation. The atrial chambers and the interatrial septum should also be inspected, and the patency of the foramen ovale should be determined. The mitral and tricuspid valves, including any prosthetic valves, should be evaluated, and the integrity of the papillary muscles and chordae tendineae should be assessed.

The coronary ostia should be examined with regard to their shape, location, number, and patency. Dissection of the coronary arteries constitutes one of the most important steps of the autopsy. The size, course, and dominance of the epicardial coronary arteries should be assessed, and multiple transverse sections should be made at 3 mm intervals along their course, including the side branches, in order to evaluate luminal patency. If only a limited period has elapsed since stent implantation, the stents may be removed longitudinally and examined for thrombus. Coronary artery bypass grafts should likewise be carefully evaluated by transverse sectioning, with particular attention to the proximal and distal anastomotic sites. Triphenyltetrazolium chloride (TTC) staining may be used in the autopsy room as a preliminary method for identifying acute myocardial infarction (Basso, et al., 2017: 691–705). Parallel transverse sections of the heart should be obtained beginning at the mid-ventricular level. These sections allow assessment of changes involving the endocardium, myocardium, and ventricular cavities on the cut surface. After complete drainage of the blood, the total heart weight should be measured. At the mid-ventricular level, the thickness of the free walls of the left and right ventricles, as well as that of the interventricular septum, should be measured excluding trabeculations. These measurements should be compared with reference tables for normal wall thickness according to age, sex, and body mass index (Vanhaebost, et al., 2014: 615–620). Additional measurements may be performed when necessary to determine

cardiac chamber dimensions more accurately. All cardiac valves, together with the ventricular inflow and outflow tracts, should be examined. If electrocardiographic findings suggest pre-excitation, the atrioventricular annuli should be preserved and subjected to histological examination when indicated.

The diseases responsible for SCD may be classified as coronary and non-coronary causes. Coronary causes include atherosclerosis, coronary artery disease, myocardial infarction, coronary dissection, coronary embolism, congenital anomalies of the coronary arteries, coronary artery aneurysms, myocardial bridging, and arteritis. Non-coronary causes include cardiomyopathies such as dilated cardiomyopathy, hypertrophic cardiomyopathy, non-compaction cardiomyopathy, and arrhythmogenic right ventricular dysplasia, as well as valvular heart diseases, myocarditis of bacterial, viral, autoimmune, or toxic origin, cardiac conduction disorders, tumors, and cardiac arrhythmias including long and short QT syndromes, other channelopathies, and ventricular tachyarrhythmias. In descending order of frequency, coronary artery disease, cardiomyopathies, inherited cardiac arrhythmias, and valvular heart diseases appear to be the most common causes of SCD (Markwerth, et al., 2021: 483–495).

Coronary Causes of Sudden Cardiac Death

Although there are variations among countries, coronary heart disease appears to be the most common cause of SCD in men over 35 years of age (Kramer, et al., 2010: 122–132). In cases of SCD related to the coronary arteries, the principal mechanism is thought to be ventricular tachyarrhythmias triggered by acute ischemia. In addition to arrhythmic mechanisms, SCD may also occur as a result of myocardial rupture involving the free wall, papillary muscles, or ventricular septum. Macroscopic examination of the coronary arteries may reveal coronary aneurysms, coronary

dissection, anomalous coronary origins, and myocardial bridging. In cases of coronary aneurysm, thrombus formation within the aneurysmal sac and subsequent embolization may lead to acute myocardial infarction and ultimately result in SCD. In SCD associated with coronary aneurysms, concomitant coronary thrombosis is frequently identified. Coronary artery dissections can usually be detected macroscopically at autopsy. In cases of anomalous coronary origin and myocardial bridging, SCD generally occurs secondary to cardiac arrhythmia; therefore, no additional autopsy findings are often present. When no other pathology capable of explaining SCD is identified, these findings may be accepted as the probable cause of death.

Tissue samples should be obtained from the coronary arteries for histological examination. In addition, when coronary thrombus is identified, samples should also be collected for histological and immunohistochemical analysis. Such specimens may help determine the age of the infarction (Aljakna, Fracasso, & Sabatasso, 2018: 425–438). The collected material should be fixed in formalin, and sectioning should be performed after 24 hours of fixation. Approximately two-thirds of detected coronary thrombi are organized and are regarded as the definitive cause of SCD. In autopsy studies of victims of SCD, the prevalence of acute coronary thrombus or significant coronary lesions has been reported to range between 19% and 74% (Davies & Thomas, 1984: 1137–1140; Farb, et al., 1995: 1701–1709).

Non-Coronary Causes of Sudden Cardiac Death

Cardiomyopathies

Cardiomyopathies represent the second most common cause of SCD in developed countries (Chugh, et al., 2004: 1268–1275). In addition, the prevalence of cardiomyopathies in autopsy series of SCD among individuals under 35 years of age is higher than that

observed in older individuals (Margey, et al., 2011: 1411–1418; Puranik, et al., 2005: 1277–1282).

Non-ischemic dilated cardiomyopathy (NIDCM) may develop secondary to hypertension, valvular heart disease, genetic mutations, myocarditis resulting from viral, bacterial, fungal, or parasitic infections, heavy alcohol consumption, chemotherapeutic agents, heavy metals, autoimmune disorders, and toxic exposures. At autopsy, cardiomegaly, dilatation of the cardiac chambers, and reduced ventricular wall thickness may be identified, whereas no significant stenosis is observed in the coronary arteries. Histological examination may reveal diffuse patchy fibrosis, inflammatory cell infiltration, particularly in cases secondary to myocarditis, myocyte hypertrophy, nuclear enlargement, and hyperchromasia. In toxin-related cases, myocyte vacuolization and degeneration may also be observed (Calabrese, et al., 2025). If familial NIDCM is suspected, genetic testing may be performed. Autosomal dominant inheritance has been identified in up to 40% of cases of inherited NIDCM. To date, more than 40 gene mutations associated with NIDCM have been reported. Among these, TTN, MYH7, TNNT2, and LMNA are the most frequently identified (Lakdawala, Winterfield, & Funke, 2013: 228–237).

In hypertrophic cardiomyopathy (HCM), macroscopic examination of the heart reveals increased heart weight and thickening of the left ventricular wall. Histological examination may demonstrate myocytes arranged in a disorganized pattern, with loss of parallel alignment and a whorled appearance, together with areas of interstitial and patchy fibrosis. In addition, enlarged hyperchromatic myocyte nuclei, thickening of the intimal and medial layers of the intramural coronary arteries, and findings consistent with microvascular ischemia may be observed (Duncanson & Mackey-Bojack, 2018: 565–615; Tabib, et al., 2003: 3000–3005). Before establishing a diagnosis of HCM, it should be

confirmed that abnormal loading conditions such as valvular heart disease, hypertension, and diabetes are not present. More than 1,500 mutations in over 11 genes associated with HCM have been identified. The most frequently detected mutations involve the genes encoding beta-myosin heavy chain and myosin-binding protein C. Genetic analysis is recommended in suspected cases (Grupa Robocza Europejskiego Towarzystwa Kardiologicznego do spraw rozpoznawania i postepowania w kardiomiopatii, et al., 2014: 1054–1126).

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC) is a disorder characterized by fibrolipomatous replacement of the right ventricular myocardium. It is estimated that in nearly 50% of cases, the first arrhythmic event leads to SCD (Quarta, et al., 2011: 2701–2709). At autopsy, macroscopic examination may reveal thinning of the right ventricular free wall, right ventricular dilatation, a yellowish discoloration of the ventricular wall due to fatty infiltration, and focal aneurysmal areas (Thiene, et al., 1988: 129–133). Histological examination may show fibrofatty degeneration of the myocardium, loss of myocytes, interstitial fibrosis, adipose tissue between myocardial fibers, and mild inflammatory infiltrates in some areas. Another characteristic finding is a structural abnormality involving the right ventricular inflow tract, outflow tract, and apex. This pattern is known as the triangle of dysplasia (Bueno-Beti & Asimaki, 2021: 746321; Burke, et al., 1998: 1571–1580). Approximately 15 gene mutations have been reported in association with ARVC. Up to 60% of these mutations show autosomal dominant inheritance. mutations in the genes encoding plakophilin-2, desmoglein-2, and desmoplakin are the most frequently identified (den Haan, et al., 2009: 428–435). When autopsy and histological examination demonstrate findings consistent with ARVC, genetic testing and family screening should be considered.

Valvular Heart Diseases

Valvular heart disease is responsible for 1% to 5% of SCD (Chugh, et al., 2004: 1268–1275; Loire & Tabib, 1996: 13–18). Severe aortic stenosis, bicuspid aortic valve, and severe mitral regurgitation due to chordal rupture are recognized causes of SCD. The role of mitral valve prolapse (MVP) in SCD remains controversial (Han, et al., 2018: e010584). Although most cases of MVP are considered benign, certain features appear to be associated with higher risk. These include leaflet thickening, greater prolapse severity, and increased left ventricular diameter (Hayek, Gring, & Griffin, 2005: 507–518). Recent data also suggest that women with bileaflet prolapse and complex ventricular ectopy may be at particularly high risk (Sriram, et al., 2013: 222–230). During autopsy, the integrity of all valves, papillary muscles, and chordae tendineae should be examined. If a prosthetic valve is present, it should be evaluated for valve dysfunction. When pannus formation or vegetation is identified, tissue samples should be obtained and fixed (Basso, et al., 2017: 691–705).

Myocarditis

If SCD is thought to be related to myocarditis or cardiomyopathy, several small tissue samples should be fixed in 2.5% glutaraldehyde as early as possible for electron microscopic examination (Markwerth, et al., 2021: 483–495). Samples for histological analysis should be taken from the ventricular walls, the interventricular septum, and the atria. In deaths related to myocarditis, macroscopic examination may reveal edematous myocardial tissue, while microscopic examination may show inflammatory infiltrates and myocytolysis. At the microscopic level, myocarditis is considered highly probable when more than two T lymphocytes (CD3, CD45R0) are identified in the field of view at ×400 magnification, when more than seven inflammatory cells per

mm² are present, and when more than 14 CD68-positive cells, including T lymphocytes and macrophages, are detected in each visual field. For each count, 20 visual fields should be examined and the average value should be calculated. If inflammatory infiltrates are identified without myocytolysis, a diagnosis of myocarditis should not be made immediately. Instead, the number of samples and sections should be increased. If myocardial infiltrates are repeatedly demonstrated, the diagnosis of myocarditis may be regarded as probable (Basso, et al., 2017: 691–705).

If a cardiotropic virus can be isolated, focal inflammatory infiltrates may support a diagnosis of viral myocarditis (Basso, et al., 2001: 290–300). Extensive myocytolysis and diffuse myocarditis may lead to death through ventricular fibrillation or acute heart failure (Baroldi, Oliveira, & Silver, 1997: 263–268). When no other pathology is found that can explain SCD, the presence of minor cellular infiltration together with isolation of a viral genome may suggest an arrhythmic cause of death (Dettmeyer, et al., 2004: 947–952). In addition, bacteriological, virological, and immune complex analyses may help clarify the cause of death. In myocarditis-related deaths, viral myocarditis is the most common form, whereas bacterial and fungal myocarditis are much less frequent. Deaths caused by cardiac sarcoidosis, cardiac involvement of tuberculosis, and rheumatoid myocarditis are extremely rare (Markwerth, et al., 2021: 483–495). Among cases of viral myocarditis leading to SCD, Coxsackie viruses are the most commonly isolated agents. More recent findings, however, have shown that viral lymphocytic myocarditis may also occur during COVID-19 infection (Kandolf, 1995: 430–438; Siripanthong, et al., 2020: 1463–1471).

Cardiac Arrhythmias

Sudden deaths with no detectable findings at autopsy are reported more often in younger individuals. The reported frequency

of autopsy-negative SCD varies across studies. These differences may reflect regional genetic variation. More detailed histological examination in all victims of sudden cardiac arrest may reduce the proportion of cases classified as autopsy negative. In nearly 50% of cases with no pathological findings at autopsy, inherited arrhythmic syndromes such as long QT syndrome (LQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and early repolarization syndrome (ERS) are identified (Wever & Robles de Medina, 2004: 1137–1144). In such cases, molecular autopsy and sequential screening of family members may help determine the cause of death and may also allow identification of individuals who are at potential risk of SCD.

Long QT syndrome (LQTS) is an inherited disorder characterized by delayed myocardial repolarization. It causes prolongation of the QT interval on a 12-lead electrocardiography (ECG) and creates a predisposition to torsades de pointes, which may lead to SCD (SCD). A large proportion of patients with LQTS carry mutations affecting potassium channels such as KCNQ1 and KCNH2 or the sodium channel gene SCN5A (Goldenberg, Zareba, & Moss, 2008: 629–694). No distinct pathological finding is usually identified at autopsy in cases of SCD related to LQTS. However, the diagnosis may be established through genetic testing and molecular autopsy.

Brugada syndrome (BrS) is a genetic disorder that predominantly affects middle-aged men. The first arrhythmic event usually occurs during sleep at around 40 years of age. Type 1 Brugada pattern on a resting 12-lead ECG is characterized by a coved ST-segment elevation, J-point elevation of at least 2 mm (0.2 mV), and a negative T wave in the right precordial leads V1 to V3. The diagnosis of BrS is made when type 1 Brugada features are observed spontaneously or after administration of sodium channel blockers in at least one right precordial lead, particularly V1 or V2.

More than 500 pathogenic variants have so far been associated with BrS, which supports an autosomal dominant pattern of inheritance (Sarquella-Brugada, et al., 2016: 3–12). No specific finding suggestive of Brugada syndrome is detected at autopsy. Even so, family history should always be carefully investigated.

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a familial arrhythmic disorder characterized by polymorphic ventricular tachyarrhythmias or bidirectional ventricular tachycardia triggered by physical exertion or emotional stress. Patients do not have detectable structural cardiac abnormalities, and the resting ECG is usually normal apart from a relatively low heart rate. Affected individuals generally develop arrhythmic events during adrenergic stimulation in the first or second decade of life (Hayashi, et al., 2012: 1344–1351).

Early repolarization syndrome (ERS) is defined by the presence of J-point elevation of at least 0.1 mV in at least two contiguous inferior or lateral leads. For many years, this finding was considered benign and unrelated to serious cardiac events. This view has changed in light of more recent studies showing that an early repolarization pattern in the inferior and/or lateral leads is more common in patients with idiopathic ventricular fibrillation than in control subjects (Haissaguerre, et al., 2008: 2016–2023; Rosso, et al., 2008: 1231–1238).

Molecular Autopsy

Cases in which the heart appears structurally normal at forensic autopsy are described as a negative or silent autopsy. In such cases, SCD is often attributed to an arrhythmic and inherited etiology. Even when the forensic autopsy is negative, it may still represent the final opportunity to identify the underlying cause of death in SCD. In autopsy-negative cases, molecular autopsy may provide a diagnosis. Molecular autopsy refers to postmortem genetic

analysis of deoxyribonucleic acid (DNA) obtained from postmortem blood samples or from appropriately preserved tissues. Studies have shown that this method can reveal the underlying genetic cause in approximately 30% of SCD cases (Tester & Ackerman, 2006: 166–172). Inherited causes of SCD may be classified into arrhythmic syndromes, premature atherosclerosis, and cardiomyopathies. A common feature of these conditions is that SCD may be the first clinical manifestation. A substantial proportion of these disorders show autosomal dominant inheritance. For this reason, the risk of transmission of the mutation to first-degree relatives of the victim is 50%. Molecular autopsy therefore not only helps establish the cause of death but also plays a vital role in the risk assessment of family members.

Molecular autopsy is recommended in cases of suspected cardiomyopathy, inherited arrhythmic syndrome, or unexplained sudden death (Stiles, et al., 2021: 481–534). It is also recommended in conditions such as thoracic aortic dissection, pulmonary embolism, and spontaneous coronary dissection (Basso, et al., 2017: 691–705). In this context, proper preservation of suitable tissue samples obtained during autopsy, including blood, spleen, and muscle, is of great importance for DNA analysis. When the genetic diagnosis established by molecular autopsy is evaluated together with the findings obtained from cardiological assessment of first-degree relatives, it may enable early identification of relatives at risk. In this way, a new episode of SCD within the family may be prevented through regular follow-up, lifestyle modification, medical treatment, or protective interventions such as an implantable defibrillator. Molecular autopsy is therefore not only a retrospective assessment of SCD but also a prospective strategy for prevention. For this reason, appropriate samples should be secured and families should be referred to specialized centers.

Genetic Panel Testing and Variant Interpretation: The Problem of Variants of Uncertain Significance (VUS)

Sudden cardiac death in young adults may be the first manifestation of an inherited syndrome. In cases where the exact cause cannot be determined despite a comprehensive autopsy, genetic testing may help reduce the risk of SCD among family members. Next-generation sequencing technologies allow rapid and cost-effective screening of a large number of genes. However, it should be kept in mind that genetic tests do not always provide definitive results and are often probabilistic in nature. In addition, the clinical value of genetic testing depends on accurate assessment of whether the detected DNA variants are truly causal. This process is referred to as variant interpretation.

The American College of Medical Genetics and Genomics (ACMG) has classified variants into five categories in its published guideline: pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign (Richards, et al., 2015: 405–424). As new evidence accumulates, a VUS may later be reclassified as either pathogenic or benign. Although some variants can be identified with confidence as pathogenic or benign, sufficient data are still lacking for most variants. When evidence is insufficient, the clinical utility of genetic testing also remains limited. With the widespread use of next-generation sequencing technologies, VUSs are being detected more frequently. In most of these variants, there is not enough evidence to support pathogenicity. Misinterpretation of such variants may lead to an incorrect genetic diagnosis, unnecessary treatment, or failure to provide appropriate treatment to an at-risk individual. This situation may place both families and physicians in a difficult position (Scheiper-Welling, et al., 2022: 475–482).

Different sources of evidence may be used to assess variant pathogenicity. In silico tools such as DANN, MutationTaster, FATHMM, MutationAssessor, PolyPhen-2, SIFT, and PROVEAN can be used to predict the possible effect of a mutation on protein function. Mutations that alter protein structure or replace a critical amino acid with another amino acid that has different chemical properties are more likely to produce functional consequences. The functional effects of mutations can be demonstrated more clearly by in vitro cellular expression systems or transgenic animal models. However, these studies are costly and time-consuming. For that reason, their use in routine evaluation remains limited. Although it is not always straightforward, combined assessment of phenotype and genotype within the family may be one of the most useful approaches for determining the pathogenicity of a variant (Richards, et al., 2015: 405–424).

The interpretation of VUSs is a challenging process. For this reason, it requires the involvement of an experienced multidisciplinary team. This is particularly important for the protection of relatives after SCD in a young individual. Accurate interpretation is essential for treatment decisions and family counselling.

Screening of Family Members (ECG, Echocardiography, Exercise Testing, Holter Monitoring, and CMR)

In cases of SCD, the underlying cardiac disorder often remains undiagnosed before death, and the event usually occurs unexpectedly. Even after autopsy, the exact cause of death may not be established, and no specific pathological finding may be identified. In such situations, the clinical evaluation of family members may play an important role in the diagnostic process. Since a large proportion of inherited cardiac diseases follow an autosomal dominant pattern of inheritance, all first-degree relatives should be

screened. The probability that an autosomal dominant genetic mutation will be transmitted to offspring is considered to be 50% (Ferrero-Miliani, et al., 2010: 619–635). Systematic family screening is critical not only for identifying existing disease but also for recognizing individuals who may be at risk. A wide range of genetic and inherited cardiovascular disorders may underlie SCD, and these may vary according to region, age, ethnicity, and sex. For this reason, systematic screening of first-degree relatives of victims of SCD is of great importance for the early detection of possible inherited disorders and for the prevention of further deaths (Stiles, et al., 2021: e1–e50).

Studies on family screening have shown that systematic clinical evaluation provides an important diagnostic benefit. Some studies have reported that ECG, echocardiography, and long-term follow-up in first-degree relatives identify inherited cardiovascular disease in approximately 10% to 15% of cases (Tan, et al., 2005: 207–213). A substantial proportion of these diagnoses are established within the first five years. The phenotypic features of some inherited cardiac disorders may emerge in early adulthood. For this reason, screening programs in pediatric and young individuals are recommended to continue for a longer period (Behr, et al., 2008: 1670–1680).

Evaluation of first-degree relatives usually begins with a detailed medical history, physical examination, and standard 12-lead ECG (Stiles, et al., 2021: e1–e50). ECG may reveal findings suggestive of long and short QT syndromes, pre-excitation syndromes, Brugada syndrome, cardiomyopathies, and early ischemic heart disease (Priori, et al., 2013: 1389–1406). In suspected Brugada syndrome, provocation tests with sodium channel blockers may unmask the diagnostic ECG pattern. Likewise, long QT syndrome may become more apparent in some patients during exercise testing, epinephrine testing, or orthostatic stress testing. In

addition, the circumstances in which sudden death occurred may provide important diagnostic clues. Sudden death during fever or sleep, particularly in young men, may suggest Brugada syndrome, whereas sudden death during physical activity may raise suspicion for conditions such as long QT syndrome or catecholaminergic polymorphic ventricular tachycardia (Semsarian & Ingles, 2016: 359–365). For this reason, careful evaluation of the manner in which the event occurred may also guide the selection of tests used in family screening.

After the initial evaluation, transthoracic echocardiography, 24-hour Holter monitoring, and exercise stress testing may be added (Stiles, et al., 2021: e1–e50). Echocardiography can identify structural heart disease, cardiomyopathies, valvular disorders, and diseases of the great vessels. Exercise testing may reveal findings suggestive of polymorphic ventricular tachycardia and ischemic heart disease. According to the clinical setting, further investigations may also be performed. These may include lipid profile assessment, pharmacological provocation tests, cardiac magnetic resonance imaging (CMR), coronary CT angiography, and genetic analysis (Priori, et al., 2013: 1389–1406). CMR can provide highly valuable information in the evaluation of structural heart disease, scar tissue, and cardiomyopathies (Grupa Robocza Europejskiego Towarzystwa Kardiologicznego do spraw rozpoznawania i postepowania w kardiomiopatii, et al., 2014: 1054–1126). In selected cases, electrophysiological studies and cardiac biopsy may also contribute to the diagnosis. This comprehensive approach helps enable early recognition of inherited cardiovascular diseases and facilitates identification of at-risk individuals within the family.

In conclusion, systematic evaluation of first-degree relatives in cases of SCD is of great importance for the early recognition of inherited cardiovascular disorders. Through the combined use of clinical assessment, genetic analysis, and long-term follow-up

programs, individuals at risk can be identified and appropriate preventive measures can be implemented. This approach is critical not only for the diagnostic process but also for the prevention of further sudden deaths within the family.

Approach in Suspected Channelopathy

Channelopathies are a heterogeneous group of disorders caused by genetic abnormalities of ion channels in the absence of structural heart disease. They often give rise to malignant arrhythmias. Long QT syndrome, short QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT) are the best-known examples in this group. These disorders are among the major causes of SCD, especially in young individuals with structurally normal hearts. When channelopathy is suspected in an autopsy-negative victim, the relatives should undergo a comprehensive evaluation for In suspected channelopathy, the first step in evaluation is a detailed clinical history. Previous episodes of syncope, presyncope, or palpitations should be carefully investigated. Particular attention should be paid to whether syncope was triggered by exercise, emotional stress, or sudden acoustic stimuli. Although physical examination is often unremarkable, some findings related to inherited syndromes may be present. For example, congenital deafness may be seen in certain types of long QT syndrome (Schwartz, et al., 2006: 783–790). For this reason, systemic examination may also be useful in addition to cardiac assessment.

The most fundamental diagnostic tool in suspected channelopathy is the 12-lead ECG. ECG may reveal characteristic findings of long QT syndrome, short QT syndrome, Brugada syndrome, and pre-excitation syndromes. In long QT syndrome, prolongation of the QT interval may be observed. In Brugada syndrome, a typical ST-segment elevation may be detected,

especially in the right precordial leads. However, ECG findings may be intermittent in some patients. Therefore, a single ECG recording may not be sufficient to exclude the diagnosis (Krahn, et al., 2022: 386–405).

Dynamic testing plays an important role in the identification of channelopathies. Exercise stress testing is particularly useful in the evaluation of disorders such as long QT syndrome and catecholaminergic polymorphic ventricular tachycardia. Changes in the QT interval during or after exercise, as well as the occurrence of ventricular arrhythmias, may contribute to the diagnosis. In patients with CPVT, the appearance of bidirectional or polymorphic ventricular tachycardia during exercise is a typical finding. In some forms of long QT syndrome, pathological QT prolongation may also be revealed by epinephrine testing or orthostatic stress testing. In patients with suspected Brugada syndrome, pharmacological provocation tests are an important diagnostic tool. Tests performed with sodium channel blockers such as ajmaline, flecainide, or procainamide may unmask a type 1 Brugada ECG pattern that is not present at rest. However, because these tests may trigger arrhythmias, they should be carried out in experienced centers under appropriate monitoring.

Ambulatory rhythm monitoring methods are also an important part of the evaluation process. Twenty-four-hour Holter monitoring or longer rhythm recordings may help detect intermittent arrhythmias. These methods may provide valuable information, especially in patients with syncope or palpitations. However, since rhythm disturbances in channelopathies often occur in response to specific triggers, short-term rhythm monitoring is not always diagnostic.

In suspected channelopathy, exclusion of structural heart disease is also an essential step. Transthoracic echocardiography is

usually the first imaging method of choice and allows assessment of structural abnormalities such as cardiomyopathies or valvular disease. In suspicious cases, cardiac magnetic resonance imaging (CMR) can provide more detailed tissue characterization and may assist in the differential diagnosis of disorders such as arrhythmogenic cardiomyopathy. Nevertheless, in classical channelopathies the heart is expected to be structurally normal.

Genetic testing is playing an increasingly important role in the diagnosis of channelopathies and in family screening. Specific gene mutations have been identified in a substantial proportion of disorders such as long QT syndrome, Brugada syndrome, and CPVT (Ackerman, et al., 2011: 1308–1339). A positive genetic test not only helps clarify the cause of SCD but also allows family members to be screened in a more targeted manner.

The circumstances in which the event occurs may also provide important diagnostic clues in suspected channelopathy. Sudden death during sleep or during febrile illness may particularly suggest Brugada syndrome. Sudden cardiac events that occur during physical activity may raise suspicion for long QT syndrome or CPVT. For this reason, the timing of the event, the triggering factors, and the characteristics of the symptoms should be evaluated carefully.

In conclusion, the diagnostic approach in suspected channelopathy requires a comprehensive evaluation. Diagnosis can be achieved through the combined use of detailed clinical history, family history, ECG analysis, provocation tests, rhythm monitoring methods, imaging techniques, and genetic investigations. This systematic approach contributes not only to establishing the diagnosis in the patient but also to identifying family members at risk and preventing SCD. Through early diagnosis and appropriate risk assessment, preventive strategies such as lifestyle modification,

pharmacological treatment, or an implantable cardioverter-defibrillator can be planned, thereby helping prevent potentially fatal arrhythmic events.

Psychosocial and Ethical Dimensions

Sudden cardiac death is not only a medical event but also one with major psychosocial and ethical consequences, especially when it occurs in young individuals who were previously considered healthy. Such unexpected deaths may lead to intense grief, uncertainty, and anxiety about the future among family members. When the cause of death cannot be clearly established, this psychological burden may become even greater. Feelings of guilt, fear, and persistent health-related चिंता can develop within the family. For this reason, the evaluation of SCD should not be limited to medical investigations alone. It also requires a holistic approach that addresses the psychosocial needs of family members.

The clinical and genetic evaluation carried out after SCD may create both hope and anxiety in relatives. On the one hand, identifying the underlying cause and recognizing individuals at risk may provide reassurance. On the other hand, the detection of an inherited disorder may have important psychological effects, particularly in young people, by influencing expectations about life, participation in sports, career plans, and decisions about starting a family. For this reason, the psychological condition of individuals should be taken into account when planning genetic testing and family screening, and psychological support should be provided when necessary.

With the growing use of genetic investigations, ethical issues have become increasingly important. Genetic tests used in the diagnosis of inherited cardiovascular diseases may produce results that concern not only the tested individual but also the entire family. The identification of a pathogenic genetic variant in one person

indicates that other relatives who may carry the same mutation could also be at risk. This raises ethical questions related to communication within the family, sharing of information, and confidentiality. In particular, the question of which family members should receive genetic information and how that information should be communicated requires careful consideration by clinicians.

Informed consent is one of the fundamental ethical principles of genetic testing. Before testing is performed, individuals should be given a clear explanation of the purpose of the test, its possible results, its limitations, and the potential impact of the findings on family members. They should be able to decide freely whether or not to undergo testing. In the same way, the confidentiality of test results must be protected, and appropriate safeguards should be taken to prevent misuse of genetic information. Concerns that genetic information may lead to discrimination in areas such as insurance, employment, and social life form an important part of the ethical debate. Some family members may find regular screening programs reassuring, whereas for others this process may trigger persistent anxiety about disease. For this reason, clinicians must consider not only medical risks but also the psychological adaptation of individuals. Within a multidisciplinary approach, cooperation among cardiologists, genetic specialists, forensic experts, and psychologists will help address both the medical and psychosocial needs of families.

In conclusion, the evaluation of SCD is not only a diagnostic process but also a health issue with important psychosocial and ethical dimensions. Informing family members, applying genetic testing in accordance with ethical principles, and providing psychological support mechanisms are essential components of this process. This holistic approach will help protect individuals at risk and reduce the psychological burden experienced by families.

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