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Biomarkers of Sudden Cardiac Death: From Troponins to Circulating microRNAs

Aditya Krishna^{1*}, Pasupuleti Ankitha², Darren Fernandez^{3*} and Navya Praneetha⁴¹Mamata Academy of Medical Sciences, Hyderabad, Telangana, India²Maharajah's Institute of Medical Sciences, Nellimarla, Andhra Pradesh, India³Father Muller Medical College, Mangaluru, Karnataka, India⁴Sri Siddhartha Medical College, Tumkur, Karnataka, India

Abstract

Sudden cardiac death (SCD) remains a leading cause of mortality worldwide, often striking without warning in seemingly healthy individuals. The limitations of traditional risk stratification models and established biomarkers like cardiac troponins (cTn) necessitate the exploration of novel, more predictive tools. This review addresses the critical need to synthesize recent advancements in biomarker research to improve early detection and risk assessment for SCD. This review elucidates the evolving role of high-sensitivity cTn assays (hs-cTn) in detecting subclinical myocardial injury and their power in SCD prediction. We explore the considerable promise of circulating microRNAs (miRNAs) as stable, tissue-specific biomarkers that offer insights into pathophysiological processes preceding electrical instability. Furthermore, we examine the prognostic value of other emerging markets, including inflammatory cytokines, growth differentiation factor-15 (GDF-15), and perilipin-5, which reflect diverse pathways like inflammation, fibrosis, and metabolic stress. The significant synergy achieved by combining multiple biomarkers into integrated panels is highlighted as a key strategy for enhancing predictive accuracy. Finally, we cover technological innovations in biosensing that are paving the way for rapid, point-of-care detection of these biomarkers. Future research must prioritize large-scale, multicenter prospective studies to validate the clinical utility of novel biomarker panels. Efforts should also focus on standardizing detection assays and integrating biomarker data with genetic, clinical, and imaging markers using artificial intelligence. Ultimately, overcoming these challenges is essential for translating these advancements into personalized preventive strategies and reducing the global burden of SCD.

Keywords: Biomarkers, Circulating microRNAs, Risk stratification, Sudden cardiac death, Troponin, Prognosis, Forensic pathology

***Correspondence to:** Aditya Krishna and Darren Fernandez, Mamata Academy of Medical Sciences, Hyderabad, Telangana, India and Father Muller Medical College, Mangaluru, Karnataka, India.

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Introduction

SCD remains a significant global health challenge, often presenting without warning and resulting in rapid mortality [1-6]. Early and accurate diagnosis of underlying cardiac conditions is crucial for risk stratification and preventative intervention. Biomarkers play a pivotal role in identifying individuals at risk and guiding clinical decision-making. Traditionally, cTn have been the gold standard for detecting myocardial injury, but emerging research suggests the potential of circulating miRNAs and other novel biomarkers to enhance diagnostic accuracy and predictive power for SCD [7-12]. This article will explore the evolution of biomarkers in SCD, focusing on the utility of Tn and the promise of miRNAs, while also considering other relevant markers and diagnostic strategies.

The quest for reliable biomarkers to predict and diagnose SCD has garnered significant attention in recent years, driven by the need for early detection and improved forensic and clinical outcomes [13-17]. Traditional biomarkers such as cTn have long been established in clinical practice, yet emerging molecular markers like circulating

miRNAs are increasingly recognized for their potential to enhance diagnostic accuracy and prognostic assessment. Initial investigations into myocardial biomarkers have primarily focused on enzymatic and protein markers detectable postmortem or in clinical settings [18-23]. Sacco et al. [24] conducted a comprehensive analysis of five cardiac markers—creatine kinase-MB (CK-MB), myoglobin, TnI, B-type natriuretic peptide (BNP), and D-dimer—in peripheral blood samples from autopsied cadavers. Their study distinguished between SCD cases and controls, demonstrating the utility of these markers in postmortem analysis. Notably, TnI emerged as a significant indicator, aligning with its established role in detecting myocardial injury [24].

Building upon this foundation, the development of non-invasive, rapid detection methods has gained momentum. Wu et al. [25] introduced a printed immunosensing photonic crystal biochip (PCB) capable of detecting cTnT from a single drop of saliva or urine within 10 min. This innovative approach underscores the potential for point-of-care testing, facilitating timely diagnosis of acute myocardial infarction (AMI) and, by extension, SCD risk assessment [25]. Such advancements highlight the transition from traditional blood-based assays to more



accessible, non-invasive platforms. While Tn remain central to current diagnostic paradigms, recent research emphasizes the importance of circulating miRNAs as novel biomarkers. MiRNAs are small, non-coding RNA molecules involved in post-transcriptional regulation of gene expression, and their stability in peripheral blood makes them attractive candidates for biomarker development. Emerging evidence suggests that specific circulating miRNAs are associated with various cardiac pathologies, including heart failure, MI, and SCD [26].

The genetic underpinnings of SCD further reinforce the significance of molecular biomarkers [27-30]. Variants in genes such as TNNT2, MYH7, and MYBPC3 have been linked to increased susceptibility to SCD, with TNNT2 encoding cTnT being particularly noteworthy. The gene result for TNNT2 highlights its role as a postmortem biomarker for AMI, emphasizing its relevance in forensic investigations of SCD [31]. These genetic associations suggest that integrating genetic and molecular biomarker data could improve risk stratification. In clinical practice, the inclusion of hs-cTn assays (hs-TnT/I) has revolutionized early detection of myocardial injury. Advancements in assay sensitivity allow for the detection of minute elevations in Tn levels, which can precede overt clinical symptoms. This has significant implications for identifying individuals at imminent risk of SCD, especially in populations with subclinical cardiac disease [13]. Moreover, the combination of circulating miRNAs with traditional peptide biomarkers enhances prognostic accuracy. For instance, combined assays of miRNAs and hs-cTn have demonstrated improved predictive power for adverse cardiac events, including SCD [32].

The potential of circulating miRNAs extends beyond diagnosis to prognostication [33-38]. Wang et al. [39] has demonstrated that specific miRNA profiles can predict cardiac death post-discharge in patients with acute coronary syndromes. These miRNAs are involved in pathways related to myocardial stress, apoptosis, and remodeling, which are critical processes in the pathogenesis of SCD [39]. The stability of miRNAs in blood and their disease-specific expression patterns make them promising candidates for routine clinical and forensic use. Further research explores the integration of epigenetic-sensitive biomarkers, including miRNAs, for personalized therapy and risk assessment. For example, miRNA-210 has been identified as a biomarker for congestive heart failure, a condition that predisposes to SCD. Such findings suggest that miRNAs could serve as both diagnostic and therapeutic targets, offering a more nuanced understanding of individual risk profiles [40].

In the context of acute coronary syndrome, circulating miRNAs have been extensively reviewed as diagnostic markers. Their expression patterns correlate with myocardial injury severity and can complement

Tn measurements, providing a more comprehensive assessment of cardiac risk [41]. The combined use of miRNAs and Tn enhances the sensitivity and specificity of SCD prediction models, which is crucial for timely intervention. The paradigm shift from solely relying on traditional biomarkers like Tn to incorporating circulating miRNAs reflects a broader trend toward molecular precision medicine. MiRNAs not only serve as indicators of ongoing myocardial injury but also offer insights into the underlying pathophysiological mechanisms leading to SCD. Their role in forensic investigations is also gaining recognition, with studies demonstrating their utility in postmortem body fluid analysis for identifying cardiac events [42].

Overall, the landscape of biomarkers for SCD is evolving from conventional protein markers such as Tn to sophisticated molecular signatures like circulating miRNAs. While Tn remain integral to early detection and clinical management, miRNAs provide additional layers of diagnostic and prognostic information, especially in complex or ambiguous cases. The integration of genetic, proteomic, and miRNA data holds promise for more accurate risk stratification, personalized therapy, and forensic diagnosis of SCD. Continued research into these biomarkers will likely refine our understanding and improve outcomes in patients at risk of SCD.

cTn: The Established Marker

cTn, specifically TnT and TnI, have emerged as critical biomarkers in the diagnosis of MI and are increasingly being utilized in the context of SCD. These proteins are released into the bloodstream when myocardial injury occurs, making them highly specific indicators of cardiac damage. Their role in postmortem diagnostics is particularly valuable, as traditional autopsy findings can sometimes be inconclusive. The use of cTn in forensic medicine has been explored extensively, with studies highlighting their sensitivity and specificity in detecting myocardial lesions postmortem (Table 1).

Role and limitations

cTn, specifically cTnI and cTnT, are structural proteins found in cardiac muscle [43, 44]. Their release into the bloodstream indicates myocardial damage, making them highly specific biomarkers for AMI and other cardiac injuries [44]. hs-cTnT and hs-cTnI have further improved the ability to detect subtle myocardial injury, aiding in earlier diagnosis [45-47]. However, Tn elevation is not always specific to AMI and can be observed in other conditions, such as myocarditis [43], hypertrophic cardiomyopathy (HCM) [46, 48], and even acute respiratory distress syndrome [49], and cardiotoxicity after chimeric

Table 1: cTn in SCD: utility, limitations, and advancements.

Aspect	Key points	Details and considerations
Role and utility	Gold standard for myocardial injury	Highly specific indicators of cardiomyocyte damage. Central to diagnosing AMI and assessing SCD risk
	Postmortem diagnosis	Valuable in forensic contexts when autopsy is inconclusive. Measurement in pericardial fluid shows high sensitivity within a short postmortem interval (PMI) (<48 h)
	Risk stratification	Elevated levels (especially with hs-cTn) are associated with adverse outcomes in conditions like HCM
Key limitations	Lack of specificity	Levels can be elevated in non-ischemic conditions (e.g., myocarditis, renal failure, heart failure, cardiotoxicity), complicating interpretation
	Postmortem stability	Reliability decreases with a longer PMI due to protein degradation, affecting diagnostic accuracy
	Context dependence	Elevated levels do not always indicate cardiac-related death (e.g., can occur in trauma), requiring integration with other findings
Novel detection methods	Non-invasive sampling	Emerging biosensors can detect Tn in saliva and urine, enabling rapid point-of-care testing (e.g., PCB)
	Enhanced sensitivity	New platforms (e.g., quantum dot immunoassays, electrochemical sensors) offer ultra-low detection limits (e.g., attograms/mL), allowing for earlier detection
	Rapid results	Technologies like silicon biosensors and interferometers reduce detection from time to minute, aligning with the need for quick therapeutic decisions



antigen receptor T (CAR-T)-cell immunotherapy [50]. In checkpoint inhibitor-associated myocarditis and myositis, the cardiac specificity of cTnT has been questioned because patients with neuromuscular diseases, including myositis, may have elevated cTnT without clinical evidence of myocardial injury [43]. Ang et al. [43] suggests that cTnI may be a more appropriate biomarker for diagnosing and monitoring inhibitor-associated myocarditis in the context of concurrent inhibitor-associated myositis.

- **Diagnostic utility:** cTn, particularly cTnT, have been shown to be valuable in diagnosing myocardial ischemia (MI) postmortem, especially when measured in pericardial fluid. This is due to their high sensitivity and specificity within a short PMI, typically under 48 h [51]. The cTnI pericardial fluid/serum ratio has also been associated with AMI in SCD cases, providing a complementary method to traditional autopsy findings [52].

- **Sample types:** Various sample types, including serum, femoral blood, and pericardial fluid, have been used to measure Tn levels. Pericardial fluid has been found to provide the most consistent results, followed by serum and femoral blood [51]. The combined analysis of multiple biomarkers, such as N-terminal prohormone (NT-proBNP) and CK-MB, alongside cTnT, can enhance diagnostic efficiency [53].

- **PMI:** The reliability of Tn measurements decreases with longer PMIs due to postmortem degradation, which can affect the stability of Tn levels [51]. This degradation poses a significant challenge in accurately diagnosing MI in cases where the PMI is extended.

- **Specificity issues:** Tn levels have been found to lack specificity in postmortem samples, as no significant difference was observed in Tn levels across different causes of death, including non-cardiac-related deaths [54]. This suggests that elevated Tn levels may not always indicate cardiac-related death, complicating their use as a definitive diagnostic tool.

- **Assay sensitivity:** While hs-cTn have improved the detection of low-level Tn concentrations, these elevations can occur in non-ischemic conditions, leading to potential misinterpretation [54]. This highlights the need for careful consideration of assay results in the context of the overall clinical and forensic picture.

Tn in specific cardiac conditions

In HCM, elevated hs-cTnT has been associated with adverse outcomes, including SCD [46]. Gommans et al. [46] prospectively confirmed the association of elevated hs-cTnT with adverse outcomes in a 5-year follow-up study, suggesting its potential to improve risk prediction in HCM. Similarly, Zhang et al. [48] found that higher levels of cTnI and CK-MB were associated with increased risks of all-cause death, cardiovascular death, and SCD in HCM patients. Their study highlighted that patients with elevated levels of both cTnI and CK-MB had worse prognoses, suggesting that comprehensive evaluations of these biomarkers can improve risk stratification in HCM. Hernández-Romero et al. [52] explored the diagnostic application of postmortem cTnI pericardial fluid/serum ratio in SCD. The study found that the cTnI ratio was significantly associated with the diagnosis of AMI death and was an independent predictor of death from MI, which can be used as a complementary method to facilitate diagnosis in nonconclusive autopsies [52].

- Tn are highly sensitive markers for myocardial injury. In a study, cTnI and cTnT showed a sensitivity of 100% for predicting SCD,

although specificity was lower at 85% for cTnT in distinguishing AMI at autopsy [55, 56].

- Another study highlighted that while cTnT is sensitive, it lacks specificity as a diagnostic tool for AMI in postmortem settings, with a specificity of only 5% [56].

- Tn levels can be elevated in a variety of conditions beyond AMI, such as myopericarditis, renal failure, and heart failure, complicating their interpretation in SCD cases [57].

- In cases of ischemic heart disease, elevated Tn levels are indicative of myocardial injury, but they are not exclusive to AMI, as they can also be elevated in other cardiac-related deaths [58].

- The combination of Tn with other biomarkers, such as NT-proBNP and CK-MB, enhances diagnostic accuracy for SCD. The combined analysis of these markers in pericardial fluid has shown better diagnostic efficiency than using Tn alone [53].

- The ratio of cTnT to CK-MB can be particularly useful in distinguishing AMI from other causes of SCD, with a specific cutoff value providing a diagnostic advantage [53].

Despite their utility, Tn are not always reliable in isolation due to potential false positives and the influence of extracardiac factors. For instance, elevated Tn levels can occur in non-cardiac-related deaths, such as those involving trauma or other diseases, which can lead to diagnostic challenges [54, 57]. The interpretation of Tn levels must consider the context of death and be integrated with other clinical and pathological findings to improve diagnostic accuracy in SCD cases [59].

Novel methods for Tn detection

The detection of cTn, particularly cTnI, is crucial for diagnosing myocardial injury and SCD. Recent advancements have introduced novel methods for Tn detection, enhancing sensitivity, specificity, and convenience. These methods leverage cutting-edge technologies such as quantum dots, graphene-based materials, and biosensors, offering promising alternatives to traditional assays.

- Wu et al. [25] proposed a printed immunosensing PCB for the sensitive, convenient, and non-invasive detection of cTnT in saliva or urine. The PCB enables detection of cTnT within 10 min, with a limit of detection of 0.25 pg/mL, compared to the conventional enzyme-linked immunosorbent assay (ELISA) (2.5 h, 30 pg/mL) [25]. The PCB assay exhibited consistencies of 0.998, 0.999, and 0.999 with ELISA for serum, saliva, and urine, respectively, which can enable rapid therapeutic intervention within 30 min.

- A study developed a quantum dot fluorescence immunoassay for hs-cTnI detection in peripheral blood, demonstrating high correlation and consistency with venous blood methods. This method is advantageous due to its rapidity and convenience, with a sensitivity of 82.69% and a specificity of 89.5% for AMI diagnosis [60].

- A novel electrochemical sensor using silver nanoparticles, molybdenum disulfide, and reduced graphene oxide was designed for cTnI detection. This sensor offers high sensitivity and a broad detection range (0.3 pg/mL to 0.2 ng/mL), with resistance to common interferents like glucose and hemoglobin, making it suitable for clinical applications [61].

- An ultra-sensitive nanobiosensor using a gold nanoparticle-quantum dot hybrid was developed for cTnI detection in saliva. This non-invasive method has a detection limit of 0.3 fM and a response



range of 0.4 - 2500 fM, providing a rapid and sensitive alternative for AMI diagnosis [62].

- A silicon-on-insulator biosensor was designed for label-free, real-time cTnI detection. This biosensor uses anti-TnI DNA aptamers and can detect Tn concentrations as low as 10^{-11} mol/L, offering a rapid detection time of 200 to 300 s per sample [63].
- An electrochemical biosensor utilizing a novel monoclonal antibody and an Ir(III)-based metal complex achieved a detection limit of 10 ag/mL for cTnI. This method allows for early-stage detection of cardiac events, potentially enabling point-of-care applications [64].
- A silicon Mach-Zehnder interferometer biosensor with integrated microfluidics was developed for cTnI detection. It offers high sensitivity and selectivity, with a detection limit of 3 ng/mL, and can provide results within 10 min, aligning with international clinical guidelines for AMI diagnosis [65].

These novel methods for Tn detection represent significant advancements in the field, offering improved sensitivity, specificity, and convenience over traditional assays. However, challenges remain, such as the need for validation in diverse clinical settings and the development of cost-effective, portable devices for widespread use. Additionally, while these methods show promise for early detection and diagnosis, their integration into routine clinical practice will require further research and development to address these challenges.

Circulating miRNAs: Emerging Biomarkers

Circulating miRNAs have emerged as promising biomarkers for SCD due to their stability in the bloodstream and their role in regulating gene expression in cardiovascular diseases. These small non-coding RNAs are detectable in body fluids and have been associated with various cardiac conditions, making them potential tools for diagnosis and prognosis. The exploration of specific miRNA signatures could enhance the understanding and management of SCD, particularly in cases where traditional autopsy findings are inconclusive (Table 2).

Role of miRNAs in cardiovascular disease

MiRNAs are small, non-coding RNA molecules that regulate

gene expression and play critical roles in cardiovascular physiology and pathophysiology [66]. They are involved in processes like cardiac hypertrophy, vascular tone maintenance, and responses to vascular injury. Aberrant miRNA expression profiles have been linked to coronary artery disease and its risk factors, making them potential biomarkers for predicting disease and risk-stratifying patients [66]. MiRNAs are crucial in regulating cardiac cell differentiation and maturation, which are essential during heart development and in maintaining adult cardiac function [67]. They modulate signaling pathways and cellular processes in cardiomyocytes, endothelial cells, smooth muscle cells, and fibroblasts, impacting heart function and structure [68]. In cardiac microvascular endothelial cells, miRNAs regulate nutrient exchange and oxygen-carbon cycling, protecting cardiomyocytes from damage [69].

Dysregulation of miRNAs is associated with various cardiovascular diseases, including arrhythmias, hypertension, atherosclerosis, and heart failure [67]. MiRNAs influence oxidative stress, a key factor in cardiovascular disease progression, by regulating reactive oxygen species and their impact on cellular health [70]. Specific miRNA profiles differ between AMI and chronic heart failure, indicating their role in disease-specific pathways [71]. Extracellular miRNAs, detectable in blood, serve as non-invasive biomarkers for assessing cardiovascular disease risk and prognosis [72]. MiRNAs have potential as therapeutic targets, with ongoing research into miRNA-based drugs for cardiovascular disease treatment [73]. Clinical trials are exploring patient-specific miRNA levels to predict heart disease and tailor interventions [69].

While miRNAs offer significant potential in understanding and managing cardiovascular diseases, challenges remain in translating these findings into clinical practice. The variability in miRNA expression profiles and the complexity of their regulatory networks require further investigation to harness their full potential as biomarkers and therapeutic agents. Continued research and technological advancements are essential to overcome these hurdles and integrate miRNA-based strategies into routine cardiovascular care.

MiRNAs as diagnostic and prognostic tools

Specific miRNAs, such as miR-3113-5p, miR-223-3p, miR-499a-

Table 2: Circulating miRNAs in SCD: promise and challenges.

Aspect	Key points	Examples and details
Mechanism and promise	Regulatory function	Small, non-coding RNAs that regulate gene expression post-transcriptionally. Involved in key cardiac processes like hypertrophy, fibrosis, apoptosis, and arrhythmogenesis
	Stability and detectability	Remarkably stable in peripheral blood and other body fluids, making them ideal candidates for both clinical and postmortem biomarker development
	Diagnostic potential	Specific signatures can distinguish SCD from other causes of death, even with negative autopsy findings, e.g., miR-3113-5p, miR-223-3p, miR-499a-5p, and miR-133a-3p
	Prognostic potential	miRNA profiles can predict adverse outcomes (e.g., cardiac death post-ACS) and reflect disease progression in conditions like HCM, aiding in risk stratification
	Therapeutic target	Manipulation of specific miRNAs (e.g., miR-365 for AP duration) may offer novel therapeutic avenues to prevent malignant arrhythmias
Key challenges	Lack of standardization	Variability in sample collection, processing, and analysis methodologies hinders reproducibility and comparability between studies
	Specificity and variability	Expression profiles can vary between individuals and overlap across different cardiac pathologies, creating potential for diagnostic ambiguity
	Complex integration	Translating miRNA findings into clinical practice requires integration with existing diagnostic tools and risk scores, which is not yet standardized
Future directions	Multi-miRNA panels	Using panels of miRNAs (e.g., miR-126-5p + miR-499a-5p) is more promising than single miRNAs for improving diagnostic and prognostic accuracy
	Validation and standardization	Large-scale, multicenter studies are needed to validate specific miRNA signatures and establish standardized protocols for clinical use
	Mechanistic insights	Further research into the functional roles of miRNAs can provide deeper insights into SCD pathophysiology and identify new therapeutic targets



5p, and miR-133a-3p, have been identified as sensitive biomarkers for diagnosing SCD, especially in cases with negative autopsy findings. These miRNAs were significantly up regulated in SCD samples compared to controls, with high sensitivity and specificity in distinguishing SCD from other causes of death [74]. In HCM, a condition associated with an increased risk of SCD, circulating miRNAs may reflect disease progression and help in risk stratification. Advanced cardiac magnetic resonance imaging combined with miRNA profiling could identify adverse myocardial features, such as fibrosis, which are linked to SCD risk [75].

Abdou et al. [45] evaluated the diagnostic value of circulating miRNA-499 versus hs-cTnT in the early diagnosis of ST-segment elevation MI (STEMI). The study found that miRNA-499 was significantly elevated in STEMI patients compared to healthy controls and displayed a significant positive correlation with hs-cTnT [45]. Moreover, miRNA-499 exhibited higher expression than hs-cTnT in the first 3 h of chest pain, suggesting its potential as a reliable biomarker for early STEMI detection. Esfandyari et al. [76] identified miR-365 as a miRNAs that regulates human cardiac action potential duration. Their research showed that manipulation of miR-365 could therapeutically modulate action potential abnormalities in patient-specific induced pluripotent stem cell-derived cardiac myocytes, suggesting its potential role in preventing malignant cardiac arrhythmias and SCD [76].

Liu et al. [77] found that cardiac fibroblasts secrete exosomes containing increased levels of miR-133a under hypoxia/reoxygenation conditions. These exosomes deliver miR-133a into cardiomyocytes to target ELAVL1 and repress cardiomyocyte pyroptosis, protecting cardiomyocytes against MI/reperfusion (MI/R)-induced injury [77]. This finding provides a novel molecular basis for understanding and treating MI/R injury and suggests using exosome biomarker in forensic for the postmortem diagnosis of MI/R injury induced SCD. Jiao et al. [78] showed that an increase in a long noncoding RNA ANRIL in peripheral plasma is an indicator of stable angina. The levels of ANRIL in peripheral plasma could be used as a good biomarker for stable angina [78].

Challenges and considerations

While miRNAs hold great promise, several challenges need to be addressed before their widespread clinical adoption. Fazmin et al. [66] highlighted limitations such as the cost of miRNA assays, the presence of confounding factors affecting miRNA profiles, and difficulties in normalizing miRNA values between studies due to pre-analytical variations in samples. Standardizing miRNA measurement protocols and establishing reference ranges are crucial for reliable clinical application.

- **Variability in expression:** miRNAs such as miR-126-5p and miR-499a-5p have shown potential in diagnosing coronary artery disease-induced SCD, but their expression can vary significantly between individuals and conditions, complicating their use as standalone diagnostic markers [79].
- **Differentiation of cardiac conditions:** miRNAs like miR-1, miR-133a, and miR-26a have demonstrated high diagnostic power in distinguishing between myocardial injury and other cardiac death causes, yet the overlap in miRNA profiles across different cardiac events can lead to diagnostic ambiguity [80].
- **Prognostic value in AMI:** Circulating miRNAs have been linked to left ventricular remodeling and major adverse cardiovascular events post-AMI, suggesting their utility in risk stratification. However,

the reproducibility of these findings across different cohorts remains a challenge [81].

- **Integration with existing tools:** While miRNAs offer additional prognostic information, their integration with traditional risk scores and stratification tools is necessary to enhance their clinical utility. This requires standardization in miRNA measurement and analysis [82].
- **Standardization of methodologies:** The lack of standardized methodologies for miRNA detection and quantification poses a significant barrier to their clinical application. Variability in sample types (e.g., blood, tissue) and analytical techniques can lead to inconsistent results [81, 83].
- **Combination of miRNAs:** Studies suggest that using panels of miRNAs rather than single miRNAs may improve diagnostic and prognostic accuracy. For instance, combining miR-126-5p and miR-499a-5p enhances the discriminative capacity for SCD cases [79, 84].

While miRNAs hold promises as diagnostic and prognostic tools in SCD, their clinical implementation is hindered by several challenges. The variability in miRNA expression and the need for standardized methodologies are significant hurdles. Moreover, the integration of miRNA data with existing diagnostic frameworks is crucial for their effective use. Future research should focus on large-scale, multicenter studies to validate miRNA panels and develop standardized protocols for their clinical application. Additionally, exploring the therapeutic potential of miRNAs could provide new avenues for managing cardiac conditions [85, 86].

Other Relevant Biomarkers

Beyond Tn and miRNAs, a spectrum of other biomarkers provides critical insights into the diverse pathophysiological pathways leading to SCD. This section explores the roles of inflammatory markers, GDF-15, perilipin-5, and NP in risk stratification and the underlying mechanisms of sudden death.

Inflammatory markers

Inflammatory markers play a significant role in the context of SCD, as they are often associated with the underlying pathophysiology of cardiovascular events that can lead to SCD. These markers are indicative of systemic inflammation, which is a known contributor to cardiovascular diseases and can influence both short-term and long-term mortality outcomes.

Key inflammatory markers

- **Interleukins (IL-6, IL-8, and IL-10):** These cytokines are significantly associated with mortality in AMI patients. IL-6, in particular, has been highlighted for its strong association with fatal cardiovascular events compared to nonfatal ones, suggesting its potential role in predicting SCD [87, 88].
- **C-reactive protein (CRP):** CRP is a well-established marker of inflammation and has been linked to the severity of coronary heart disease and mortality risk. Elevated CRP levels are associated with increased risk of cardiovascular mortality, including SCD, and are indicative of acute-phase inflammatory responses [89, 90].
- **Neutrophils and leucocytes:** Higher levels of these cells are associated with increased mortality following out-of-hospital cardiac arrest, suggesting their potential as early predictors of poor outcomes, including SCD [91].



- Pentraxin 3 and soluble suppression of tumorigenicity 2: These novel markers have been associated with multiple organ dysfunction syndrome and early death post-cardiac arrest, indicating their relevance in the context of SCD [92].

Association with SCD

- AMI: Inflammatory markers such as IL-6 and CRP are associated with short-term mortality in AMI patients, which can lead to SCD. These markers are indicative of the inflammatory response that exacerbates cardiac conditions [87, 89].
- Out-of-hospital cardiac arrest: Inflammatory responses following out-of-hospital cardiac arrest, characterized by elevated leucocyte and neutrophil levels, are linked to increased mortality, highlighting the role of inflammation in SCD outcomes [91].
- Sudden infant death syndrome: Although not directly related to adult SCD, studies on sudden infant death syndrome show that inflammatory markers like CRP and IL-6 can help identify infection-related deaths, providing insights into the inflammatory mechanisms that might also be relevant in adult SCD [93].

GDF-15

GDF-15 has emerged as a novel biomarker to predict all-cause death in community-dwelling individuals and patients with cardiovascular disease [94]. Negishi et al. [94] evaluated the prognostic value of GDF-15 in outpatients with cardiovascular risk factors and found that higher GDF-15 levels were associated with risks of all-cause death and stroke events. Incorporating GDF-15 into predictive models for all-cause death improved discrimination and reclassification significantly, suggesting its potential to improve risk stratification.

- GDF-15 levels are strongly associated with heart failure hospitalization and mortality. In patients with cardiomyopathy, higher GDF-15 levels were linked to increased mortality risk, but not to ventricular arrhythmic events, which are directly related to SCD [95].
- In nonischemic dilated cardiomyopathy, GDF-15 was independently associated with serious arrhythmic events and overall mortality, suggesting its potential role in risk stratification for SCD in this subgroup [96].
- GDF-15 is elevated in patients with AMI and is associated with major adverse cardiac events at follow-up. This includes a significant association with mortality, which could indirectly relate to SCD risk [97].
- In emergency department patients with suspected acute coronary syndrome, GDF-15 was a predictor of AMI and death at 30 and 90 days, indicating its utility in short-term risk stratification [98].
- A meta-analysis showed that GDF-15 is a robust predictor of cardiovascular death and heart failure hospitalization across various presentations of atherosclerotic cardiovascular disease. However, its predictive power for MI and stroke was less consistent, particularly in acute settings [99].
- In stable coronary artery disease, GDF-15 provided prognostic information for cardiovascular events and all-cause mortality, suggesting its broader applicability in cardiovascular risk assessment [100].

Perilipin-5

Perilipin-5 plays a significant role in cardiac health, particularly in

the context of SCD, by modulating lipid metabolism and protecting against lipotoxicity and oxidative stress. Perilipin-5 is a lipid droplet-associated protein that regulates lipid storage and metabolism, which is crucial for maintaining cardiac function. Its involvement in various cardiac pathologies, including MI/R injury and diabetic cardiomyopathy, highlights its potential as a therapeutic target for preventing SCD. Ethem and Hacıoğlu [101] investigated whether perilipin-5 are a potential biomarker by examining changes in perilipin-5 serum levels along with hs-cTnI during a heart attack. They found that hs-cTnI and perilipin-5 levels increased in patients with heart attack compared to control, and perilipin-5 mRNA and protein levels in heart attack patients increased by 48.2 and 23.6%, respectively, compared to the control group [101]. Their results suggested that perilipin-5 together with hs-cTnI could be a promising biomarker in heart attack.

- Perilipin-5 is essential for regulating lipid droplet metabolism in cardiomyocytes, protecting the heart from lipotoxicity by inhibiting excessive lipolysis and fatty acid oxidation. This regulation helps maintain lipid homeostasis and prevents the accumulation of toxic lipid intermediates that can lead to cardiac dysfunction [102].
- In the context of diabetic cardiomyopathy, perilipin-5 modulates lipid metabolism by protecting lipid droplets from lipase activity, thereby reducing lipotoxicity and associated oxidative stress [103].
- Perilipin-5 reduces oxidative stress in cardiomyocytes by decreasing reactive oxygen species production and enhancing antioxidant defenses. This is achieved through the activation of signaling pathways such as PI3K/Akt and ERK, which lead to the upregulation of antioxidant enzymes [102].
- The suppression of lipotoxicity and ferroptosis in cardiomyocytes by perilipin-5 involves the modulation of the PIR/NF- κ B axis, which further underscores its protective role against oxidative damage [104].
- The deficiency of perilipin-5 has been linked to increased susceptibility to cardiac dysfunction due to enhanced oxidative stress and mitochondrial damage, which are critical factors in the pathogenesis of SCD [102].
- Perilipin-5's ability to maintain mitochondrial function and prevent excessive lipid accumulation suggests its potential in mitigating the risk of SCD, particularly in metabolic disorders like diabetes [105].

NP

NP, particularly BNP and its NT-proBNP, have been extensively studied for their role in predicting SCD. These peptides are biomarkers of cardiac stress and dysfunction, and their elevated levels have been associated with an increased risk of SCD in various cardiac conditions. The research highlights the potential of these biomarkers in risk stratification and management of patients at risk of SCD, particularly those with heart failure and post-MI. Lee et al. [50] found that day 5 BNP levels were higher in patients with adverse cardiac events (new-onset cardiomyopathy/heart failure, acute coronary syndrome, arrhythmia and cardiovascular death) after CAR-T therapy compared to those without, suggesting that BNP could be used to identify the patients at risk of cardiotoxicity after CAR-T therapy.

- NT-proBNP is a significant predictor of SCD in patients with chronic heart failure. Elevated levels of NT-proBNP are associated with



a four-fold increased risk of SCD in these patients, indicating its utility in long-term risk assessment [106].

- In forensic settings, postmortem NT-proBNP levels in pericardial fluid are significantly higher in SCD cases compared to non-SCD cases, suggesting its potential as an ancillary indicator for evaluating agonal cardiac function [107].
- BNP levels are elevated in patients with left ventricular dysfunction following an AMI, and these elevated levels are strong predictors of SCD. A rise in BNP above a certain threshold significantly impacts the prediction of SCD [108].
- Differential expression of BNP between the left and right ventricles has been observed in SCD cases, with left ventricular dysfunction predominating in acute ischemic heart disease and right ventricular dysfunction in arrhythmogenic right ventricular cardiomyopathy [109].
- BNP has been shown to predict SCD and ventricular arrhythmias with a relative risk of 3.68 for SCD and 2.54 for ventricular arrhythmias, highlighting its value in risk stratification across various populations [110].
- In patients with chronic heart failure, BNP levels are a significant predictor of sudden death, with elevated levels correlating with electrophysiological abnormalities that may predispose to arrhythmias [111].
- In a study focusing on women, NT-proBNP levels were found to predict SCD risk, although the trend was not statistically significant across quartiles. This suggests potential gender differences in the predictive value of NT-proBNP [112].

In conclusion, the biomarkers discussed in this section significantly expand the diagnostic and prognostic toolkit for SCD beyond traditional markers. Inflammatory markers like IL-6 and CRP provide insight into the crucial role of systemic inflammation, while GDF-15 offers robust prognostic value for all-cause and cardiovascular mortality. Perilipin-5 emerges as a novel player in mitigating lipotoxicity and oxidative stress, offering a potential link between metabolic dysfunction and SCD risk. Furthermore, NP (BNP and NT-proBNP) remain cornerstone indicators of cardiac wall stress and powerful predictors of arrhythmic death. Collectively, these diverse biomarkers illuminate various pathophysiological pathways, underscoring the necessity of a multi-modal approach for effective SCD risk stratification.

Multi-biomarker Strategies and Diagnostic Approaches

Multi-biomarker strategies have emerged as promising approaches to improve the diagnosis and understanding of SCD. These strategies involve the use of various biomarkers, including miRNAs, cardiac proteins, and other molecular markers, to enhance diagnostic accuracy and provide insights into the underlying causes of SCD.

Combining biomarkers for enhanced accuracy

Given the limitations of individual biomarkers, multi-biomarker strategies are gaining traction. Guo et al. [47] developed a three-biomarker joint strategy for early and accurate diagnosis of AMI via an electrochemiluminescence immunoarray coupled with robust machine learning. The model, which simultaneously detected cTnI, heart-type fatty acid-binding protein, and copeptin, achieved perfect discrimination for AMI vs non-AMI patients, significantly outperforming cTnT alone [47]. This approach highlights the potential

of combining multiple biomarkers to improve diagnostic accuracy, particularly in the early stages of AMI.

Integrating biomarkers with other diagnostic tools

Costache et al. [113] assessed the use of combined cardiopulmonary exercise testing (CPET) and cardiac biomarker determinants in young professional athletes. While cTnI and NT-proBNP levels were undetectable, variations in myoglobin, CK-MB, and D-dimers showed significant correlations with CPET parameters, highlighting the potential use of combined CPET and biomarker determinants to evaluate professional athletes [113]. Integrating biomarkers with electrocardiography, echocardiography, and other imaging modalities can provide a more comprehensive assessment of cardiac risk and improve the prediction of SCD.

Forensic applications

Sacco et al. [24] evaluated the potential of cardiac markers in peripheral blood for diagnosing SCD in forensic contexts. The study identified statistically significant differences in myoglobin and TnI levels between the SCD group and the control group, with TnI emerging as a more robust marker for SCD [24]. This approach offers a less invasive, economical, and practical method for forensic investigations.

Case Studies and Clinical Trials

Several case studies and controlled trials investigating biomarkers for SCD have explored various biomarkers to improve risk stratification and diagnosis. These trials have focused on both living patients and postmortem analyses, aiming to identify reliable indicators of SCD risk and occurrence. The studies highlight the potential of certain biomarkers in predicting SCD, though challenges remain in their application and interpretation.

The ARTEMIS study by Lepojärvi et al. [114] investigated the performance of various biomarkers in predicting SCD among patients with coronary artery disease and preserved left ventricular function. The study population comprised 1,946 coronary artery disease patients, predominantly male (68%) with a mean age of 66.9 ± 8.6 years, and 43% having type 2 diabetes. The primary endpoint was SCD. Over a mean follow-up period of 76 ± 20 months, 50 patients experienced SCD. During the follow-up, 205 deaths occurred, with 99 determined to be of cardiac cause, including the 50 SCDs (8 of which were aborted cardiac arrests). Non-SCD accounted for 44 subjects, including pump failure and heart failure deaths. Univariate analysis showed that elevated hs-CRP ($p = 0.001$), soluble ST2 (sST2, $p < 0.001$), BNP ($p < 0.001$), and hs-TnT ($p < 0.001$) all predicted the occurrence of SCD. In adjusted analysis, using optimal cutoff points, elevated sST2 (≥ 27.45 ng/mL) and hs-TnT (≥ 15 ng/mL) were the strongest predictors of SCD. Elevated sST2 had a hazard ratio (HR) of 2.7 (95% confidence interval (CI): 1.4 to 5.1, $p = 0.003$). Elevated hs-TnT had an HR of 2.9 (95% CI: 1.5 to 5.6, $p = 0.002$). hs-CRP (HR: 2.4; 95% CI: 1.3 to 4.4, $p = 0.004$) and BNP (HR: 1.9; 95% CI 1.0 to 3.7, $p = 0.046$) followed as significant predictors in adjusted analysis (Figure 1). Elevated sST2 and hs-TnT were identified as the most powerful predictors in both univariate and multivariate analyses. They also proved to be the most significant risk markers in crude and adjusted multimarker Cox regression, showing independence from hs-CRP and BNP. The combination of elevated hs-TnT and sST2 yielded a significantly higher adjusted HR of 6.4 (95% CI: 2.6 to 15.5, $p < 0.001$) for SCD compared to those with both biomarkers at normal levels. The C-index improved from 0.732 (95% CI: 0.665 to 0.799) to 0.780 when both elevated hs-TnT and sST2 were

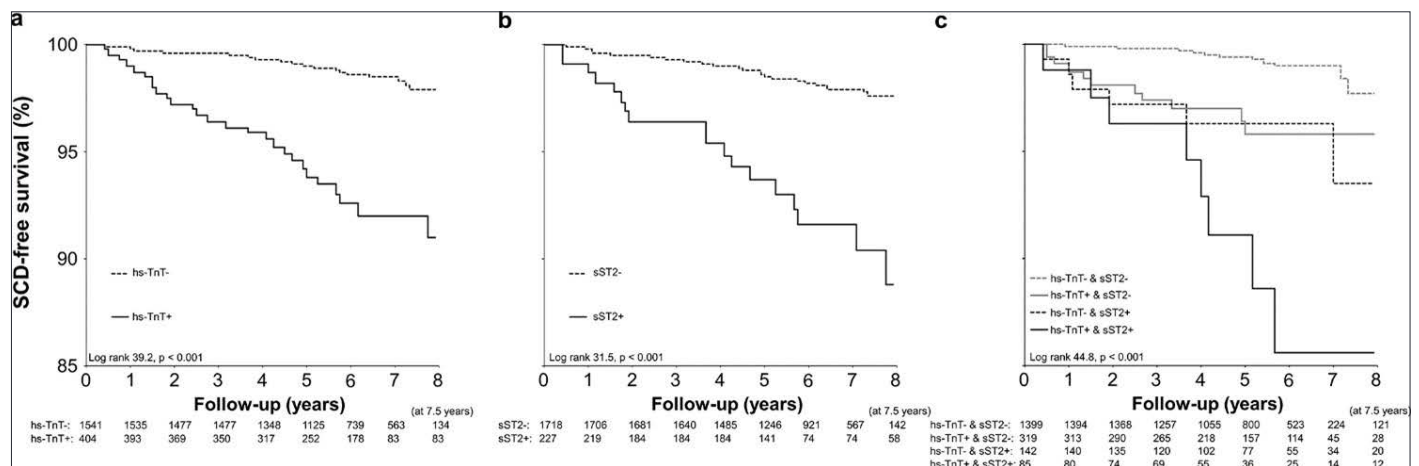


Figure 1: Kaplan-Meier curves depict the probability of SCD-free survival for patients. (a) Result for hs-TnT levels, (b) sST2 levels, and (c) for the combination of both biomarkers. Elevated levels (denoted by '+') are compared to non-elevated levels (denoted by '-') based on optimal cutoff values [114].

added to the established model. hs-TnT, hs-CRP, BNP, and sST2 were also significant predictors of all-cause mortality in multivariate analysis ($p < 0.001$ for all). In coronary artery disease patients with type 2 diabetes, abnormal hs-TnT and hs-CRP were the only variables that predicted SCD (34 events, 4.1%) in multivariate analysis. hs-TnT showed an HR of 3.0 (95% CI: 1.2 to 7.2, $p = 0.014$). hs-CRP showed an HR of 2.6 (95% CI: 1.2 to 5.4, $p = 0.012$). Among non-type 2 diabetes patients, only abnormal sST2 predicted the primary outcome (16 events, 1.4%) with an HR of 7.2 (95% CI: 2.4 to 22.0, $p = 0.001$). Overall, the study demonstrates that sST2 and hs-TnT are strong independent predictors of SCD in coronary artery disease patients with preserved left ventricular function, and their combined elevation significantly increases the risk, suggesting their utility in risk assessment.

In a discovery cohort study by Zhang et al. [115], which included 210 participants (105 SCD cases), mass spectrometry identified 44 differential proteins not previously linked to SCD. Through targeted proteomics, an optimal protein combination for predicting out-of-hospital SCD post-AMI was identified. This combination, termed SCD-warning three protein combinations (SCD-W3P), consists of coronin-1A, haptoglobin, and complement factor D. A model based on the expression levels of SCD-W3P demonstrated superior predictive performance compared to left ventricular ejection fraction (LVEF) alone. The C-statistic for the SCD-W3P model was 0.752, significantly higher than LVEF's 0.548 ($p < 0.001$). This indicates a substantial improvement in risk prediction, with a Δ C-statistic of 0.281 ($p < 0.001$). The model also showed a net reclassification improvement of 9.5% ($p < 0.001$). Similar incremental discrimination metrics were observed when SCD-W3P was combined with two other reported stratification models, particularly within the LVEF-preserved population. The findings were consistently validated in two independent cohorts. Validation cohort 1 included 160 participants (40 SCD cases). Validation cohort 2 included 96 participants (24 SCD cases). Further support for the biological relevance of complement factor D, a critical protein in SCD-W3P, was provided by experiments showing that complement factor D inhibition protected against mortality and pro-malignant arrhythmia in AMI mice. In summary, this study successfully identified and validated a novel three-protein biomarker panel (SCD-W3P) that significantly improves the prediction of out-of-hospital SCD after MI, outperforming traditional risk assessment methods like LVEF. The findings were robustly confirmed across multiple cohorts and supported by biological evidence.

A meta-analysis by Rossello et al. [116] of three randomized-controlled trials investigated the impact of mineralocorticoid receptor antagonists (MRAs) on the risk of SCD in patients with heart failure and left-ventricular systolic dysfunction. Patients treated with MRAs showed a significantly lower risk of SCD compared to those receiving placebo. Specifically, MRAs reduced the risk for SCD by 23%. The HR for SCD in MRA-treated patients was 0.77, with a 95% CI of 0.66 to 0.89. This finding was based on a mean follow-up period of 18 months. The beneficial effect of MRAs on SCD risk was consistent across the three trials included in the meta-analysis: randomized aldactone evaluation study, eplerenone post-AMI heart failure efficacy and survival study, and eplerenone in mild patients' hospitalization and survival study in heart failure. The effect remained substantially unchanged even after adjusting for 14 baseline co-variables. The benefits of MRAs were generally consistent across various study subgroups. A greater effect was observed in patients younger than 65 years old and in those who were using beta-blockers. The consistent effect was also found in relevant subsets of patients defined by heart failure cause, New York Heart Association class, or LVEF $\leq 35\%$. The findings suggest that optimizing the use of MRAs, in addition to other evidence-based medications, is crucial for patients with heart failure and left-ventricular systolic dysfunction to reduce SCD risk. The study also points out that the benefit of implantable cardiac defibrillator placement might need re-assessment, as previous implantable cardiac defibrillator trials enrolled patients who were not receiving MRAs. In summary, MRAs significantly reduce the risk of SCD in patients with heart failure and left-ventricular systolic dysfunction, highlighting their importance in the management of these patients.

A study by Sfairopoulos et al. [117] results of sodium-glucose cotransporter-2 (SGLT2) inhibitor therapy on SCD and ventricular arrhythmias. SGLT2 inhibitor therapy was not significantly associated with a lower risk of SCD. The risk ratio (RR) for SCD was 0.74, with a 95% CI of 0.50 to 1.08, and a p of 0.12. SCD events were reported in 9 randomized controlled trials (Figure 2), with 48 patients in the SGLT2i group and 57 in the placebo group. SGLT2 inhibitor therapy was not associated with a lower overall risk of ventricular arrhythmias. The RR for ventricular arrhythmias was 0.84, with a 95% CI of 0.66 to 1.06, and a p of 0.14. Ventricular arrhythmias were reported in 17 randomized controlled trials, involving 126 patients receiving SGLT2i and 134 controls. A specific subgroup analysis showed that low-dosage SGLT2i therapy demonstrated a decreased risk of ventricular arrhythmia

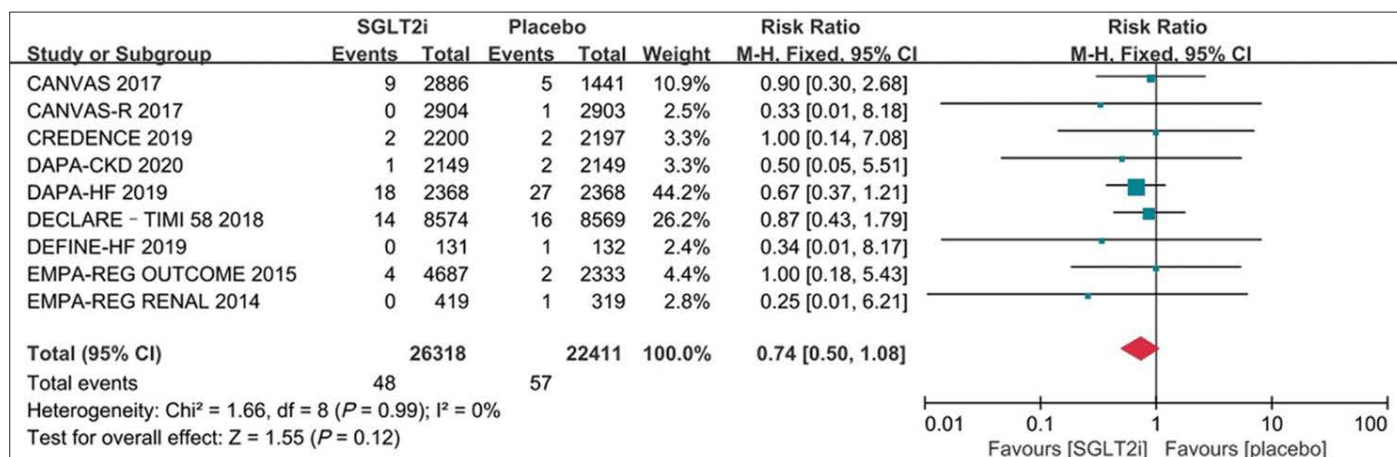


Figure 2: Forest plot comparing incidence of SCD between SGLT2i and placebo [117].

compared to control (RR 0.45, 95% CI: 0.25 to 0.82; $p = 0.009$). This benefit was also observed when compared to placebo (RR 0.46, 95% CI: 0.25 to 0.85; $p = 0.01$). Beyond this low-dosage subgroup, no other subgroup analysis demonstrated significant differences. Overall, SGLT2 inhibitor therapy was not associated with a lower risk of SCD or ventricular arrhythmias in patients with type 2 diabetes mellitus, heart failure, or chronic kidney disease. However, the study noted that the number of SCD and ventricular arrhythmias events was relatively few, leading to wide CI. Despite the lack of overall statistical significance, the point estimates suggested potential benefits, indicating a need for further research. The meta-analysis included 19 randomized controlled trials with a total of 55,590 participants, comparing SGLT2 inhibitors to placebo or active control in patients with type 2 diabetes mellitus, heart failure, or chronic kidney disease.

While these studies underscore the potential of biomarkers in predicting and diagnosing SCD, challenges remain. The specificity and sensitivity of biomarkers can vary, and their utility in different clinical settings needs further validation. Additionally, the integration of novel biomarkers into existing clinical frameworks requires careful consideration to ensure they complement traditional risk assessment tools effectively.

Conclusion

The literature on biomarkers of SCD underscores significant progress in identifying and validating both protein-based and RNA-based biomarkers that enhance diagnostic and prognostic capabilities beyond traditional clinical metrics. cTn remain the cornerstone biomarkers for myocardial injury detection, widely integrated into clinical and forensic practice due to their high sensitivity, specificity, and well-understood kinetics. However, their limitations in detecting early ischemic events without necrosis and in discriminating against diverse SCD etiologies have motivated exploration of novel biomarkers. Circulating miRNAs, characterized by remarkable stability and tissue specificity, emerge as promising complementary or alternative biomarkers. Specific miRNA signatures, including combinations of miR-3113-5p, miR-223-3p, miR-499a-5p, and others, demonstrate high diagnostic accuracy, even in cases with negative autopsy findings, suggesting their potential for both clinical and postmortem SCD diagnosis. Moreover, multimarker panels integrating protein biomarkers with miRNAs or extracellular vesicle cargo improve risk stratification and diagnostic precision, reflecting the complex pathophysiology of SCD.

Mechanistic studies elucidate that these biomarkers reflect underlying biological processes such as myocardial injury, apoptosis, fibrosis, inflammation, and electrical heterogeneity, reinforcing their pathophysiological relevance. Genetic and transcriptomic research expands understanding by identifying regulatory variants and molecular pathways influencing biomarker expression and SCD susceptibility. Despite these advances, causal relationships and the heterogeneity of SCD etiologies pose challenges to universal biomarker application. Clinically, while established protein biomarkers guide acute care and risk assessment, integration of novel biomarkers into routine practice is constrained by variability in detection methods, lack of assay standardization, and insufficient large-scale prospective validation. Forensic applications benefit from advances in biomarker stability and less invasive sampling methods, yet standardization remains an issue.

Technological innovations such as high-throughput proteomics, next-generation sequencing, and machine learning facilitate comprehensive biomarker discovery and personalized risk modeling, but face hurdles related to cost, complexity, and ethical considerations. Comparative evaluations reveal protein biomarkers excel in rapid, cost-effective diagnostics, whereas RNA biomarkers offer enhanced specificity and the ability to detect subtle molecular changes. Their combined use holds the greatest promise for improving SCD prediction and diagnosis. Overall, the literature advocates continued multidisciplinary research focusing on standardization, large cohort validations, and integrated multimodal biomarker panels to translate these findings into effective clinical and forensic tools, ultimately aiming to enhance early intervention strategies and reduce the global burden of SCD.

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None.

Conflict of Interest

None.

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