Sudden cardiac death (SCD) accounts for most cardiovascular deaths in the United States, claiming an estimated 300,000 lives per year. Despite intense efforts to develop resuscitation techniques, survival rates are still low, at ≈5%. This has led to a renewed focus in this field directed toward optimizing risk prediction to identify the candidate that would qualify for prophylactic or preventive interventions. At present, the clinical risk stratification is largely limited to the use of left ventricular ejection fraction (LVEF) for identifying primary prophylaxis candidates, but specificity of this predictor is modest. Moreover, the absolute numbers of these high-risk patients in the general population are low. Instead, the highest prevalence of SCD is likely observed among previously asymptomatic individuals, even though it is well-known that coronary artery disease (CAD) is present in most SCD cases. This underscores the need for the development of risk stratification models that can be applied to the general population where the largest health benefit is likely to be realized.

The underpinnings of SCD are complex, and it is reasonable to believe that the risk stratification instrument of the future is likely to involve other components beyond clinical risk markers. Novel genomic variants show promise but are still in early phases of development as risk stratification targets. However, the “unbiased” approaches made possible through genomewide association studies have led to the recent identification of specific genetic variants that could predict SCD. This has rekindled interest in plasma biomarkers as a means for risk stratification. This article will review the emerging evidence and role of plasma biomarkers in predicting SCD in the general population and suggest a blueprint for future studies of potential utility.

Risk Markers for SCD

Uniform Definition of SCD

Given the complexity and dynamic nature of the condition, there has been some variability in defining SCD in the published literature. The need for a uniform definition of SCD is increasingly acknowledged, and at a recent consensus conference, the condition was defined as follows: “A case of established SCD is an unexpected death without obvious extracardiac cause, occurring with a rapid witnessed collapse, or if unwitnessed, occurring within 1 hour after the onset of symptoms. A probable SCD is an unexpected death without obvious extracardiac cause that occurred within the previous 24 hours. In any situation, the death should not occur in the setting of a prior terminal condition, such as a malignancy that is not in remission or end-stage chronic obstructive lung disease.”

Current Status of Risk Markers for SCD

Traditional cardiovascular risk factors, such as diabetes, obesity, dyslipidemia, and hypertension, have all been linked to SCD. Furthermore, several electrocardiographic risk markers have emerged from cohorts and community-based studies more likely to reflect the general population. These include a prolonged QT interval and the Tpeak–Tend interval (from the peak to the end of the T wave). At present, the LVEF is the most common clinically used risk predictor of SCD, with LVEF <35% indicating the need for implantable cardioverter-defibrillator (ICD) implantation. However, it is well recognized that this selection parameter is likely to have limited effectiveness. The ICD cohort studies indicate that less than a quarter of all patients implanted with an ICD based on the LVEF criterion will receive adequate therapies over an intermediate follow-up period of 3 to 5 years. Furthermore, most (>65%) of patients with SCD do not have severely reduced LVEF and, therefore, cannot be risk stratified based on this parameter. Moreover, a significant proportion of the individuals at risk will present with SCD as their first cardiac manifestation. Taken together, it is likely that previous studies of biomarkers performed in populations with ischemic heart disease or heart failure will have limited applicability to SCD risk stratification. As was recently noted in a consensus document, this also applies to ICD therapies, that turn out to be a poor surrogate marker for SCD. Consequently, more investigational efforts are warranted from studies that reflect events in the general population. Effective risk stratification in such subjects will require the availability of tools that can be used at an early stage in the natural history of the condition. Ideally, such tools should be inexpensive and cost efficient, easy to use and interpret, and widely available. Because plasma biomarkers could fulfill these criteria, we would suggest that there is a critical need for the development of risk stratification models that can be applied to the general population where the largest health benefit is likely to be realized.
SCD Biomarkers From Cohort Studies

Blood Lipids
The link between blood lipids and CAD development is widely accepted, but the association with risk of SCD is less clear. A prospective study of \( \approx 8000 \) British middle-aged men, by Wannamethee et al.,\(^{23}\) reported an association of cholesterol with increased risk of SCD in men. The relative risk (RR) of SCD was 3.5 for subjects without preexisting ischemic heart disease when comparing extreme quintiles \( (P<0.01) \); and 1.48 per 1 mmol/L increase of cholesterol when examining overall subjects with and without preexisting ischemic heart disease. However, the small number of SCD cases is a limitation of this study, along with the fact that the presence of preexisting ischemic heart disease was largely ascertained through self-reporting.

A prospective nested case-control study,\(^{17}\) analyzing data from the Physicians’ Health Study, could not verify an association between plasma lipid levels (total cholesterol, triglyceride, and low- and high-density lipoprotein cholesterol) and SCD. Another marker with lack of any association reported in this study was homocysteine. The study population comprised 22,000 presumably healthy middle-aged men with 97 cases of SCD occurring over the 17-year follow-up period. The authors speculated that the study was underpowered to detect small effects, emphasizing the difficulties associated with studying biomarkers in the general population through prospective cohort studies.

Plasma lipids may not be adequate markers for the early stages of CAD either. Instead, remnant proteins could be more promising, as has been suggested by Nakajima et al.,\(^{29}\) who reported postmortem data. The potential role of blood lipids in predicting SCD in the general population merits further investigation.

Inflammatory Markers
A significant proportion of SCD cases are related to CAD, with the possibility of plaque rupture playing a significant mechanistic role. The importance of inflammation in the development of the vulnerable plaque is well-known\(^{30}\) and, consequently, biomarkers reflecting increased inflammatory activity have been the focus of extensive research in CAD, and also increasingly for SCD (Figure 2). C-reactive protein (CRP), an acute-phase reactant, is the inflammatory marker that has been studied the most. In particular, the analysis of highly sensitive CRP (hsCRP) has allowed for ascertainment of elevated CRP levels that are subclinical. Several studies have demonstrated that hsCRP has a predictive value for development of CAD\(^{31,32}\) and the ability to reclassify a substantial proportion of individuals of intermediate risk into a different risk category.\(^{33}\) However, whether this biomarker is useful in reclassifying an individual’s risk level for CAD in a clinically significant manner remains controversial.\(^{34}\)

In the context of SCD in the general population, analyses from the Physicians’ Health Study\(^{17}\) showed that CRP levels were an independent risk factor for SCD in males after correcting for potential confounders (RR for highest versus lowest quartile, 2.65; 95% CI, 0.79–8.83; \( P=0.03 \)). To our knowledge, this study was the first to evaluate CRP in

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Figure 1. Qualities of an ideal plasma biomarker for sudden cardiac death (SCD). In the box, the requirements for an ideal biomarker are listed. This includes clinical utility, such as the ability to successfully shift individuals between different risk classes.
association with SCD as a specific end point. In contrast, a prospective, nested, case-control study performed in a large cohort (>120,000 presumably healthy women) did not show any significant correlation between SCD and hsCRP \(^{18}\) (\(P=0.34\)). Again, the number of SCD cases was small (n=99). As is often the case, this analysis was based on single assays conducted at baseline, which is likely to constitute a limitation when studying an association with an end point occurring several years or even decades later.

In 2007, Blangy et al\(^{35}\) reported an association between CRP levels and ventricular tachycardia in a group of ICD recipients with ischemic heart disease. Again, this might be of limited relevance to SCD cases without established CAD especially since recurrence of ventricular arrhythmia in an ICD population may not be an effective surrogate for sudden cardiac arrest occurrence.\(^3\)

Interleukin (IL) 6 is another inflammatory marker that has been associated with CAD. To date, 1 large prospective investigation, the PRIME study [Prospective Epidemiological Study of Myocardial Infarction], has investigated the association of SCD and IL-6.\(^{19}\) The investigators observed nearly 10,000 asymptomatic European middle-aged men for >10 years and reported that IL-6 was associated with an increased risk of SCD (adjusted hazard ratio [HR] for extreme tertiles, 3.06; 95% CI, 1.20–7.81; \(P=0.02\)). Interestingly, and in contrast, no significant associations were seen for hsCRP and SCD. This study was also limited by low numbers of events. Other biomarkers that participate in the development of CAD and vulnerable plaques that also hold promise in SCD are shown in Figure 2; they include myeloperoxidase, metalloproteinases, and IL-18. All of these require further evaluations, particularly in the context of SCD.

### Hemodynamic Markers

Natriuretic peptides are hormones secreted during cardiac hemodynamic stress. At present, these biomarkers are mainly used to rule out cardiac hemodynamic compromise in a clinical setting.\(^{36}\) Several studies have reported the ability of B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) to predict risk of SCD and appropriate ICD therapies.\(^{37,38}\) However, most of the studies were performed in patients with established ischemic heart disease and/or heart failure. Indeed, there are only 2 large studies performed in presumably healthy subjects with SCD as a specific

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**Table. A Summary of Studies on Biomarkers and SCD**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Source</th>
<th>Population (Sex)</th>
<th>Risk</th>
<th>Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>2002(^{17})</td>
<td>97/192 (M)</td>
<td>RR, 2.65 (0.79–8.83)*</td>
<td>17</td>
</tr>
<tr>
<td>hsCRP</td>
<td>2009(^{18})</td>
<td>99/294 (F)</td>
<td>NS*</td>
<td>16</td>
</tr>
<tr>
<td>hsCRP</td>
<td>2010(^{19})</td>
<td>50/100 (M)</td>
<td>NS†</td>
<td>16</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>2009(^{18})</td>
<td>99/294 (F)</td>
<td>RR, 1.49 (1.09–2.05)*</td>
<td>16</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>2011(^{20})</td>
<td>289/0 (M, F)</td>
<td>HR, 2.5 (1.6–3.8)†</td>
<td>16</td>
</tr>
<tr>
<td>NEFA</td>
<td>2001(^{21})</td>
<td>91/0 (M)</td>
<td>RR, 1.70 (1.21–2.13)‡</td>
<td>22</td>
</tr>
<tr>
<td>LCn3FA</td>
<td>2002(^{22})</td>
<td>94/184 (M)</td>
<td>RR, 0.19 (0.05–0.71)*</td>
<td>17</td>
</tr>
<tr>
<td>TC</td>
<td>1995(^{23})</td>
<td>106/0 (M)</td>
<td>RR, 1.46</td>
<td>8</td>
</tr>
<tr>
<td>TC, TG, and LDL</td>
<td>2002(^{17})</td>
<td>97/192 (M)</td>
<td>NS*</td>
<td>17</td>
</tr>
<tr>
<td>homocysteine</td>
<td>2002(^{17})</td>
<td>97/192 (M)</td>
<td>NS*</td>
<td>17</td>
</tr>
<tr>
<td>Magnesium</td>
<td>2010(^{24})</td>
<td>264/0 (M, F)</td>
<td>HR, 0.62 (0.42–0.93)*</td>
<td>12</td>
</tr>
<tr>
<td>Magnesium</td>
<td>2010(^{25})</td>
<td>505/0 (F)</td>
<td>RR, 0.23 (0.09–0.60)*</td>
<td>26</td>
</tr>
<tr>
<td>Glucose</td>
<td>2005(^{26})</td>
<td>2040/3800 (M, F)</td>
<td>OR, 1.20 (1.12–1.28)§</td>
<td>14</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>2009(^{27})</td>
<td>91/0 (M, F)</td>
<td>HR, 2.67 (1.33–5.35)†</td>
<td>12</td>
</tr>
<tr>
<td>Interleukin 6</td>
<td>2010(^{19})</td>
<td>50/100 (M)</td>
<td>HR, 3.06 (1.20–7.81)†</td>
<td>10</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>2010(^{19})</td>
<td>50/100 (M)</td>
<td>NS†</td>
<td>10</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>2009(^{28})</td>
<td>207/0 (M, F)</td>
<td>RR, 2.56 (1.76–3.73)†</td>
<td>12</td>
</tr>
<tr>
<td>vWF</td>
<td>2009(^{28})</td>
<td>207/0 (M, F)</td>
<td>RR, 2.67 (1.80–3.96)†</td>
<td>12</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>2009(^{28})</td>
<td>207/0 (M, F)</td>
<td>RR, 2.58 (1.77–3.78)†</td>
<td>12</td>
</tr>
</tbody>
</table>

This table summarizes existing larger studies on biomarkers and risk of SCD that have reported risk variables, including CIs and \(P\) values. Source denotes year published and reference list number. Population denotes number of cases/controls (sex). Risk includes the 95% CI in parentheses. Period indicates the follow-up period (in years).

SCD indicates sudden cardiac death; CRP, C-reactive protein; RR, relative risk; hsCRP, highly sensitive CRP; NS, nonsignificant; NT-proBNP, N-terminal pro-B-type natriuretic peptide; HR, hazard ratio; NEFA, nonesterified free fatty acid; LCn3FA, long-chain n-3 fatty acid; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; OR, odds ratio; vWF, von Willebrand factor.

*Highest vs lowest quartile.
†Highest vs lowest tertile.
‡Highest vs lowest quintile.
§Per 1-SD increment.

Per 1 mmol/L increase.
The association between renal disease and cardiovascular disease (CVD) that show promise as predictors of sudden cardiac death (SCD). The schematic illustrates that different plasma biomarkers seem to be useful at different stages of CAD. Markers of other conditions, such as hemodynamic compromise, might also prove to be linked to SCD risk. These biomarkers are clearly of interest but require further evaluation.

Free Fatty Acids
Nonesterified free fatty acids (NEFAs) are thought to be proarrhythmic based on their ability to modulate potassium and calcium channels, and perhaps also because of direct toxic effects. Based on the association of NEFA with arrhythmias and SCD in ischemic patients, Jouven and coworkers decided to study NEFAs as a risk factor in a nonischemic population. More than 5000 men (aged 42–53 years) were observed within the framework of the Paris Prospective Study I for a mean of 22 years.21 NEFAs were an independent risk factor for SCD in this population (adjusted HR, 1.70; 95% CI, 1.21–2.13).

Recent studies are lacking. In a study by Jouven and coworkers,26 a 16-year follow-up period when comparing extreme quintiles (adjusted HR, 2.5; 95% CI, 1.6–3.8; P<0.001). The authors concluded that NT-proBNP provided information regarding the risk of SCD in a community-based population of older adults, beyond traditional risk factors, but also noted that the specificity of elevated peptide levels for SCD compared with other causes of cardiovascular mortality is unclear.

Other Biomarkers
A few studies have reported that markers of hemostasis are associated with SCD. Kucharska-Newton et al28 analyzing data from the Atherosclerosis Risk in Communities cohort, reported that elevated levels of von Willebrand factor, factor VIIIc, and fibrinogen were all associated with SCD (adjusted RR [95% CI] for extreme tertiles, 2.67 [1.80–3.96], 2.58 [1.77–3.78], and 2.56 [1.76–3.73], respectively). From the same study, a moderate inverse relationship between albumin levels and risk of SCD was also reported. In contrast, Empana et al19 did not find any statistically significant association between fibrinogen levels and SCD in the PRIME study.

Magnesium regulates membrane electric stability of the cardiac myocyte and may have antiarrhythmic properties.41 Recently, 2 studies were published that showed an inverse relationship between increased magnesium levels and risk of SCD. Peacock and coworkers reported that, in a middle-aged biracial population,24 individuals in the highest quintile of serum magnesium had a 40% reduced risk of SCD (HR, 0.62; 95% CI, 0.42–0.93) compared with the lowest quintile. A second study performed in healthy women reported that an increase of 1 SD in plasma magnesium was associated with a 41% (95% CI, 15%–58%) lower risk of SCD.25

Elevated plasma renin levels were recently reported to be independently and strongly associated with an increased risk for death due to heart failure, cardiovascular events, and SCD.42 This study was performed in older whites referred for coronary angiography and has limited generalizability. Previous similar studies in fewer subjects have been inconsistent. However, the finding is interesting and merits further investigation in a larger prospective community-wide setting.

There is a growing body of evidence supporting the association between diabetes mellitus and increased risk of SCD.26 This might not be surprising given the link between diabetes and CAD, but large, prospective, community-wide studies are lacking. In a study by Jouven and coworkers,26 a 1-SD increase in glucose levels was associated with a slightly elevated risk for SCD (odds ratio, 1.20; 95% CI, 1.12–1.28) after adjusting for possible confounders.

The association between renal disease and cardiovascular morbidity and mortality is well established. To date, there is
Challenges and Future Directions

There is significant potential for development of biomarkers that will facilitate early identification of asymptomatic individuals at risk of SCD in the general population. However, on an individual basis, currently known candidate biomarkers will require significant additional evaluation to extend beyond the moderate efficacy marker. Most importantly, there is a need for the evaluation of large numbers of subjects, especially to assess the possibility that specific biomarkers may be more efficacious for the prediction of risk in specific subgroups of SCD patients. Analogous to the usefulness of biomarkers for prediction of future events in survivors of acute coronary syndromes, there is a special subgroup of patients in whom SCD biomarkers could be of special utility. These are patients with preserved LVEF who manifest with acute coronary syndromes. This group is likely to constitute an intermediate-risk subgroup that could provide sufficient power for biomarker analysis by analysis of relatively fewer subjects.

Another widely held hypothesis is that a multimarker strategy (Figure 3) is more likely to be useful. So far, these models seem to add only moderately to risk prediction. As ongoing evaluations of the genome and proteome yield additional results, these are going to provide a growing number of additional candidate biomarkers. A systematic strategy will need to be used to evaluate these potential SCD biomarkers.

Thus far, the cohort studies that have evaluated biomarkers have significant similarities in study design, with samples being drawn at baseline. However, the relevance of an elevated biomarker for an event that occurred 10 to 16 years subsequently has been questioned. These biomarkers may indicate early stages of SCD risk-producing cardiac disease development. However, this may also represent a coincidental finding unrelated to disease mechanisms. Such results underscore the need for replicating findings in distinct and different populations.

Moreover, the pathophysiological processes also merit further investigation because the issue of causality is still unexplored in most cases of biomarkers. This includes evaluation of the possible temporal variations of risk characteristics. Future studies could plan to repeat measurements throughout the follow-up period to minimize the time between sample collection and event occurrence. To further assess potential competing risks and specificity for SCD, it would be prudent to make comparisons of candidate biomarkers with subjects who experience nonsudden cardiac death, as well as noncardiac death.

An important challenge that remains to be overcome is that of sample size. Existing cohorts, even when combined, may not be large enough to be adequately powered for biomarker evaluation. There is an existing model for prospective community-based investigation of SCD biomarkers that provides significantly larger sample sizes and overcomes the difficulty of an uncommon end point. However, this approach poses a separate set of research design challenges. Because the samples are drawn by first responders during the resuscitation process for sudden cardiac arrest, identified biomarkers need to be evaluated for potential association with the sudden cardiac arrest event itself, likely in animal models. Last, it is important to make a clear distinction between statistical significance for association of a particular biomarker with SCD and the clinical usefulness of that biomarker. If a biomarker identifies individuals as being at higher SCD risk, it is likely that additional diagnostic tests (eg, electrophysiological studies) will be required to refine the identification of subjects at highest risk, which is likely to be an important step to maximize the usefulness of preventive interventions, such as the ICD.

Designing the Ideal SCD Biomarker Study

What, then, would be the ideal study design for identification of early risk markers for SCD? The first requirement is the availability of a sufficiently large, adequately powered sample size of a well-defined and carefully characterized SCD phenotype. Ideally, repeated clinical measures of the phenotype, such as the EKG and echocardiogram, would be made available in a large community-wide study. Repeated measurements of biomarkers would be performed in parallel with genomic evaluation, with subsequent validation of identified candidate markers in separate populations; comparisons would be conducted between the sexes within and across multiple ethnicities.
Conclusions

There is a critical need for better methods to identify individuals in the general population who are at high risk of SCD. Future risk stratification models will rely on multiple predictors, and a single plasma biomarker is likely to solve a piece of this puzzle. At present, some biomarkers have shown promise, but none of these are ready for clinical use. Future investigative approaches should use a uniform definition of SCD and perform evaluations in many subjects representing the general population, with analyses performed within and across the sexes, multiple ethnicities, and age groups.

Sources of Funding

This study was supported by a grant from the Swedish Research Council (Dr Hamsten) and by grants R01HL088416 and R01HL105170 from the National Heart, Lung, and Blood Institute (Dr Chugh). Dr Chugh is the Pauline and Harold Price Professor of Cardiac Electrophysiology at the Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA.

Disclosures

None.

References


**Key Words:** sudden cardiac arrest | sudden death | biomarker | ventricular arrhythmia | risk marker
Plasma Biomarkers for Prediction of Sudden Cardiac Death: Another Piece of the Risk Stratification Puzzle?
Rasmus Havmöller and Sumeet S. Chugh

Circ Arrhythm Electrophysiol. 2012;5:237-243
doi: 10.1161/CIRCEP.111.968057

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