Biomarkers to Predict Cardiovascular Death

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KEYWORDS

• Biomarkers • Cardiovascular death • Risk score • Risk stratification

KEY POINTS

- Risk prediction models in identifying the "vulnerable" patient at risk for cardiovascular death are presently limited.
- Pathway-specific biomarkers of inflammation, thrombosis, immune function, and cell stress improve risk prediction for cardiovascular death in patients with coronary artery disease and heart failure.
- Similarly, markers of inflammation, myocardial stretch, and others improve risk prediction in patients with heart failure.

Cardiovascular disease (CVD) is the leading cause of mortality worldwide.[1] Several population-based CVD risk models have been incorporated into guidelines to target primary prevention with the goal of appropriate risk stratification for at-risk individuals. Despite these models, a sizable gap in the current ability to risk stratify remains, as evidenced by most cases of sudden cardiac death (SCD) occurring in previously asymptomatic individuals in whom death can be the first manifestation of CVD.[2] Improving risk stratification is an important step in enhancing the ability to identify individuals who would benefit from prophylactic and preventative measures. One area of current investigation is the use of biomarkers to assist prediction of cardiovascular death. A useful biomarker (1) separates individuals with or without risk (discrimination), (2) stratifies individuals appropriately and thus potentially change clinical course (classification), and (3) denotes how well the predicted risk matches actual risk in the community (calibration).[3] Clinical tools such as the Framingham risk score predict long-term risk of coronary heart disease outcomes in the healthy population,[4,5] but fail to reliably predict risk of adverse outcomes in patients with established coronary artery disease (CAD).[6] Biomarkers that are surrogates for pathophysiologic processes associated with acute CAD progression to plaque instability, erosion, and rupture and possibly for arrhythmogenesis may be better predictors of future risk of cardiovascular death. This article considers biomarkers that have been shown to identify subjects at increased risk for cardiovascular death within the (1) general population, (2) in those with established CAD, and (3) in those with heart failure (HF) (**Fig. 1**).

BIOMARKERS OF CARDIOVASCULAR DEATH IN THE GENERAL POPULATION

Metabolic

Abnormal lipid profiles are central to many current risk prediction calculators, and do serve to identify subjects with increased likelihood of underlying CAD.[7] Although the Physicians Health Study did not find an association between plasma lipids and SCD,[8] possibly because of the low power of the

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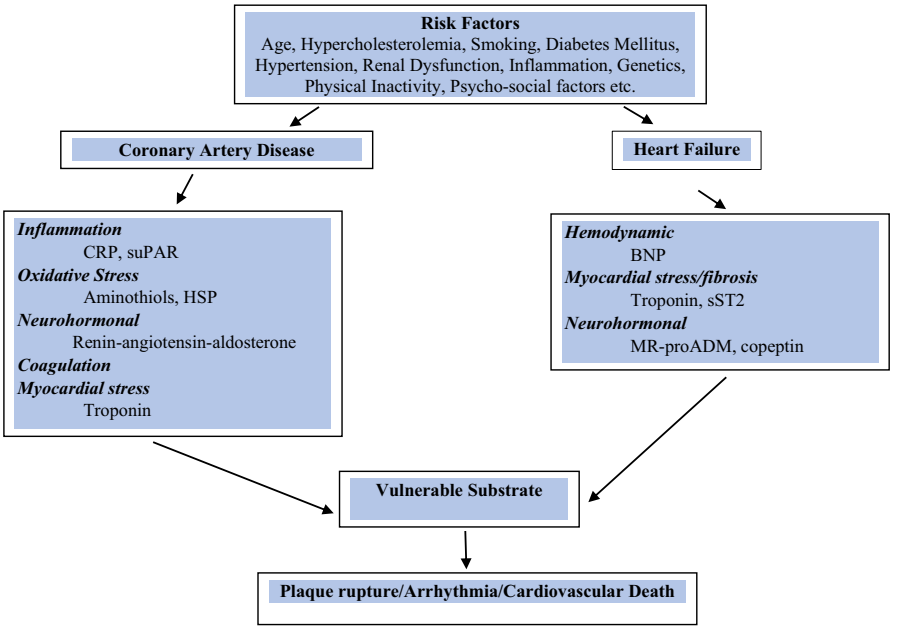

Fig. 1. Biomarkers in cardiovascular death in the heart failure and coronary artery disease population. BNP, brain natriuretic peptide; CRP, C-reactive protein; HSP, heat-shock proteins; MR-proADM, mid-regional proadrenomedullin; suPAR, soluble urokinase plasminogen activator receptor.

study, in a prospective evaluation of nearly 8000 British men, a 3.5-fold increased risk of SCD was observed between extreme quintiles in plasma lipids in subjects without any self-reported history of CAD.[9] Of note, SCD was defined as death within 1 hour of symptoms in these studies.

High-density lipoprotein cholesterol (HDL-C) is one such component of the lipid profile that is featured in several risk prediction models. In post hoc analyses of the Treating to New Targets (TNT) study and the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, there was little to no association between HDL-C levels and adverse cardiovascular events in patients on statin therapy.[10] Although the robust prospective observational data links lower HDL-C levels and CVD, causality remains unestablished. Additionally, raising HDL, with such therapy as niacin and CETP inhibition, does not seem to affect outcomes.[11]

Other potential biomarkers for cardiovascular death are the nonesterified free fatty acids. Nonesterified free fatty acids are believed to be proarrythmogenic because they modulate potassium and calcium channels and possibly have direct toxic effects.[12] In a nonischemic population of 5000 middle-aged men followed for 22 years in the Paris Prospective Study I, nonesterified free fatty acids were found to be independent risk factors for SCD (risk ratio [RR], 1.70; 95% confidence interval [CI], 1.21–2.13).[13]

Inflammatory and Prothrombotic Markers

High-sensitivity C-reactive protein (hsCRP) is an inflammatory marker that has been studied extensively in a variety of clinical contexts, including CAD.[3,14] HsCRP has been proposed as a useful biomarker for evaluation and for decision-making regarding treatment in asymptomatic subjects. In the JUPITER trial, asymptomatic individuals with elevated hsCRP and low-density lipoprotein cholesterol who were randomized to statin therapy had a 47% reduction in the risk of nonfatal myocardial infarction (MI), stroke, and cardiovascular death compared with those randomized to placebo.[15] Largely based on these data, the 2013 American College of Cardiology/American Heart Association Cholesterol Management guidelines advise consideration of hs-CRP use when treatment decision is uncertain in intermediate-risk groups.[16] However, when evaluated for its role in predicting SCD, the results have been mixed. In the Physician's Health Study, CRP was an independent predictor of SCD with an RR of 2.65 when comparing the highest with the lowest quartile.[8] However, in two other studies, the Nurses Health Study and the Prospective Epidemiological Study of Myocardial Infarction (PRIME) study, there were no observed associations between CRP levels and SCD.[17,18]

Lipoprotein phospholipase A_2, a novel lipid-related biomarker that plays a role in the depletion