Risky lipids: refining the ceramide score that measures cardiovascular health

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This editorial refers to ‘Development and validation of a ceramide- and phospholipid-based cardiovascular risk estimation score for coronary artery disease patients’, by M. Hilvo et al., on page 371.

Serum lipids such as cholesterol and triglycerides, which are the most abundant lipids in the circulation, are well-known biomarkers of risk of major adverse cardiac events. Recent advances in lipidomic technologies have allowed researchers to measure a more comprehensive array of lipids in large clinical cohorts, revealing that a lowly abundant class of lipids termed ceramides are particularly robust indicators of cardiometabolic health. Indeed, these ceramides reportedly outperform conventional cardiovascular (CV) risk markers, to the extent that some clinics began measuring serum ceramides as a means of identifying at-risk patients. In this issue of the European Heart Journal, Hilvo et al. improved upon their prior ceramide score (CERT1) to produce CERT2 (Figure 1), a refined ceramide-based score for predicting recurrence of major adverse cardiac events.

CERT2 demonstrates enhanced prognostic utility over conventional CV disease markers, including troponin T (TnT) and LDL cholesterol (LDL-C). The study, which included three large, prospective coronary heart disease cohorts, identifies CERT2 as a powerful prognostic tool to assess risk of residual coronary heart disease and CV-related death.

These ceramide-based scores build upon a large number of studies in prospective cohorts, revealing that three specific ceramide species [Cer(d18:1/16:0), Cer(d18:1/18:0), and Cer(d18:1/24:1)] predict the severity of CV disease. The authors also included another ceramide [Cer(d18:1/24:0)], which showed no such relationship with measures of disease and could be used for normalization. In the first-generation CERT1 score, the authors constructed a 12-point algorithm, with a higher score revealing levels of these deleterious ceramides in upper patient quartiles. CERT1 boasted odds ratios (ORs) predicting coronary death over three times higher than LDL-C. This study also described ceramides as significantly higher in acute coronary syndrome patients that died 1 year following their cardiac event than in those that survived. Furthermore, ceramide levels were also associated with recurrent adverse cardiac events. Patients could be classified into one of four risk categories—low, moderate, increased, and high—which correspond to score ranges 0–2, 3–6, 7–9, and 10–12, respectively. Clinics have started using the CERT1 score to identify patients at risk for cardiometabolic diseases.

Studies in clinical cohorts and pre-clinical models suggest that these ceramides, which probably traffic between tissues in lipoproteins, play causal roles in heart failure. In humans, ceramides and ceramide-synthesizing enzymes are elevated in the failing myocardium. Moreover, in mice, a pharmacological inhibitor of ceramide synthesis prevented heart failure caused by ischaemic cardiomyopathy and reduced ventricular remodelling, fibrosis, and macrophage content following myocardial infarction. Beyond these direct actions in the heart, ceramides also promote dyslipidaemia, insulin resistance, and coronary artery disease, which are underlying disorders that increase risk of heart disease. Studies in rodents indicate that pharmacological or genetic inhibition of enzymes driving ceramide biosynthesis ameliorates these conditions as well.

Ceramides, despite being low in abundance, are one of the more toxic molecules that accumulate in individuals with the metabolic syndrome.

The study by Hilvo and colleagues sought to identify a lipidomics-based metric that could predict recurrent heart attacks and CV-related death in patients that had previously undergone a major adverse cardiac event. Traditional biomarkers of CV health such as LDL-C and serum triglycerides, which identify patients that are highly susceptible to a first major event, only weakly associate with future CV event outcomes (e.g., mortality). In this study, the ceramide species [Cer(d18:1/16:0), Cer(d18:1/18:0), and Cer(d18:1/24:1)] in CERT1 again proved to be good markers of CV events and death in this vulnerable population. The authors produced a refined, next-generation ceramide-based score (CERT2) based on this data set, which outperformed traditional biomarkers [LDL-C, triglycerides, Apolipoprotein B-100 (ApoB), C-reactive protein (CRP), Apolipoprotein A-1 (ApoA1), and fibrinogen] in预测ing recurrent major CV events and death in this vulnerable population.
are enigmatic. Moreover, while PC donates choline in a reaction ratioes elicit metabolic dysfunction, but the downstream mechanisms work has shown that imbalances in PC to phosphatidylethanolamine disease is much smaller than that surrounding ceramides. Some prior is unclear. The body of literature relating these species to metabolic utility of this score, though the biological basis for this improvement levels grows. 

Surprisingly, the CERT2 score included a few phosphatidylcholine (PC) species which tracked with recurrent CV disease. One fairly abundant PC species, 16:0/16:0, showed good predictive utility, while (PC) species which tracked with recurrent CV disease. One fairly minor (PC 16:0/22:5 and PC 36:6). Trevor S. Tippetts contributed to figure design.

Figure 1 Serum ceramide and phosphatidylcholine levels reflect risk of recurrent cardiovascular disease. A new clinical risk assessment score, CERT2, combines the power of positively (red) and negatively (green) disease-associated lipids to identify subjects at risk for cardiovascular (CV) composite events and CV-related mortality. Positively associated species: PC 16, PC 16:0/16:0; C18 Cer, Cer d(18:1, 18:0); C24:1 Cer, Cer d(18:1, 24:1); C16 Cer, Cer d(18:1, 16:0). Negatively associated species: C24, Per d(18:1, 24:0); PC22:5, PC 16:0/22:5; PC 36:6. Trevor S. Tippetts contributed to figure design.

and TnT] and CERT1 as a measure of forecasting CV death and CV composite events (CV death, myocardial infarction, and death). This finding is of clinical relevance as survival rates from CV events increase and the need to identify patients exceeding acceptable risk levels grows.

The clinical utility of these ceramide-based scores is bolstered by their simplicity and practicality. Unlike other clunky algorithms containing upwards of 15 variables, CERT2 includes just six lipid species, suggesting that it could show feasibility for clinical implementation in a laboratory blood-based predictive assay with rapid turnaround and strong estimation of risk of coronary heart disease. Both ceramides and PCs are analytically stable and easily detectable through a high-throughput liquid chromatography–mass spectrometry (LC-MS) assay. Additionally, hazard ratios increase when CERT2 is combined with the non-lipid clinical marker TnT, leading to the possibility that a more comprehensive risk assessment panel may be generated for patients by combining the most sensitive biomarkers of various biological origins.

**Conflict of interest:** S.S. is a consultant for Centaurus Therapeutics. The remaining authors have no conflicts to declare.

**References**


