Publications on CERT and Ceramides

CERT in Primary Prevention

1. Hilvo et al. 2021 Absolute and relative risk prediction in cardiovascular primary prevention with a modified SCORE chart incorporating ceramide-phospholipid risk score and diabetes mellitus, European Heart Journal Open, Volume 1, Issue 3, November 2021

   *** Pivotal paper showing performance and prognostic value of CERT2 over routine lipid measurements. As a result, an improved risk evaluation chart was developed with clear advantages compared to existing ESC Score chart.

2. Vasile & Jaffe 2021 An enhanced ceramide-based approach for primary prevention of atherosclerotic events. European Heart Journal Open, Volume 1, Issue 3, November 2021.

   ** A commentary on the above listed work by Hilvo et al by the Mayo Clinic clinical investigators.

3. Havulinna et al. 2016 Circulating Ceramides Predict Cardiovascular Outcomes in the Population-Based FINRISK 2002 Cohort, Arterioscler Thromb Vasc Biol. 2016; 36

   *** First large scale study showing the linkage between ceramides / CERT score and incident CVD events in a large scale primary prevention population.

4. Vasile VC, et al. Ceramide Scores Predict Cardiovascular Risk in the Community. Arterioscler Thromb Vasc Biol. 2021 Apr;41(4):1558-1569. Epub 2021 Feb 18. PMID: 33596665.

   ** Independent validation study in a North American population based study by Mayo Clinic investigators.

5. Peterson et al. 2018 Ceramide Remodeling and Risk of Cardiovascular Events and Mortality. J Am Heart Assoc. 2018 May 3;7(10):e007931.
   ** Value of the ceramide ratio as a novel biomarker of CHD risk, HF risk, and all-cause mortality in the community.

CERT in Secondary Prevention

6. Hilvo et al. 2021 Prior myocardial infarction, coronary artery disease extent, diabetes mellitus, and CERT2 score for risk stratification in stable coronary artery disease, Eur J Prev Cardiology, Published 28 August 2021

   *** A practical and user friendly risk chart for stable CHD patients providing granular risk information based on CERT2, coronary angiography /CT findings, presence of DM2 and known history of prior MI. Helps greatly in identification of very high risk CHD patients (i.e. > 3% annual CVD mortality rate as defined by ESC).

7. Leiherer et al. 2021 Comparison of recent ceramide-based coronary risk prediction scores in cardiovascular disease patients, Eur J Prev Cardiology, Published 21 August 2021

   * Comparison between CERT1, CERT2 and the ESC SCORE. Shows superiority and additional value of CERT scores over ESC SCORE.

8. Gencer et al. 2020 Plasma ceramide and phospholipid-based risk score and the risk of cardiovascular death in patients after acute coronary syndrome. Eur. J. Prev. Cardiol. Published online Dec 2020

   ** A collaborative paper based on the SOLID trial involving Zora and the TIMI group in Boston (Harvard) reporting a significant independent prognostic value of CERT2 in CHD patients with very recent acute coronary syndrome.

9. Hilvo et al. 2020 Prediction of Residual Risk by Ceramide-Phospholipid Score in Patients With Stable Coronary Heart Disease on Optimal Medical Therapy JAHA published online May 7, 2020.

   ** A collaborative paper with the STABILITY study group proving the prognostic value of CERT2 in stable CHD patients on optimized medical therapy.

10. Mantovani et al. 2020 Associations between specific plasma ceramides and severity of coronary-artery stenosis assessed by coronary angiography. Diabetes & Metabolism, 46(2): 150-157.

    * A cross-sectional study on associations between ceramides and coronary stenosis.

11. Hilvo et al. 2020 Development and validation of a ceramide- and phospholipid-based cardiovascular risk estimation score for coronary artery disease patients. Eur Heart J. 2020; 41:371-380.

    *** Early work describing CERT2 score and its development in three independent and well characterized large scale CHD patient cohorts.

12. Poss et al.2020 Risky lipids: Refining the ceramide score that measures cardiovascular health. European Heart Journal, 41(3): 381–382.

    *** Invited commentary by the leading ceramide expert Scott Summers (Utah) on the above Hilvo et al 2020 paper.

13. Meeusen et al. 2018 Plasma Ceramides – A Novel Predictor of Major Adverse Cardiovascular Events After Coronary Angiography. Arterioscler Thromb Vasc Biol. 2018 Aug;38(8):1933-1939. doi: 10.1161/ATVBAHA.118.311199

    ** Independent validation study of the prognostic value of ceramides in CHD by the Mayo Clinic team using their own clinical cohort material – ceramides were superior risk markers compared to all other markers studied by the Mayo group in their cohort.

14. Carvalho et al. 2018 Plasma Ceramides as Prognostic Biomarkers and Their Arterial and Myocardial Tissue Correlates in Acute Myocardial Infarction JACC Basic Transl Sci. 2018 May 30;3(2):163-175.

    * The authors identified a plasma signature of ceramides and dihydroceramides predictive of major adverse cardiovascular events in patients with acute myocardial infarction (AMI). Additional experimental studies suggested ischemic myocardium as a possible source of this ceramide signature.

15. Laaksonen et al. 2016 Plasma ceramides predict cardiovascular death in patients with stable coronary artery disease and acute coronary syndromes beyond LDL-cholesterol, Eur Heart J . 2016 Jul 1;37(25):1967-76.

    *** First large scale evidence on the prognostic value of ceramides in CHD. Data from three independent cohorts published together with lead European expert KOLs.

16. Anroedh et al. 2018 Plasma concentrations of molecular lipid species predict long-term clinical outcome in coronary artery disease patients. JLR June 2018, 59(6).

* An extension of the previously published study by Cheng et al 2015; 3-year follow-up results reported on predictive value of ceramide species in IVUS verified CHD patients.

17. Cheng et al. 2015 Plasma concentrations of molecular lipid species in relation to coronary plaque characteristics and cardiovascular outcome: Results of the ATHEROREMO-IVUS study, Atherosclerosis 2015 Dec;243(2):560-6.

 ** Paper on predictive value of ceramide species in IVUS verified CHD patients – a one year follow-up study. In addition, certain associations between coronary plaques characteristics related to vulnerability and ceramide species were reported.

CERT and Diabetes Risk

18. Hilvo et al. 2018 Ceramide stearic to palmitic acid ratio predicts incident diabetes, Diabetologia 2018; 61: 1424-1434.

*** First publication on the Zora developed predictive score for DM2 in two independent large cohorts from Finland and Norway. While additional validation studies are needed, however, wealth of scientific evidence unequivocally support the tight association between ceramides and diabetes.

Other Relevant Publications on Ceramides

19. Wang DD et al. 2017 Plasma Ceramides, Mediterranean Diet, and Incident Cardiovascular Disease in the PREDIMED Trial (Prevención con Dieta Mediterránea). Circulation. 2017, 135(21):2028-2040.

*** This study validated the positive association between baseline plasma ceramide concentrations and incident CVD. Importantly, a Mediterranean dietary intervention seemed to mitigate potential deleterious effects of elevated plasma ceramide concentrations on CVD. Of note was that the beneficial health effects of the Mediterranean diet was observed only in subjects with elevated ceramide levels, not in subjects with average or low serum concentrations of ceramides.

20. Ye Q, et al. Effect of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors on Plasma Ceramide Levels. Am J Cardiol. 2020 Aug 1;128:163-167.

*** Treatment with PCSK9 inhibitors is associated with significant reduction in Ceramide Risk Score and distinct ceramide levels

21. Hilvo, Simolin, et al. PCSK9 inhibition alters the lipidome of plasma and lipoprotein fractions. Atherosclerosis. (2018) 269:159-65.

*** PCSK9 antibody alters the plasma ceramides.

22. Petrocelli et al. 2020 Ceramide Biomarkers Predictive of Cardiovascular Disease Risk Increase in Healthy Older Adults After Bed Rest. J Gerontol A Biol Sci Med Sci. 2020 Sep 16;75(9):1663-1670

* The results of this study highlight the sensitivity of circulating ceramides to detect potential CV dysfunction that may occur with acute physical inactivity in aging.

23. Kasumov et al. 2015 Improved insulin sensitivity after exercise training is linked to reduced plasma C14:0 ceramide in obesity and type 2 diabetes. Obesity (Silver Spring). 2015 Jul;23(7):1414-21.

    ** One of the initial papers showing that Ceramides are linked to exercise training-induced improvements in insulin sensitivity.

24. Ng, Ooi, Watts et al. Dose-dependent effects of rosuvastatin on the plasma sphingolipidome and phospholipidome in the metabolic syndrome. J. Clin. Endocrinol Metab. (2014) 99:E2335-40.

    ** Rosuvastatin dose-dependently lowers plasma ceramides in men with the metabolic syndrome.

25. Han, Kim, Jung et al. Metabolic Alterations Associated with Atorvastatin/Fenofibric Acid Combination in Patients with Atherogenic Dyslipidaemia: A Randomized Trial for Comparison with Escalated-Dose Atorvastatin. Sci Rep. 2018 Oct 2;8(1):14642.

    **Atorvastatin/fenofibric acid combination treatment reduces ceramides.

26. Camacho-Muñoz D et al. Omega-3 carboxylic acids and fenofibrate differentially alter plasma lipid mediators in patients with non-alcoholic fatty liver disease. FASEB J. 2021 Nov;35(11):e21976.

    ** Fenofibrate significantly reduces plasma ceramides, pro-inflammatory lipids associated with CV disease risk.

27. Croyal M et al. Fenofibrate decreases plasma ceramide in type 2 diabetes patients: A novel marker of CVD? Diabetes Metab. 2018 Mar;44(2):143-149. doi: 10.1016/j.diabet.2017.04.003. Epub 2017 May 9. PMID: 28499696.

    ** Fenofibrate lowers plasma ceramide independently of the usual lipid parameters.

28. Marfella R et al. Lipid Accumulation in Hearts Transplanted From Nondiabetic Donors to Diabetic Recipients. J Am Coll Cardiol. 2020 Mar 24;75(11):1249-1262.

    **Metformin use was associated with reduced lipid accumulation independently of immunosuppressive therapy.

29. Djekic D et al. Effects of a Lacto-Ovo-Vegetarian Diet on the Plasma Lipidome and Its Association with Atherosclerotic Burden in Patients with Coronary Artery Disease-A Randomized, Open-Label, Cross-over Study. Nutrients. 2020 Nov 23;12(11):3586.

    ** Vegetarian diet lowered certain cardiovascular risk ceramides.

30. Zobel EH et al. Ceramides and phospholipids are downregulated with liraglutide treatment: results from the LiraFlame randomized controlled trial. BMJ Open Diabetes Res Care. 2021 Sep;9(1):e002395.

    ** GLP-1 agonist treatment led to a significant downregulation in ceramides, phospholipids and triglycerides, which all are linked to higher risk of CVD.

31. Vijay A et al. Dietary Interventions Reduce Traditional and Novel Cardiovascular Risk Markers by Altering the Gut Microbiome and Their Metabolites. Front Cardiovasc Med. 2021 Jul 14;8:691564.

    ** Omega-3 and fibre supplementation reduces specific ceramide ratios that have been shown to predict CVD mortality and major adverse cardiovascular events.

LDL performance in middle-aged adults

32. Hilvo et al. 2021 Primary cardiovascular risk prediction by LDL-cholesterol in Caucasian middle-aged and older adults: a joint analysis of three cohorts. Eur J Prev Cardiol. 2021 Jun 1;zwab075. doi: 10.1093/eurjpc/zwab075

    *** A most important paper showing that in the middle-aged and older adults, associations between LDL-C and cardiovascular endpoints are in fact very weak. Thus, these data call for better risk predictors to replace routine used lipid markers.

33. Tsaban G. Low-density lipoprotein cholesterol and cardiovascular risk: a necessary causal agent but an insufficient predictor. Eur J Prev Cardiol. 2021 Jun 15:zwab098. doi: 10.1093/eurjpc/zwab098.

    * An invited commentary about the new findings that LDL-cholesterol may be a causal factor for atherosclerosis, but an insufficient risk predictor for CVD events.

Reviews and Commentaries

34. Meeusen et al. 2020 Ceramides improve atherosclerotic cardiovascular disease risk assessment beyond standard risk factors. Clinica Chimica Acta 2020. 511: 138–142

35. Hilvo et al. 2020 Ceramides and Ceramide Scores: Clinical Applications for Cardiometabolic Risk Stratification. Front. Endocrinol., 29 September 2020

36. Carrard et al. 2021 How Ceramides Orchestrate Cardiometabolic Health—An Ode to Physically Active Living. Metabolites 2021, 11(10), 67.

37. Kovilakath et al. 2020 Sphingolipids in the Heart: From Cradle to Grave. Front. Endocrinol., 15 September 2020

38. Choi et al. 2021 Ceramides and other sphingolipids as drivers of cardiovascular disease. Nature Reviews Cardiology. Published 26 March 2021

39. Öörni et al. 2020 Why and how increased plasma ceramides predict future cardiovascular events? Atherosclerosis. 2020 Dec; 314: P71-73.

40. Summers 2018 Could Ceramides Become the New Cholesterol, Cell Metabolism 27 (2), 276-280.

41. Chaurasia B, Summers SA. 2015 Ceramides – Lipotoxic Inducers of Metabolic Disorders. Trends Endocrinol Metab. 2015, 26(10):538-50.

42. Holland WL, Summers SA. 2008 Sphingolipids, insulin resistance, and metabolic disease: new insights from in vivo manipulation of sphingolipid metabolism. Endocr Rev. 2008, 29(4):381-402.

43. Chavez JA, Summers SA. 2012 A ceramide-centric view of insulin resistance. Cell Metab, 2012, 15(5):585-94.

44. Bikman BT, Summers SA. 2011 Ceramides as modulators of cellular and whole-body metabolism. J Clin Invest. 2011, 121(11):4222-30.