The Prognostic Utility of a Plasma Ceramide and Phospholipid-Based Risk Score in Patients After An Acute Coronary Syndrome

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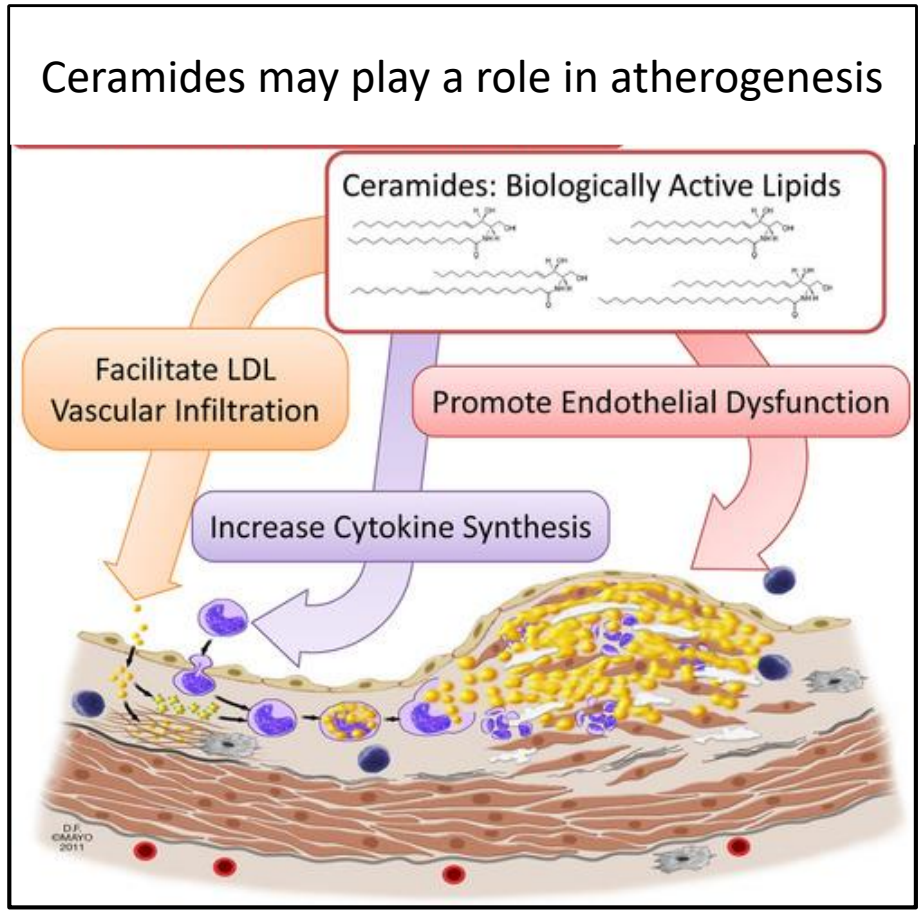
Relevant Disclosures

- The SOLID-TIMI 52 trial (NCT 01000727) was funded by GlaxoSmithKline.
- Ceramide and phospholipids for this analysis were measured by Zora Biosciences (Finland).
- Analyses were conducted by the TIMI Study Group.

Ceramides: complex high-risk lipids



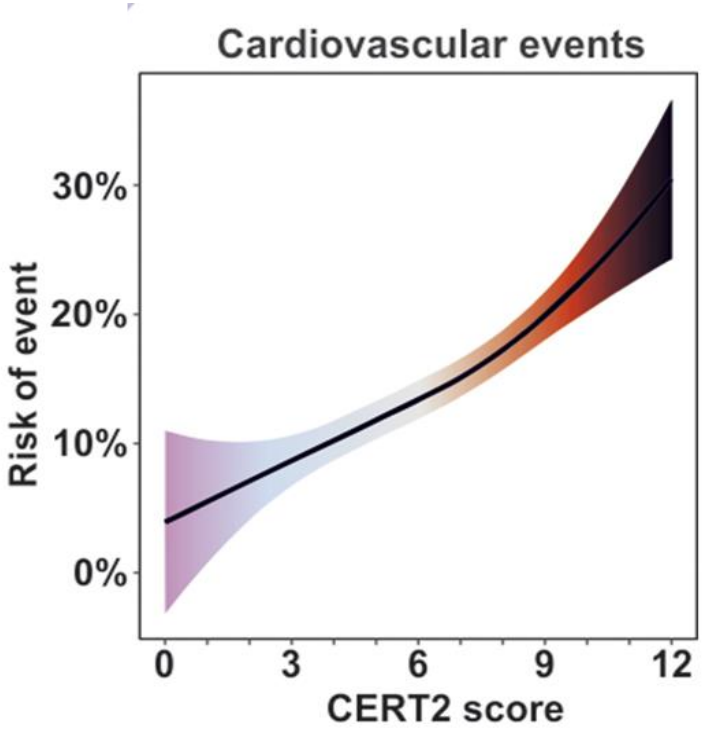
All tissues can synthesize ceramides de novo from sphingosine and (un)saturated fatty-acid chains

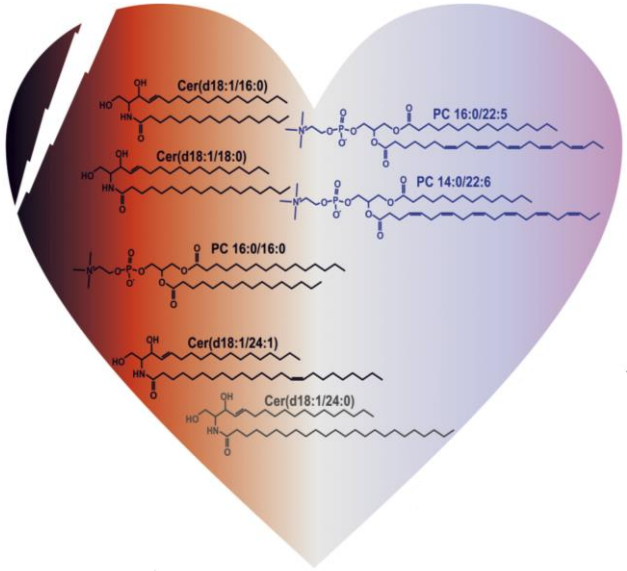
- N-palmitoyl-sphingosine [Cer(16:0)],
- N-stearoyl-sphingosine [Cer(18:0)],
- N-nervonoyl-sphingosine [Cer(24:1)],
- N-lignoceroyl-sphingosine [Cer(24:0)].

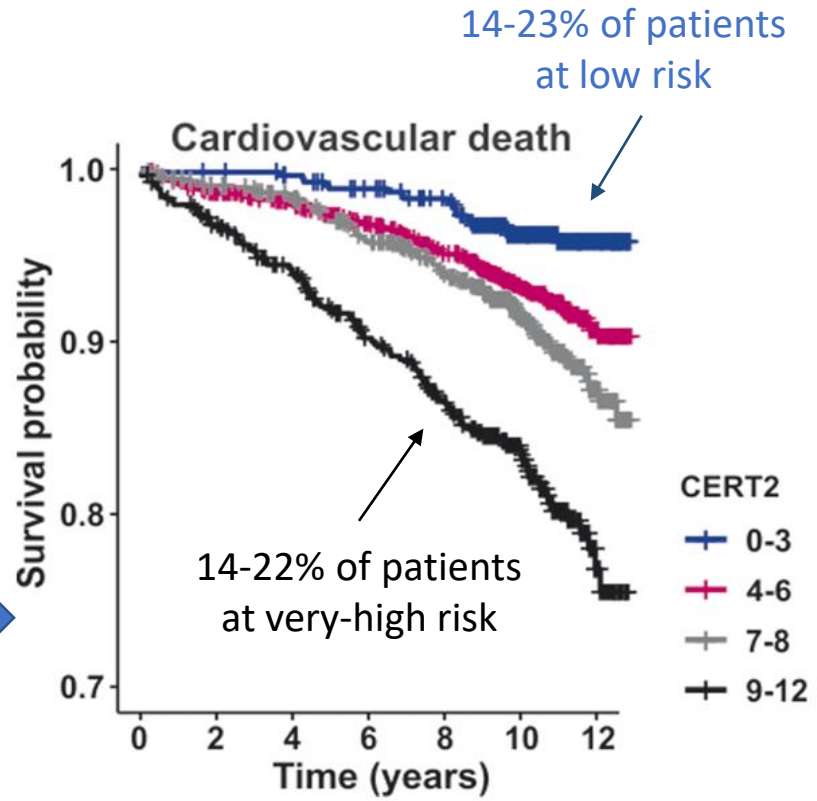
Arterioscl Thromb Vasc Biol. 2018 Aug;38(8):1933-1939.

Ceramides & CV Risk Prediction

10 803 patients with stable CAD for a total of 948 CV death events across 3 studies







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Aim/Hypothesis

- Aim: to determine the prognostic performance of a recently established **Plasma Ceramide-Phospholipid (CER-PL) Risk Score** in patients early after ACS.

- Hypothesis: higher risk of CER-PL Risk Score is associated with a higher risk of CV death in patients post-ACS independent of established risk factors and biomarkers.

Study Population

- The SOLID-TIMI 52 (Stabilization of Plaque Using Darapladib-Thrombolysis in Myocardial Infarction 52) trial randomized 13,026 within 30 days of hospitalization with ACS to darapladib (inhibitor of the lipoprotein-associated phospholipase A_2 enzyme) versus placebo.
- Median follow-up was 2.5 years.
- Biomarker samples were obtained in all consenting patients at randomization (median 14 days from hospital presentation).
- The current analysis is restricted to a randomly selected cohort of 5000 patients (outside of China) in whom 4871 had a calculatable CER-PL score.

Ceramide-Phospholipid Risk Score

Score Components					
Ceramides and Phospholipids Species	Q1	Q2	Q3	Q4	Score
Cer(d18:1/24:1) / Cer(d18:1/24:0)	0	1	2	3	0-12
Cer(d18:1/16:0) / PC 16:0/22:5	0	1	2	3	
Cer(d18:1/16:0) /PC 14:0/22:6	0	1	2	3	
PC 16:0/16:0	0	1	2	3	

Risk Group	Number of Points
Low Risk	0-3
Moderate Risk	4-6
High Risk	7-8
Very High Risk	9-12

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Cer: ceramides
PC: phosphatidyl choline

Study Endpoints

- Primary endpoint:

(1) CV Death

- Secondary endpoints:

(2) Composite of CV Death and Heart Failure (HF) hospitalization

(3) HF hospitalization

(4) Composite of CV Death, Myocardial Infarction (MI) or Stroke

(5) MI

(6) Stroke

Statistical Analysis

Modified Poisson regression was used to assess the association between the **ceramide-phospholipid risk score** and clinical outcomes across 3 models:

(1) Unadjusted

(2) Model 1: Clinical Adjustment

Adjusted for age (<65, 65-75, >75), race (white vs. non-white), sex, smoking, prior MI, systolic blood pressure, BMI, eGFR (< 60 ml/min/m^2), LDL-C and index ACS diagnosis (STEMI vs. NSTEACS).

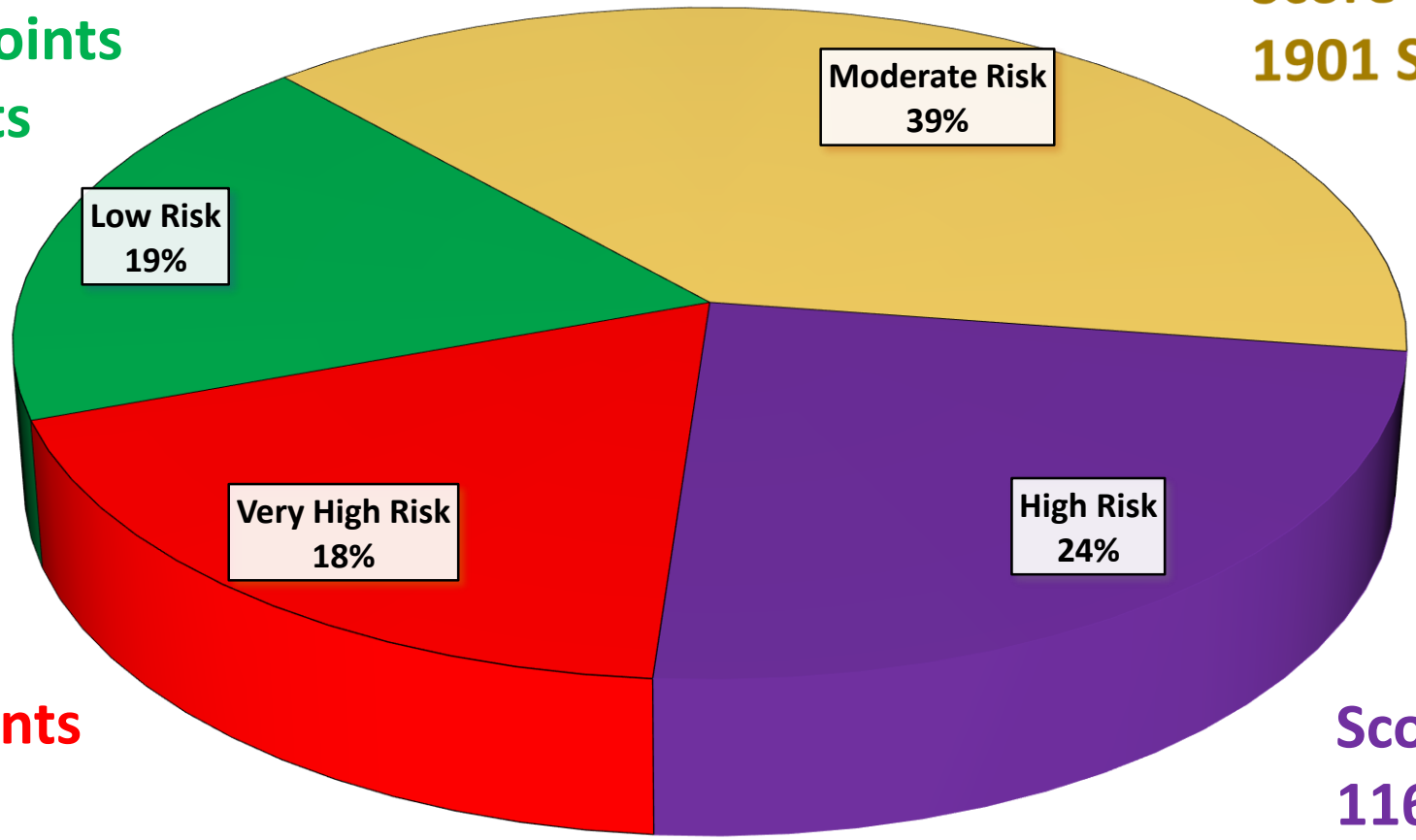
(3) Model 2: Clinical Adjustment and Established Biomarkers

Above + hs-CRP, hs-TnI, BNP and Lp-PLA$_2$ activity.

Cer-PL Risk Score Categories

Score 0-3 Points
918 Subjects

Score 4-6 Points
1901 Subjects



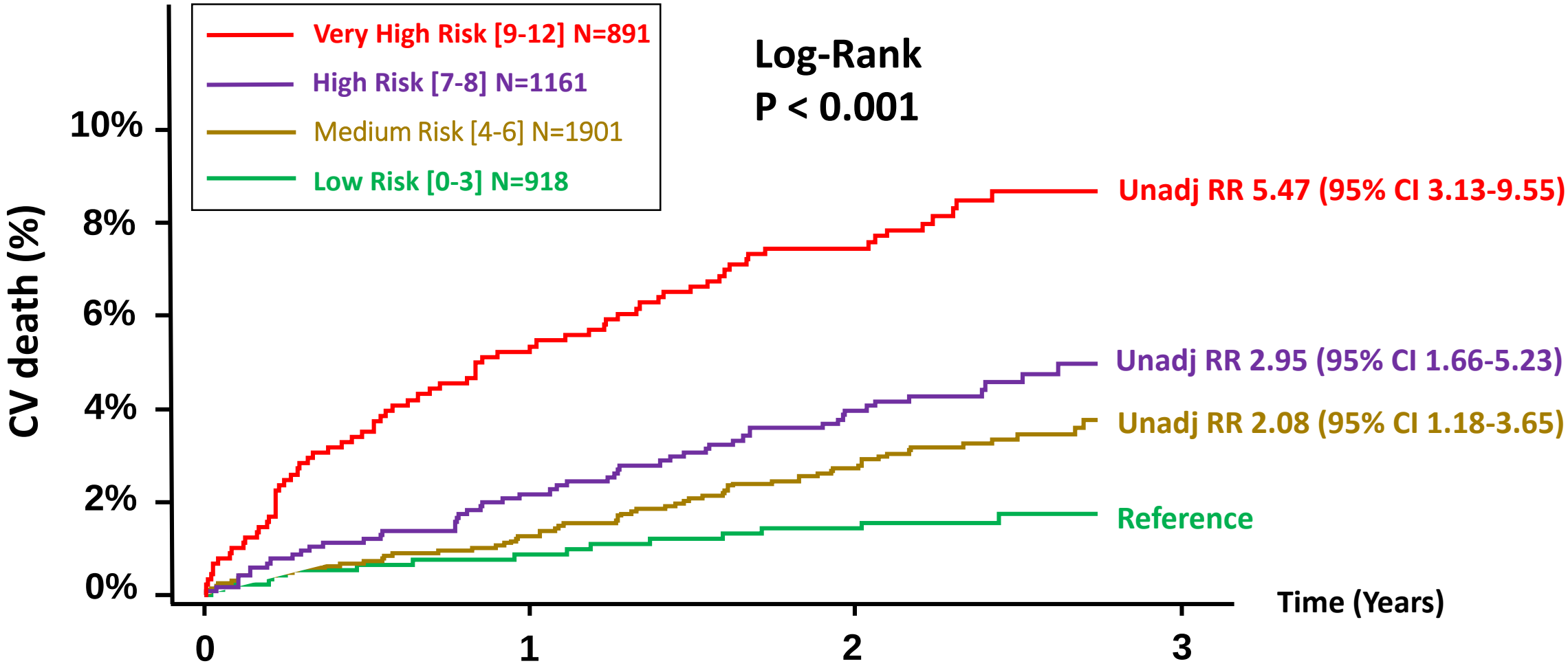
Score 9-12 Points
891 Subjects

Score 7-8 Points
1161 Subjects

Baseline characteristics

Variable	Score 0-3 Low Risk (N=918)	Score 4-6 Moderate Risk (N=1901)	Score 7-8 High Risk (N=1161)	Score 9-12 Very High Risk (N=891)	P for trend
Median age (years)	63	64	64	66	<0.001
Male, n(%)	79	75	74	68	<0.001
Smoking, n(%)	14	17	21	22	<0.001
Diabetes, n(%)	31	35	35	33	0.52
eGFR<60 ml/min/1.73m^2, n(%)	9	10	14	17	<0.001
White, n(%)	87	86	90	91	0.002
STEMI, n(%)	39	44	47	53	<0.001
Median LDL-C (mg/dL)	66	75	80	83	<0.001
Median BNP (pg/mL)	69	88	114	197	<0.001
Median Hs-CRP (mg/L)	2	3	6	14	<0.001
Median Hs-TnI (ng/L)	11	22	66	254	<0.001
Median Lp-PLA$_2$ (nmol/min/mL)	160	170	178	183	<0.001

CV Death by Cer-PL Risk Score



Adjusted Risk of MACE by Cer-PL Risk Score (Model 1)

Risk Ratios (95% Confidence Interval) after adjustment for clinical factors*				
Primary Endpoint	**Moderate Risk Score 4-6**	**High Risk Score 7-8**	**Very-High Risk Score 9-12**	**P-value Highest vs. Lowest Score**
CV death	1.75 (0.98-3.10)	**2.38 (1.32-4.29)**	**3.81 (2.13-6.82)**	**<0.001**
Secondary Endpoints				
CV death or HF	**1.67 (1.10-2.54)**	**2.12 (1.37-3.27)**	**3.76 (2.45-5.78)**	**<0.001**
HF hospitalization	1.62 (0.91-2.87)	**2.31 (1.28-4.17)**	**4.08 (2.28-7.30)**	**<0.001**
CV death, MI or stroke	**1.31 (1.01-1.69)**	**1.50 (1.14-1.97)**	**1.86 (1.40-2.46)**	**<0.001**
MI	1.33 (0.98-1.81)	1.37 (0.98-1.93)	**1.63 (1.15-2.31)**	**0.006**
Stroke	1.02 (0.58-1.80)	1.20 (0.65-2.19)	1.64 (0.91-2.96)	0.099

***Adjusted for age, sex, race, smoking, prior MI, SBP, BMI, eGFR, LDL, STEMI (vs NSTEACS).**
Referent = low risk group [score 0-3]

Adjusted Risk of MACE by Cer-PL Risk Score (Model 2)

Risk Ratios (95% Confidence Interval) after adjustment for clinical factors and biomarkers*				
Primary Endpoint	**Moderate Risk Score 4-6**	**High Risk Score 7-8**	**Very-High Risk Score 9-12**	**P-value Highest vs. Lowest Score**
CV death	**1.31 (0.72-2.38)**	**1.70 (0.91-3.16)**	**2.25 (1.19-4.27)**	**0.013**
Secondary Endpoints				
CV death or HF	**1.20 (0.77-1.85)**	**1.44 (0.91-2.30)**	**2.06 (1.27-3.35)**	**0.003**
HF hospitalization	1.07 (0.58-1.96)	1.42 (0.74-2.73)	1.86 (0.94-3.67)	0.075
CV death, MI or stroke	1.12 (0.86-1.47)	1.21 (0.90-1.64)	1.33 (0.96-1.85)	0.085
MI	1.14 (0.82-1.58)	1.09 (0.75-1.58)	1.11 (0.74-1.67)	0.63
Stroke	0.87 (0.48-1.57)	0.96 (0.49-1.88)	1.16 (0.56-2.37)	0.69

*Adjusted for age, sex, race, smoking, prior MI, SBP, BMI, eGFR, LDL, STEMI (vs NSTEACS), BNP, hsCRP, hsTnI and Lp-PLA_2 activity.
Referent = low risk group [score 0-3]

Limitations

- Serial levels were not obtained, therefore it remains unknown whether therapy or acute ACS may influence levels.
- Ceramides and phospholipids are not yet readily measured outside of specialized labs.
- Causality cannot be demonstrated.

Summary

- A plasma ceramides and phospholipid-based risk score is associated with the risk of CV death independent of established risk factors and biomarkers in patients early after ACS.
- The relationship appeared stronger for CV death than for atherosclerotic outcomes; therefore the biological pathways remain unclear.
- Future directions should include assessment of whether selected ceramides and phospholipids play a causal role in atherogenesis.

Thank you!

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