

SUPPLEMENTARY MATERIAL

CERT2 risk score predicts major cardiovascular outcomes in patients with heart failure

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Table S1. Associations of continuous CERT2 score with all-cause death and cardiovascular endpoints in Cox models for GISSI-HF participants with HF (n=626).

		Model 1		Model 2		Model 3		Model 4	
		HR (CI 95 %)	p-value	HR (CI 95 %)	p-value	HR (CI 95 %)	p-value	HR (CI 95 %)	p-value
CV death	All	1.21 (1.15-1.26)	<0.0001	1.17 (1.10-1.22)	<0.0001	1.16 (1.10-1.22)	<0.0001	1.07 (1.01-1.12)	0.013
	Ischemic	1.17 (1.10-1.24)	<0.0001	1.13 (1.06-1.20)	0.0003	1.12 (1.05-1.20)	0.0009	1.04 (0.97-1.12)	0.276
All-cause death	All	1.20 (1.16-1.25)	<0.0001	1.16 (1.11-1.21)	<0.0001	1.16 (1.11-1.21)	<0.0001	1.08 (1.04-1.13)	0.0004
	Ischemic	1.17 (1.11-1.24)	<0.0001	1.14 (1.08-1.20)	<0.0001	1.13 (1.07-1.20)	<0.0001	1.07 (1.01-1.14)	0.026
MACE	All	1.17 (1.12-1.22)	<0.0001	1.13 (1.08-1.18)	<0.0001	1.12 (1.07-1.17)	<0.0001	1.05 (1.00-1.09)	0.063
	Ischemic	1.14 (1.07-1.20)	<0.0001	1.11 (1.04-1.17)	0.0007	1.09 (1.03-1.16)	0.003	1.02 (0.96-1.09)	0.521

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¹ CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular events. ¹ Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: adjusted for age, sex, body mass index, arterial hypertension, diabetes, LVEF, eGFR and treatment group (n-3PUFA vs placebo). Model 4: model 3 + adjustment for LN-transformed NTproBNP.

Table S2A. Associations of lipid variables with CV-death, all-cause death and 3-point MACE in Cox models in COMMANDER-HF participants.

	n _{event} /n (%)	Model 1		Model 2		Model 3	
		HR (CI 95 %)	p-value	HR (CI 95 %)	p-value	HR (CI 95 %)	p-value
CV death							
Cer(d18:1/16:0)	760/4234 (17.9%)	1.18 (1.11 - 1.26)	<0.0001	1.19 (1.11 - 1.27)	<0.0001	1.17 (1.09 - 1.25)	<0.0001
Cer(d18:1/18:0)	760/4234 (17.9%)	1.06 (0.99 - 1.14)	0.094	1.09 (1.01 - 1.17)	0.023	1.11 (1.03 - 1.20)	0.004
Cer(d18:1/24:0)	760/4234 (17.9%)	0.79 (0.73 - 0.84)	<0.0001	0.81 (0.75 - 0.87)	<0.0001	0.87 (0.80 - 0.93)	0.0001
Cer(d18:1/24:1)	760/4234 (17.9%)	1.12 (1.04 - 1.20)	0.002	1.11 (1.03 - 1.19)	0.007	1.07 (0.99 - 1.15)	0.082
PC(14:0/22:6)	760/4234 (17.9%)	0.77 (0.72 - 0.82)	<0.0001	0.76 (0.72 - 0.81)	<0.0001	0.79 (0.74 - 0.84)	<0.0001
PC(16:0/16:0)	760/4234 (17.9%)	1.07 (1.01 - 1.13)	0.021	1.05 (0.99 - 1.11)	0.085	1.01 (0.95 - 1.08)	0.71
PC(16:0/22:5)	760/4234 (17.9%)	0.84 (0.78 - 0.90)	<0.0001	0.83 (0.77 - 0.90)	<0.0001	0.84 (0.78 - 0.90)	<0.0001
Cer(d18:1/24:1)/ Cer(d18:1/24:0)	760/4234 (17.9%)	1.41 (1.31 - 1.51)	<0.0001	1.37 (1.27 - 1.47)	<0.0001	1.24 (1.15 - 1.34)	<0.0001
Cer(d18:1/16:0)/ PC(16:0/22:5)	760/4234 (17.9%)	1.28 (1.21 - 1.35)	<0.0001	1.29 (1.22 - 1.36)	<0.0001	1.28 (1.20 - 1.35)	<0.0001

	n _{event} /n (%)	Model 1		Model 2		Model 3	
		HR (CI 95 %)	p-value	HR (CI 95 %)	p-value	HR (CI 95 %)	p-value
Cer(d18:1/18:0)/ PC(14:0/22:6)	760/4234 (17.9%)	1.30 (1.22 - 1.39)	<0.0001	1.31 (1.23 - 1.40)	<0.0001	1.29 (1.21 - 1.38)	<0.0001
All-cause death							
Cer(d18:1/16:0)	912/4234 (21.5%)	1.20 (1.13 - 1.27)	<0.0001	1.20 (1.13 - 1.27)	<0.0001	1.18 (1.11 - 1.25)	<0.0001
Cer(d18:1/18:0)	912/4234 (21.5%)	1.07 (1.00 - 1.14)	0.035	1.10 (1.03 - 1.17)	0.005	1.13 (1.06 - 1.20)	0.0004
Cer(d18:1/24:0)	912/4234 (21.5%)	0.78 (0.73 - 0.83)	<0.0001	0.80 (0.75 - 0.86)	<0.0001	0.86 (0.80 - 0.92)	<0.0001
Cer(d18:1/24:1)	912/4234 (21.5%)	1.15 (1.08 - 1.23)	<0.0001	1.13 (1.06 - 1.21)	0.0002	1.09 (1.02 - 1.17)	0.010
PC(14:0/22:6)	912/4234 (21.5%)	0.78 (0.74 - 0.82)	<0.0001	0.78 (0.73 - 0.82)	<0.0001	0.80 (0.75 - 0.84)	<0.0001
PC(16:0/16:0)	912/4234 (21.5%)	1.08 (1.03 - 1.14)	0.0009	1.07 (1.02 - 1.12)	0.010	1.03 (0.97 - 1.08)	0.32
PC(16:0/22:5)	912/4234 (21.5%)	0.84 (0.78 - 0.90)	<0.0001	0.83 (0.78 - 0.89)	<0.0001	0.84 (0.78 - 0.90)	<0.0001
Cer(d18:1/24:1)/ Cer(d18:1/24:0)	912/4234 (21.5%)	1.46 (1.37 - 1.55)	<0.0001	1.41 (1.32 - 1.50)	<0.0001	1.28 (1.19 - 1.37)	<0.0001
Cer(d18:1/16:0)/ PC(16:0/22:5)	912/4234 (21.5%)	1.29 (1.23 - 1.36)	<0.0001	1.30 (1.24 - 1.36)	<0.0001	1.28 (1.22 - 1.36)	<0.0001
Cer(d18:1/18:0)/	912/4234	1.28 (1.21 -	<0.0001	1.29 (1.22 - 1.37)	<0.0001	1.28 (1.21 - 1.36)	<0.0001

	n _{event} /n (%)	Model 1		Model 2		Model 3	
		HR (CI 95 %)	p-value	HR (CI 95 %)	p-value	HR (CI 95 %)	p-value
PC(14:0/22:6)	(21.5%)	1.36)					
3-point MACE							
Cer(d18:1/16:0)	1050/4234 (24.8%)	1.19 (1.12 - 1.25)	<0.0001	1.19 (1.12 - 1.25)	<0.0001	1.16 (1.10 - 1.23)	<0.0001
Cer(d18:1/18:0)	1050/4234 (24.8%)	1.07 (1.01 - 1.14)	0.020	1.10 (1.03 - 1.16)	0.003	1.12 (1.05 - 1.19)	0.0003
Cer(d18:1/24:0)	1050/4234 (24.8%)	0.81 (0.76 - 0.86)	<0.0001	0.83 (0.78 - 0.88)	<0.0001	0.88 (0.83 - 0.94)	<0.0001
Cer(d18:1/24:1)	1050/4234 (24.8%)	1.16 (1.09 - 1.23)	<0.0001	1.14 (1.07 - 1.21)	<0.0001	1.10 (1.03 - 1.17)	0.003
PC(14:0/22:6)	1050/4234 (24.8%)	0.81 (0.77 - 0.86)	<0.0001	0.81 (0.77 - 0.86)	<0.0001	0.83 (0.79 - 0.88)	<0.0001
PC(16:0/16:0)	1050/4234 (24.8%)	1.08 (1.03 - 1.13)	0.001	1.06 (1.01 - 1.11)	0.016	1.02 (0.97 - 1.08)	0.38
PC(16:0/22:5)	1050/4234 (24.8%)	0.87 (0.82 - 0.93)	<0.0001	0.86 (0.81 - 0.92)	<0.0001	0.87 (0.82 - 0.93)	<0.0001
Cer(d18:1/24:1)/ Cer(d18:1/24:0)	1050/4234 (24.8%)	1.42 (1.33 - 1.50)	<0.0001	1.37 (1.29 - 1.45)	<0.0001	1.25 (1.18 - 1.33)	<0.0001
Cer(d18:1/16:0)/ PC(16:0/22:5)	1050/4234 (24.8%)	1.26 (1.20 - 1.32)	<0.0001	1.27 (1.20 - 1.33)	<0.0001	1.25 (1.18 - 1.32)	<0.0001
Cer(d18:1/18:0)/ PC(14:0/22:6)	1050/4234 (24.8%)	1.24 (1.17 - 1.31)	<0.0001	1.25 (1.18 - 1.32)	<0.0001	1.23 (1.17 - 1.30)	<0.0001

n_{event}/n (%)	Model 1		Model 2		Model 3	
	HR (CI 95 %)	p-value	HR (CI 95 %)	p-value	HR (CI 95 %)	p-value

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² Hazard ratios (HR) with 95% confidence intervals (CI) are given per 1 SD increase in log-transformed lipid variables. Model 1: unadjusted. Model 2: adjusted for age, sex. Model 3: adjusted for age, sex, body mass index, arterial hypertension, diabetes, LVEF, eGFR and treatment group (rivaroxaban vs placebo).

Table S2B. Associations of lipid variables with CV-death, all-cause death and 3-point MACE in Cox models in GISSI-HF participants.

		Model 1		Model 2		Model 3	
	n _{event} /n (%)	HR (CI 95 %)	p-value	HR (CI 95 %)	p-value	HR (CI 95 %)	p-value
CV death							
Cer(d18:1/16:0)	242/1227	1.07 (0.95, 1.22)	0.278	0.91 (0.75, 1.10)	0.320	1.06 (0.86, 1.31)	0.601
Cer(d18:1/18:0)	242/1227	0.95 (0.83, 1.07)	0.385	0.92 (0.78, 1.10)	0.383	0.98 (0.81, 1.19)	0.874
Cer(d18:1/24:0)	242/1227	0.64 (0.57, 0.72)	<0.0001	0.63 (0.54, 0.73)	<0.0001	0.68 (0.55, 0.84)	0.0004
Cer(d18:1/24:1)	242/1227	0.97 (0.85, 1.10)	0.624	0.89 (0.74, 1.05)	0.167	1.00 (0.83, 1.22)	0.962
PC(14:0/22:6)	242/1227	0.63 (0.56, 0.71)	<0.0001	0.62 (0.53, 0.73)	<0.0001	0.67 (0.56, 0.80)	<0.0001
PC(16:0/16:0)	242/1227	1.12 (0.99, 1.28)	0.070	0.89 (0.74, 1.08)	0.243	1.00 (0.82, 1.23)	0.975
PC(16:0/22:5)	242/1227	0.67 (0.59, 0.76)	<0.0001	0.60 (0.51, 0.72)	<0.0001	0.67 (0.55, 0.82)	<0.0001
Cer(d18:1/24:1)/ Cer(d18:1/24:0)	242/1227	1.65 (1.45, 1.88)	<0.0001	1.60 (1.34, 1.92)	<0.0001	1.40 (1.15, 1.71)	<0.0001
Cer(d18:1/16:0)/ PC(16:0/22:5)	242/1227	1.52 (1.35, 1.72)	<0.0001	1.55 (1.29, 1.87)	<0.0001	1.45 (1.20, 1.75)	0.0002

	n _{event} /n (%)	Model 1		Model 2		Model 3	
		HR (CI 95 %)	p-value	HR (CI 95 %)	p-value	HR (CI 95 %)	p-value
Cer(d18:1/18:0)/ PC(14:0/22:6)	242/1227	1.44 (1.28, 1.62)	<0.0001	1.46 (1.25, 1.71)	<0.0001	1.35 (1.14, 1.59)	0.0004
All-cause death							
Cer(d18:1/16:0)	328/1227	1.11 (1.00, 1.24)	0.055	1.00 (0.85, 1.17)	0.973	1.16 (0.97, 1.40)	0.099
Cer(d18:1/18:0)	328/1227	1.03 (0.92, 1.15)	0.615	1.07 (0.92, 1.25)	0.373	1.15 (0.98, 1.36)	0.087
Cer(d18:1/24:0)	328/1227	0.66 (0.60, 0.73)	<0.0001	0.66 (0.58, 0.76)	<0.0001	0.75 (0.62, 0.90)	0.002
Cer(d18:1/24:1)	328/1227	1.01 (0.90, 1.12)	0.897	0.96 (0.83, 1.11)	0.590	1.10 (0.93, 1.30)	0.283
PC(14:0/22:6)	328/1227	0.65 (0.59, 0.72)	<0.0001	0.64 (0.56, 0.74)	<0.0001	0.71 (0.61, 0.83)	<0.0001
PC(16:0/16:0)	328/1227	1.17 (1.05, 1.30)	0.005	0.97 (0.82, 1.14)	0.677	1.08 (0.91, 1.29)	0.395
PC(16:0/22:5)	328/1227	0.70 (0.63, 0.78)	<0.0001	0.65 (0.56, 0.75)	<0.0001	0.73 (0.62, 0.86)	0.0002
Cer(d18:1/24:1)/ Cer(d18:1/24:0)	328/1227	1.50 (1.34, 1.67)	<0.0001	1.57 (1.36, 1.82)	<0.0001	1.37 (1.17, 1.61)	0.0001
Cer(d18:1/16:0)/ PC(16:0/22:5)	328/1227	1.50 (1.35, 1.66)	<0.0001	1.55 (1.32, 1.82)	<0.0001	1.43 (1.22, 1.69)	<0.0001
Cer(d18:1/18:0)/	328/1227	1.46 (1.32, 1.62)	<0.0001	1.52 (1.33, 1.74)	<0.0001	1.39 (1.21, 1.61)	<0.0001

		Model 1		Model 2		Model 3	
	n _{event} /n (%)	HR (CI 95 %)	p-value	HR (CI 95 %)	p-value	HR (CI 95 %)	p-value
PC(14:0/22:6)		1.61)					
3-point MACE							
Cer(d18:1/16:0)	295/1227	1.08 (0.96, 1.21)	0.180	0.94 (0.79, 1.12)	0.481	1.05 (0.86, 1.27)	0.638
Cer(d18:1/18:0)	295/1227	0.98 (0.88, 1.10)	0.786	0.97 (0.83, 1.14)	0.722	1.01 (0.85, 1.21)	0.871
Cer(d18:1/24:0)	295/1227	0.71 (0.63, 0.79)	<0.0001	0.70 (0.60, 0.81)	0.013	0.76 (0.62, 0.92)	0.005
Cer(d18:1/24:1)	295/1227	1.03 (0.92, 1.15)	0.622	0.94 (0.80, 1.11)	0.475	1.04 (0.87, 1.24)	0.687
PC(14:0/22:6)	295/1227	0.68 (0.61, 0.76)	<0.0001	0.68 (0.58, 0.78)	<0.0001	0.71 (0.61, 0.84)	<0.0001
PC(16:0/16:0)	295/1227	1.09 (0.97, 1.22)	0.148	0.87 (0.74, 1.04)	0.120	0.93 (0.78, 1.12)	0.464
PC(16:0/22:5)	295/1227	0.73 (0.65, 0.81)	<0.0001	0.69 (0.58, 0.80)	<0.0001	0.75 (0.63, 0.90)	0.002
Cer(d18:1/24:1)/ Cer(d18:1/24:0)	295/1227	1.54 (1.37, 1.74)	<0.0001	1.47 (1.25, 1.73)	<0.0001	1.32 (1.10, 1.58)	0.003
Cer(d18:1/16:0)/ PC(16:0/22:5)	295/1227	1.43 (1.28, 1.60)	<0.0001	1.47 (1.25, 1.73)	<0.0001	1.31 (1.10, 1.57)	0.002
Cer(d18:1/18:0)/ PC(14:0/22:6)	295/1227	1.38 (1.24, 1.54)	<0.0001	1.38 (1.20, 1.60)	<0.0001	1.31 (1.13, 1.53)	<0.0001

³ Hazard ratios (HR) with 95% confidence intervals (CI) is given per 1-SD increase in log-transformed lipid variables. Model 1: unadjusted. Model 2: adjusted for age and sex. Model 3: adjusted for age, sex, body mass index, arterial hypertension, diabetes, LVEF, eGFR and treatment group (n-3PUFA vs placebo).