ONLINE-ONLY SUPPLEMENTARY MATERIAL

Supplementary Table 1. Clinical and biochemical characteristics, basal and post-stress percentages of myocardial wall perfusion as well as basal and post-stress plasma ceramide levels in patients stratified by absence or presence of stress-induced myocardial perfusion defects on MPS.

	Without inducible ischemia (n=89)	**With inducible ischemia (n=78)**	***P* value**
Age (years)	68.8 ± 10	71.8 ± 9	0.037
Sex (men) (%)	60.7	96.2	<0.001
Body mass index (kg/m^2)	26.8 ± 4.1	27.7 ± 4.0	0.233
Systolic blood pressure (mmHg)	138 ± 18	132 ± 15	0.115
Diastolic blood pressure (mmHg)	78 ± 9	76 ± 8	0.207
$eGFR_{MDRD}$ (mL/min/1.73 m^2)	78 ± 20	79 ± 24	0.723
Fasting glucose (mmol/L), n=82	6.1 ± 1.7	6.3 ± 1.8	0.779
HbA1c (mmol/mol), n= 40	50.2 ± 6.8	46.6 ± 3.6	0.634
LV ejection fraction (%)	62.1± 10	49.5 ± 11	<0.001
Chronic kidney disease (%)	6.7	14.1	0.125
Current smokers (%)	6.8	16.7	0.140
Dyslipidemia (%)	92.1	93.6	0.722
Hypertension (%)	73.6	87.2	0.029
Coronary artery disease (%)	39.1	74.4	<0.001
Diabetes (%)	18.4	30.8	0.064
Valvular heart disease (%)	9.2	6.4	0.511
Electrocardiographic left bundle branch block (%)	6.7	8.6	0.591
Atrial fibrillation (%)	5.8	14.1	0.070
Ischemic stroke (%)	1.1	6.4	0.085
Antiplatelet drug users (%)	57.5	71.8	0.049
Anticoagulant drug users (%)	5.8	25.6	<0.001
Anti-arrhythmic drug users (%)	6.9	5.1	0.635
Beta-blocker users (%)	37.9	58.9	0.009
ACE-I/ARB users (%)	56.3	66.7	0.173
Calcium-channel blocker users (%)	11.5	10.3	0.799
Diuretic users (%)	22.9	34.6	0.099
Nitrate users (%)	9.2	24.4	0.009
Statin users (%)	50.6	74.4	0.002
Insulin users (%), n=40	2.3	5.1	0.332
Oral hypoglycemic drug users (%), n=40	14.9	23.1	0.182
Myocardial perfusion during stress MPS			
Antero-apical wall perfusion at rest (%)	74.1 ± 5.4	68.2 ± 8.7	<0.001*
Lateral-posterior wall perfusion at rest (%)	78.0 ± 14.3	68.1 ± 10.4	<0.001*
Inferior wall perfusion at rest (%)	67.7 ± 9.2	57.2 ± 9.4	<0.001*
Antero-apical wall perfusion after stress (%)	76.5 ± 5.1	69.0 ± 8.6	<0.001*
Lateral-posterior wall perfusion after stress (%)	76.4 ± 4.6	66.6 ± 10.6	<0.001*
Inferior wall perfusion after stress (%)	68.0 ± 8.2	55.6 ± 9.6	<0.001*
Plasma ceramides			
Basal Cer(d18:1/16:0) (umol/L)	0.326 ± 0.08	0.321 ± 0.08	0.361*
Basal Cer(d18:1/18:0) (umol/L)	0.138 ± 0.06	0.148 ± 0.07	0.070*
Basal Cer(d18:1/20:0) (umol/L)	0.101 ± 0.03	0.111 ± 0.04	0.038
Basal Cer(d18:1/22:0) (umol/L)	0.707 ± 0.26	0.742 ± 0.26	0.049
Basal Cer(d18:1/24:0) (umol/L)	2.849 ± 0.77	2.789 ± 0.80	0.594*
Basal Cer(d18:1/24:1) (umol/L)	1.082 ± 0.38	1.245 ± 0.47	0.026
Post-stress Cer(d18:1/16:0) (umol/L)	0.332 ± 0.08	0.324 ± 0.08	0.455*
Post-stress Cer(d18:1/18:0) (umol/L)	0.142 ± 0.07	0.154 ± 0.08	0.099*
Post-stress Cer(d18:1/20:0) (umol/L)	0.105 ± 0.04	0.111 ± 0.05	0.201*
Post-stress Cer(d18:1/22:0) (umol/L)	0.718 ± 0.27	0.743 ± 0.26	0.064*
Post-stress Cer(d18:1/24:0) (umol/L)	2.891 ± 0.78	2.822 ± 0.83	0.613*
Post-stress Cer(d18:1/24:1) (umol/L)	1.118 ± 0.40	1.285 ± 0.47	0.025*

Sample size, *n*=167 except where indicated. Data are expressed as means±SD or percentages. Differences between the two groups were tested by the chi-squared test for categorical variables, the unpaired Student's t-test for normally distributed variables or the Mann-Whitney test for non-normally distributed variables. No adjustment was made for multiplicity.

**P*-values adjusted for age and sex.

Abbreviations: ACE-I, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; e-GFR_{MDRD}, glomerular filtration rate estimated by using the Modification of Diet in Renal Diseases (MDRD) study equation; LV, left ventricular.

Note: Presence of chronic kidney disease was defined as $eGFR_{MDRD}$ <60 ml/min/1.73 m^2; dyslipidemia was defined as a total cholesterol level ≥5.2 mmol/L or lipid-lowering treatment; hypertension was defined as blood pressure ≥140/90 mmHg or use of any anti-hypertensive agents. HbA1c levels and information regarding glucose-lowering agents were available only for patients with diabetes mellitus (*n*=40).

Supplementary Table 2. Basal and post-stress plasma ceramide levels in patients stratified by sex.

	Men (n=129)	Women (n=38)	*P* value*
Basal Cer(d18:1/16:0) (umol/L)	0.311 ± 0.08	0.365 ± 0.09	0.002
Basal Cer(d18:1/18:0) (umol/L)	0.137 ± 0.07	0.162 ± 0.07	0.029
Basal Cer(d18:1/20:0) (umol/L)	0.104 ± 0.04	0.112 ± 0.04	0.182
Basal Cer(d18:1/22:0) (umol/L)	0.701 ± 0.24	0.802 ± 0.32	0.037
Basal Cer(d18:1/24:0) (umol/L)	2.762 ± 0.76	3.025 ± 0.83	0.079
Basal Cer(d18:1/24:1) (umol/L)	1.159 ± 0.43	1.156 ± 0.43	0.862
Post-stress Cer(d18:1/16:0) (umol/L)	0.315 ± 0.08	0.372 ± 0.09	0.001
Post-stress Cer(d18:1/18:0) (umol/L)	0.142 ± 0.07	0.168 ± 0.08	0.033
Post-stress Cer(d18:1/20:0) (umol/L)	0.105 ± 0.04	0.114 ± 0.04	0.216
Post-stress Cer(d18:1/22:0) (umol/L)	0.705 ± 0.24	0.813 ± 0.34	0.029
Post-stress Cer(d18:1/24:0) (umol/L)	2.796 ± 0.77	3.071 ± 0.86	0.085
Post-stress Cer(d18:1/24:1) (umol/L)	1.198 ± 0.43	1.190 ± 0.47	0.925

Sample size, *n*=167. Data are expressed as means±SD. **P*-values adjusted for age. No adjustment was made for multiplicity.

Supplementary Table 3. Basal and post-stress plasma ceramide levels in patients stratified by electrocardiographic left bundle branch block.

	Without left bundle branch block (n=154)	**With left bundle branch block (n=13)**	***P* value***
Basal Cer(d18:1/16:0) (umol/L)	0.322 ± 0.08	0.343 ± 0.08	0.685
Basal Cer(d18:1/18:0) (umol/L)	0.139 ± 0.07	0.176 ± 0.07	0.120
Basal Cer(d18:1/20:0) (umol/L)	0.104 ± 0.04	0.123 ± 0.04	0.177
Basal Cer(d18:1/22:0) (umol/L)	0.713 ± 0.26	0.852 ± 0.27	0.103
Basal Cer(d18:1/24:0) (umol/L)	2.806 ± 0.77	3.006 ± 0.87	0.446
Basal Cer(d18:1/24:1) (umol/L)	1.148 ± 0.43	1.277 ± 0.37	0.351
Post-stress Cer(d18:1/16:0) (umol/L)	0.327 ± 0.08	0.344 ± 0.07	0.828
Post-stress Cer(d18:1/18:0) (umol/L)	0.145 ± 0.07	0.178 ± 0.07	0.200
Post-stress Cer(d18:1/20:0) (umol/L)	0.106 ± 0.04	0.121 ± 0.03	0.300
Post-stress Cer(d18:1/22:0) (umol/L)	0.720 ± 0.27	0.844 ± 0.24	0.161
Post-stress Cer(d18:1/24:0) (umol/L)	2.851 ± 0.80	2.942 ± 0.81	0.796
Post-stress Cer(d18:1/24:1) (umol/L)	1.188 ± 0.44	1.292 ± 0.36	0.480

Sample size, *n*=167. Data are expressed as means±SD. **P*-values adjusted for age and sex. No adjustment was made for multiplicity.

Supplementary Table 4. Basal and post-stress plasma ceramide levels in patients stratified by presence of pre-existing diabetes.

	Without Diabetes (n=127)	**With known Diabetes (n=40)**	***P* value***
Basal Cer(d18:1/16:0) (umol/L)	0.328 ± 0.08	0.312 ± 0.08	0.368
Basal Cer(d18:1/18:0) (umol/L)	0.144 ± 0.07	0.138 ± 0.05	0.526
Basal Cer(d18:1/20:0) (umol/L)	0.108 ± 0.04	0.099 ± 0.03	0.134
Basal Cer(d18:1/22:0) (umol/L)	0.716 ± 0.27	0.749 ± 0.23	0.283
Basal Cer(d18:1/24:0) (umol/L)	2.799 ± 0.78	2.899 ± 0.79	0.195
Basal Cer(d18:1/24:1) (umol/L)	1.179 ± 0.44	1.103 ± 0.40	0.111
Post-stress Cer(d18:1/16:0) (umol/L)	0.335 ± 0.09	0.305 ± 0.08	0.074
Post-stress Cer(d18:1/18:0) (umol/L)	0.149 ± 0.08	0.141 ± 0.06	0.401
Post-stress Cer(d18:1/20:0) (umol/L)	0.111 ± 0.05	0.097 ± 0.03	0.046
Post-stress Cer(d18:1/22:0) (umol/L)	0.726 ± 0.28	0.739 ± 0.22	0.493
Post-stress Cer(d18:1/24:0) (umol/L)	2.842 ± 0.81	2.911 ± 0.78	0.281
Post-stress Cer(d18:1/24:1) (umol/L)	1.217 ± 0.46	1.138 ± 0.38	0.106

Sample size, *n*=167. Data are expressed as means±SD. **P*-values adjusted for age and sex. No adjustment was made for multiplicity.