

Supplementary Information

Endothelin-1 is associated with mortality that can be attenuated with statin therapy in patients with stable coronary artery disease

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Figure S1

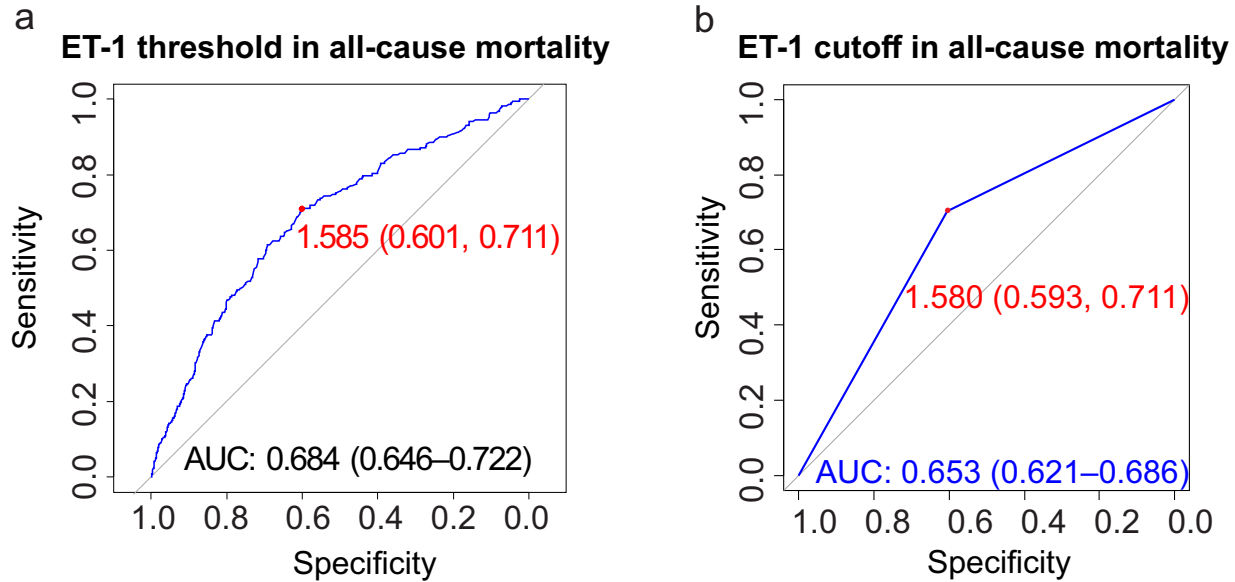
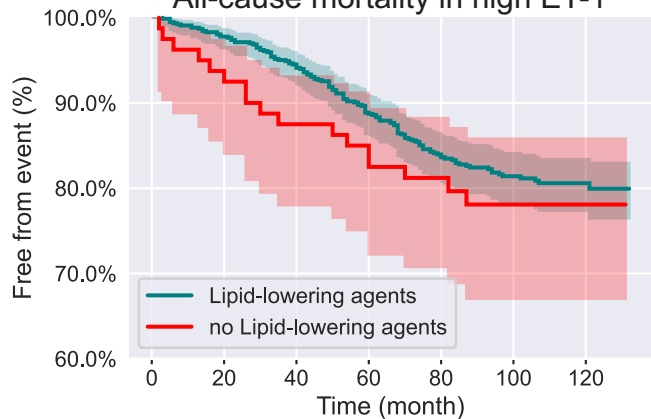


Figure S1. ROC curves for ET-1 to discriminate all-cause mortality. Receiver-operating characteristic (ROC) curve analysis was conducted to obtain the cutoff value of ET-1 for optimal sensitivity and specificity. (a) ET-1 was used as continuous variable to predict all-cause mortality, and the estimated optimal threshold of concentration was 1.585 pg/ml (AUC=0.684 [95% CI, 0.646–0.722], specificity=0.601, sensitivity=0.711). (b) ET-1 was used as cutoff of 1.580 pg/ml (AUC=0.653 [95% CI, 0.621–0.686], specificity=0.593, sensitivity=0.711). (a-b) n=1945 biologically independent samples. ET-1, endothelin-1; AUC, area under the curve

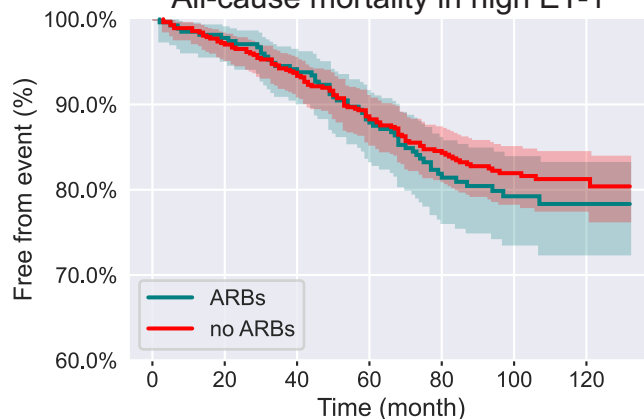
Figure S2

All-cause mortality in high ET-1



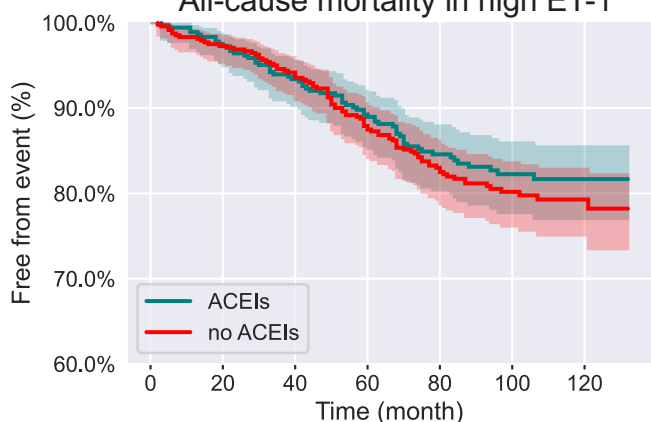
no Lipid-lowering agents							
At risk	80	74	70	66	52	27	12
Events	0	6	10	14	15	17	17
Lipid-lowering agents							
At risk	765	748	720	666	510	330	123
Events	0	17	45	86	122	134	137

All-cause mortality in high ET-1



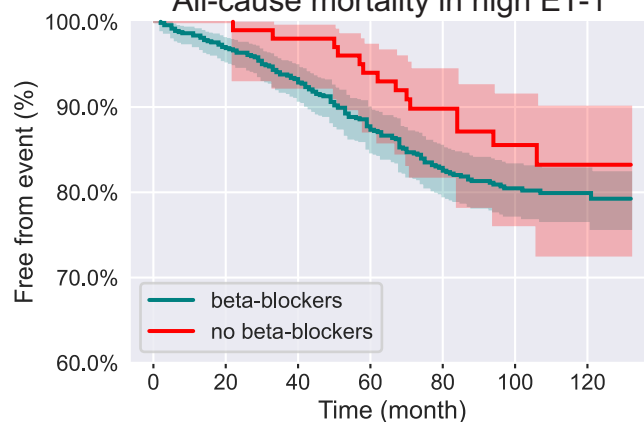
no ARBs							
At risk	572	555	534	497	389	251	95
Events	0	17	38	67	88	98	100
ARBs							
At risk	273	267	256	235	173	106	40
Events	0	6	17	33	49	53	54

All-cause mortality in high ET-1



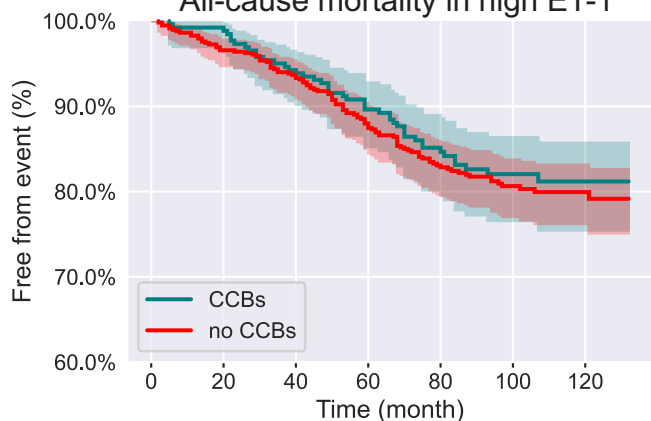
no ACEIs							
At risk	481	468	450	413	319	196	74
Events	0	13	31	60	82	90	92
ACEIs							
At risk	364	354	340	319	243	161	61
Events	0	10	24	40	55	61	62

All-cause mortality in high ET-1



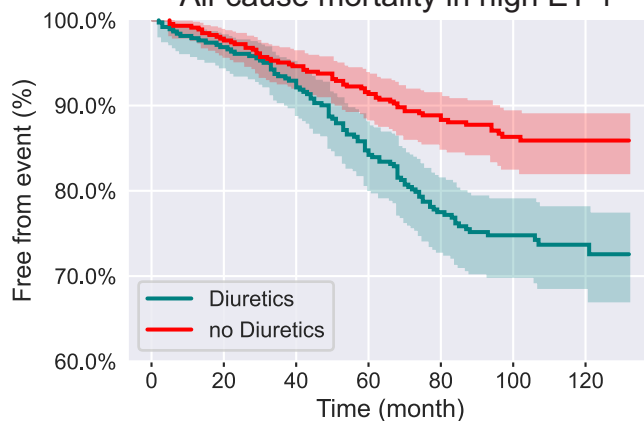
no beta-blockers							
At risk	101	101	99	93	70	43	15
Events	0	0	2	6	10	13	14
beta-blockers							
At risk	744	721	691	639	492	314	120
Events	0	23	53	94	127	138	140

All-cause mortality in high ET-1



no CCBs							
At risk	584	564	545	503	389	242	102
Events	0	20	39	73	98	107	109
CCBs							
At risk	261	258	245	229	173	115	33
Events	0	3	16	27	39	44	45

All-cause mortality in high ET-1



no Diuretics							
At risk	464	453	439	415	321	203	69
Events	0	11	25	40	53	59	60
Diuretics							
At risk	381	369	351	317	241	154	66
Events	0	12	30	60	84	92	94

Figure S2. Kaplan-Meier curves for primary endpoint in high ET-1 group upon various medication. Shown are rate of freedom from all-cause mortality over follow-up time. Chi-square and p value were derived from log-rank test between low and high ET-1 groups. Shadows indicated confident interval of estimates. ARBs, Angiotensin II receptor blocker; ACEIs, Angiotensin-Converting Enzyme Inhibitors ; beta-blockers, beta-adrenergic blockers; CCBs, calcium channel blockers; ET-1, endothelin-1.

Figure S3

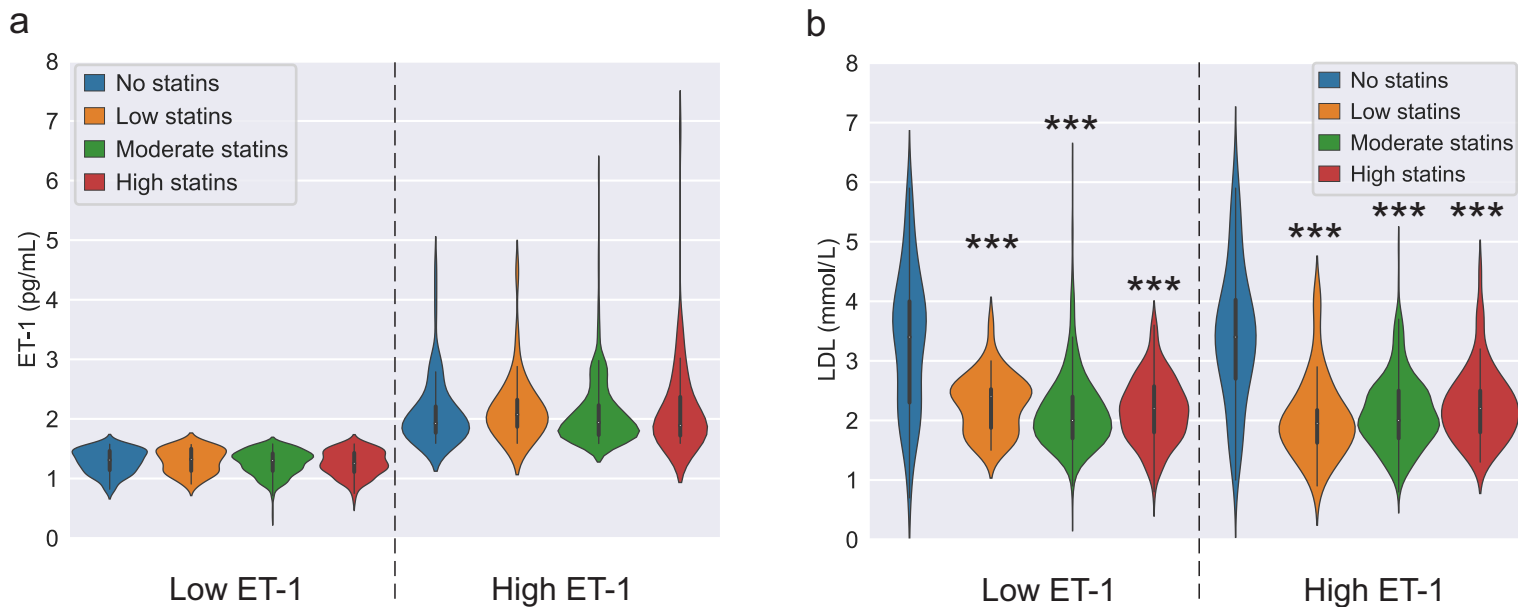


Figure S3. Analysis for circulating ET-1 and LDL concentration in subgroups.

Shown are violin plots of circulating ET-1 (a) and LDL (b) levels according to ET-1 level and statin use. Inside is a miniature of boxplot. In low ET-1 group, No statins: n=87, Low statins: n=36, Moderate statins: n=654, High statins: n=138; In high ET-1 group, No statins: n=80, Low statins: n=38, Moderate statins: n=462, High statins: n=69 biologically independent samples. ***p<0.001 vs No statins group. Wilcoxon rank-sum test was used for statistical testing due to non-normality. ET-1, endothelin-1; LDL, Low-density lipoprotein. The vertical dash lines were used to separate low and high ET-1 groups.

Figure S4

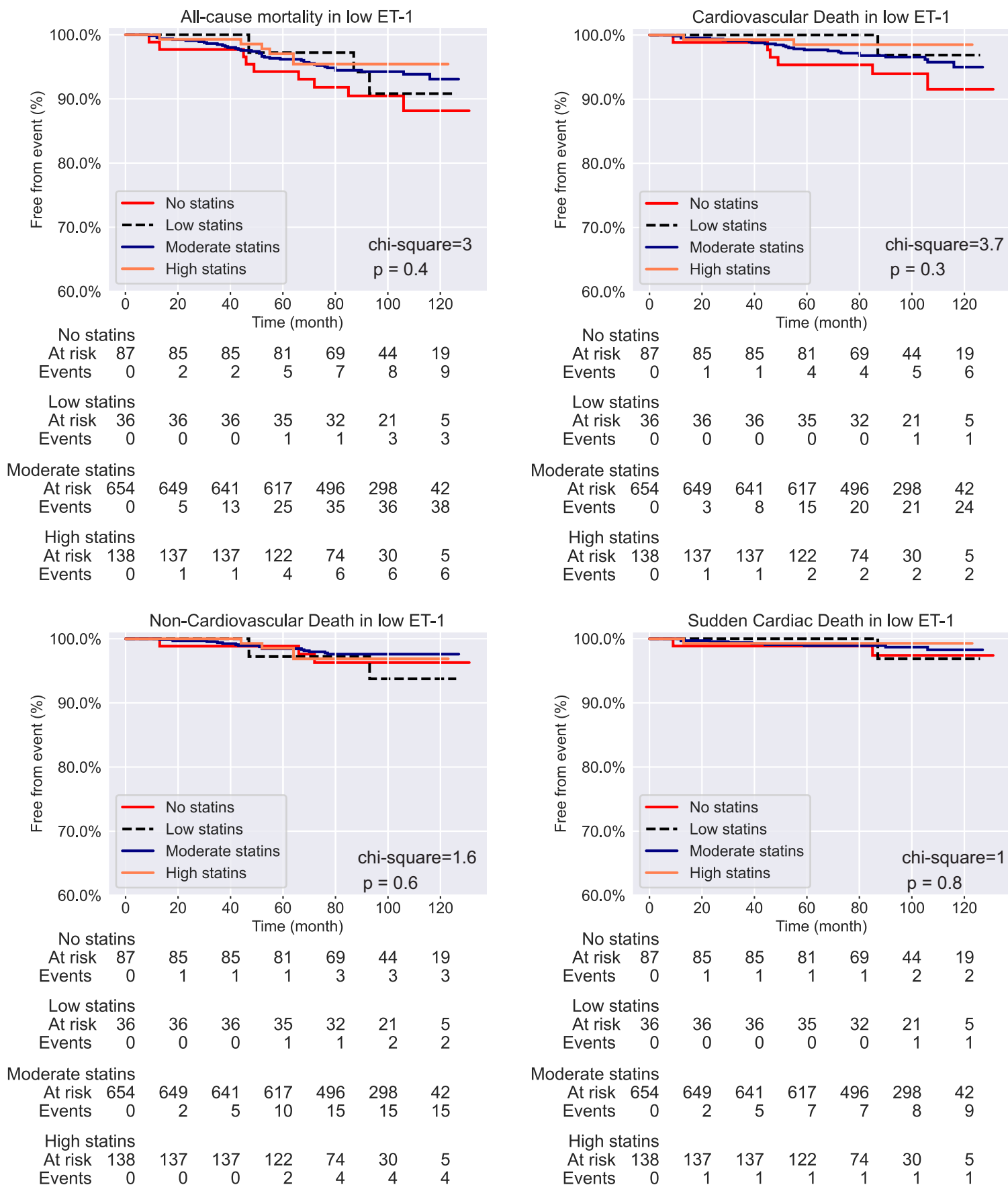


Figure S4. Kaplan-Meier curves for endpoint events in low ET-1 group according to statin use. Shown are rate of freedom from all-cause mortality, cardiovascular death, non-cardiovascular death and sudden cardiac death over follow-up time. Chi-square and p value were derived from log-rank test between statin groups. ET-1, endothelin-1.

Table S1. Baseline characteristics of patients in ET-1 quartiles

	Overall 1945	Q1 494	Q2 479	Q3 486	Q4 486	p
N						
Age (year)	67 [61, 73]	64 [59, 70]	67 [61, 72]	69 [63, 74]	70 [64, 75]	<0.0001
T2D (%)	833 (42.8)	106 (21.5)	175 (36.5)	243 (50.0)	309 (63.6)	<0.0001
Sex (%) (female)	618 (31.8)	125 (25.3)	143 (29.9)	160 (32.9)	190 (39.1)	<0.0001
LVEF (%)	65.50 [59.95, 70.10]	65.40 [60.35, 70.30]	66.00 [60.82, 69.88]	65.10 [59.08, 69.60]	65.20 [58.10, 71.00]	0.3552
BMI (kg/m ²)	28.00 [25.00, 31.00]	27.00 [25.00, 29.00]	28.00 [25.00, 31.00]	28.00 [25.00, 31.00]	29.00 [26.00, 33.00]	<0.0001
sysBP (mm Hg)	145 [129, 162]	138.50 [123.25, 154]	146 [129, 164]	149 [134, 163]	147 [131, 163.75]	<0.0001
diaBP (mm Hg)	77 [70, 84]	76 [69, 83]	77 [71, 84]	78 [70, 85]	77 [70, 85]	0.0090
BNP (pg/mL)	50.00 [25.00, 93.00]	38.00 [20.00, 73.00]	49.00 [24.00, 86.00]	51.00 [26.00, 99.50]	62.50 [31.25, 139.50]	<0.0001
Creatinine clearance (mL/min)	87.92 [70.38, 112.39]	90.84 [74.39, 112.99]	89.12 [73.62, 114.52]	83.63 [66.77, 109.82]	86.41 [66.45, 109.72]	0.0007
Insulin (mIU / L)	11.80 [7.30, 18.70]	9.90 [6.60, 14.30]	11.40 [7.20, 17.85]	12.40 [7.82, 19.42]	14.40 [8.40, 22.50]	<0.0001
GHbA1C (%)	6.10 [5.70, 6.60]	5.90 [5.60, 6.30]	6.00 [5.70, 6.40]	6.20 [5.80, 6.80]	6.50 [5.90, 7.20]	<0.0001
Total cholesterol (mmol/L)	3.80 [3.40, 4.40]	3.80 [3.40, 4.40]	3.80 [3.40, 4.30]	3.90 [3.40, 4.50]	3.80 [3.40, 4.40]	0.2918
HDL (mmol/L)	1.23 [1.03, 1.44]	1.25 [1.05, 1.50]	1.23 [1.05, 1.44]	1.21 [1.03, 1.44]	1.20 [1.01, 1.40]	0.0187
LDL (mmol/L)	2.10 [1.80, 2.60]	2.10 [1.80, 2.60]	2.10 [1.80, 2.60]	2.20 [1.80, 2.60]	2.10 [1.80, 2.60]	0.3977
Triglyceride (mmol/L)	1.21 [0.90, 1.67]	1.08 [0.82, 1.42]	1.18 [0.88, 1.62]	1.28 [0.96, 1.76]	1.34 [1.01, 1.79]	<0.0001
Resting heart rate (beats/min)	59 [53, 66]	58 [52, 63]	58 [53, 64]	60 [54, 67]	62 [55, 72]	<0.0001
NYHA (%)						
NYHA Class I	853 (44.3)	142 (29.0)	191 (40.6)	243 (50.2)	277 (57.5)	
NYHA Class II	69 (3.6)	15 (3.1)	15 (3.2)	12 (2.4)	27 (5.6)	
Medication (%)						
ARBs	558 (28.7)	104 (21.1)	148 (31.0)	135 (27.8)	171 (35.3)	<0.0001
ACEIs	783 (40.3)	179 (36.2)	183 (38.3)	224 (46.1)	197 (40.6)	0.0118
CCBs	474 (24.4)	69 (14.0)	106 (22.2)	139 (28.6)	160 (32.9)	<0.0001
Diuretics	666 (34.3)	90 (18.2)	148 (31.0)	178 (36.6)	250 (51.4)	<0.0001
β-blockers	1704 (87.7)	424 (85.8)	421 (88.1)	438 (90.1)	421 (86.6)	0.1862
Lipid-lowering therapy	1777 (91.4)	458 (92.7)	439 (91.8)	439 (90.3)	441 (90.7)	0.5358
History (%)						
Prior MI	929 (47.8)	247 (50.0)	216 (45.2)	237 (48.8)	229 (47.1)	0.4687
Prior PCI or CABG	1544 (79.6)	394 (80.1)	399 (83.5)	368 (76.2)	383 (78.8)	0.0432
Smoking	167 (8.6)	26 (5.3)	34 (7.1)	44 (9.1)	63 (13.0)	0.0001
Death (%)						
All-cause mortality	218 (11.2)	26 (5.3)	30 (6.3)	57 (11.7)	105 (21.6)	<0.0001
Cardiovascular Death	116 (6.0)	13 (2.6)	17 (3.5)	33 (6.8)	53 (10.9)	<0.0001
non-Cardiovascular Death	102 (5.2)	13 (2.6)	14 (2.9)	23 (4.7)	52 (10.7)	<0.0001
Sudden Cardiac Death	50 (2.6)	6 (1.2)	7 (1.5)	16 (3.3)	21 (4.3)	<0.0001

Values were expressed as mean ± SD, median [IQR], or counts (%) as appropriate. T2D, type 2 diabetes; LVEF, left ventricular ejection fraction; BMI, body mass index; sysBP, systolic blood pressure; diaBP, diastolic blood pressure; BNP, B-type natriuretic peptide ; %GHbA1C, percentage of glycated hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NYHA, New York Heart Association Classification; ARBs, Angiotensin II receptor blocker; ACEIs, Angiotensin-Converting Enzyme Inhibitors ; β-blockers, β-adrenergic blockers; CCBs, calcium channel blockers; MI, myocardial infarction; CABG, coronary artery bypass surgery; PCI, percutaneous coronary intervention. ET-1, endothelin-1.

Table S2. Baseline characteristics of patients with various statin dosage in high or low ET-1 group

	Overall	Low ET-1				high ET-1				p (low vs high ET-1)
		no statin	low statins	moderate statins	high statins	no statin	low statins	moderate statins	high statins	
N	1564	87	36	654	138	80	38	462	69	
Age (year)	68 [62, 74]	66 [60, 74]	69.50 [65.75, 75.25]	66 [61, 72]	63 [54.25, 67]	70.50 [64, 75]	74 [69, 76.75]	70 [64, 76]	67 [61, 74]	<0.0001
T2D (%)	605 (38.7)	26 (29.9)	14 (38.9)	175 (26.8)	45 (32.6)	49 (61.3)	19 (50.0)	236 (51.1)	41 (59.4)	<0.0001
Sex (%) (female)	487 (31.1)	28 (32.2)	14 (38.9)	172 (26.3)	36 (26.1)	30 (37.5)	17 (44.7)	162 (35.1)	28 (40.6)	0.0001
LVEF (%)	65.60 [60.02, 70.07]	65.60 [61.40, 70.53]	65.05 [60.22, 70.90]	65.88 [60.90, 70.11]	64.80 [60.30, 67.80]	64.25 [57.48, 71.10]	65.90 [58.50, 71.22]	65.70 [59.20, 70.00]	64.40 [58.00, 69.50]	0.4235
BMI (kg/m ²)	27.00 [25.00, 30.00]	27.00 [24.74, 30.50]	26.00 [24.00, 29.00]	27.00 [25.00, 29.00]	27.00 [25.00, 30.00]	28.00 [24.00, 32.00]	28.20 [24.25, 30.75]	28.00 [26.00, 32.00]	29.00 [26.00, 32.00]	<0.0001
sysBP (mm Hg)	145 [129, 162]	145 [125, 164]	152.50 [132, 164]	144 [128, 159]	135 [123, 153]	150.50 [134.75, 168.75]	135 [127.25, 160]	148 [133, 165]	142 [128, 153]	0.0001
diaBP (mm Hg)	76 [70, 84]	75 [69, 84]	78 [73.75, 85]	76 [70, 83]	77 [70, 83]	77 [71.75, 86]	72.50 [68, 80.75]	77 [70, 85.75]	74 [69, 81]	0.2833
BNP (pg/mL)	50.50 [25.00, 97.00]	39.00 [18.50, 86.00]	43.50 [21.25, 86.75]	48.50 [25.00, 83.75]	37.00 [17.25, 76.25]	60.50 [33.50, 139.75]	84.50 [39.25, 143.25]	58.00 [29.00, 123.00]	59.00 [29.00, 132.00]	<0.0001
Creatinine clearance (mL/min)	86.41 [69.40, 109.93]	92.25 [75.14, 111.39]	86.42 [72.97, 100.82]	86.10 [70.17, 109.83]	101.87 [82.55, 126.73]	86.12 [65.96, 109.63]	77.53 [65.84, 96.30]	81.81 [63.72, 105.68]	95.05 [68.95, 119.03]	0.0001
Insulin (mIU / L)	11.30 [7.20, 18.00]	9.20 [5.55, 14.90]	10.95 [6.00, 14.82]	9.90 [6.90, 15.60]	12.30 [7.40, 19.55]	12.90 [7.30, 23.85]	11.65 [6.35, 21.23]	12.75 [7.80, 20.28]	14.20 [8.95, 23.12]	<0.0001
GHbA1C (%)	6.00 [5.70, 6.50]	5.90 [5.60, 6.40]	6.05 [5.80, 6.43]	5.90 [5.60, 6.30]	5.95 [5.62, 6.30]	6.35 [5.97, 6.98]	6.20 [5.70, 6.97]	6.20 [5.80, 6.90]	6.10 [5.90, 6.60]	<0.0001
Total cholesterol (mmol/L)	3.80 [3.40, 4.40]	5.10 [4.20, 5.95]	3.90 [3.70, 4.20]	3.70 [3.30, 4.20]	3.90 [3.40, 4.30]	5.20 [4.50, 5.73]	3.65 [3.35, 4.27]	3.70 [3.30, 4.20]	3.90 [3.50, 4.40]	0.4865
HDL (mmol/L)	1.24 [1.04, 1.46]	1.25 [1.11, 1.54]	1.25 [1.05, 1.45]	1.25 [1.06, 1.47]	1.19 [1.00, 1.43]	1.25 [1.02, 1.45]	1.27 [1.12, 1.50]	1.23 [1.02, 1.43]	1.11 [0.97, 1.35]	0.0472
LDL (mmol/L)	2.10 [1.80, 2.60]	3.40 [2.30, 4.00]	2.40 [1.87, 2.52]	2.00 [1.70, 2.40]	2.20 [1.80, 2.58]	3.40 [2.70, 4.03]	1.95 [1.63, 2.18]	2.00 [1.70, 2.50]	2.20 [1.80, 2.50]	0.7366
Triglyceride (mmol/L)	1.18 [0.89, 1.62]	1.29 [0.92, 1.64]	1.08 [0.81, 1.28]	1.10 [0.83, 1.54]	1.17 [0.91, 1.57]	1.54 [1.08, 2.05]	1.21 [0.89, 1.62]	1.25 [0.96, 1.68]	1.36 [1.03, 2.01]	<0.0001
Resting heart rate (beats/min)	59 [53, 66]	58.50 [52, 65]	56 [50, 62.50]	57 [52, 64]	58 [53, 64]	64 [58, 76]	62 [56, 67]	61 [54, 68]	60 [54.50, 68]	<0.0001
NYHA (%)										
NYHA Class I	689 (44.5)	31 (36.0)	15 (41.7)	220 (34.1)	55 (40.1)	45 (57.0)	21 (55.3)	259 (56.4)	43 (62.3)	<0.0001
NYHA Class II	52 (3.3)	2 (2.3)	0 (0.0)	19 (3)	4 (2.9)	8 (10.2)	4 (10.5)	13 (2.9)	2 (2.9)	
Medication (%)										
ARBs	438 (28.0)	20 (23.0)	12 (33.3)	162 (24.8)	39 (28.3)	20 (25.0)	14 (36.8)	146 (31.7)	25 (36.2)	0.0092
ACEIs	631 (40.4)	31 (35.6)	17 (47.2)	253 (38.7)	55 (39.9)	32 (40.0)	13 (34.2)	199 (43.2)	31 (44.9)	0.1772
CCBs	373 (23.8)	17 (19.5)	16 (44.4)	122 (18.7)	20 (14.5)	18 (22.5)	19 (50.0)	135 (29.2)	26 (37.7)	<0.0001
Diuretics	515 (32.9)	23 (26.4)	13 (36.1)	159 (24.3)	33 (23.9)	27 (33.8)	24 (63.2)	205 (44.4)	31 (44.9)	<0.0001
β-blockers	1360 (87.0)	68 (78.2)	33 (91.7)	575 (87.9)	119 (86.2)	64 (80.0)	33 (86.8)	406 (87.9)	62 (89.9)	0.9815
Lipid-lowering therapy	1397 (89.3)	0 (0.0)	36 (100.0)	654 (100.0)	138 (100.0)	0 (0.0)	38 (100.0)	462 (100.0)	69 (100.0)	0.0900
History (%)										
Prior MI	754 (48.2)	29 (33.3)	14 (38.9)	315 (48.2)	85 (61.6)	30 (37.5)	16 (42.1)	226 (48.9)	39 (56.5)	0.8872
Prior PCI or CABG	1236 (79.2)	49 (57.6)	25 (69.4)	528 (81.0)	125 (90.6)	50 (62.5)	31 (81.6)	365 (79.0)	63 (91.3)	0.5511
Smoking	131 (8.4)	8 (9.2)	2 (5.6)	34 (5.2)	10 (7.2)	13 (16.5)	7 (18.4)	49 (10.6)	8 (11.6)	<0.0001
Death (%)										
All-cause mortality	165 (10.5)	9 (10.3)	3 (8.3)	38 (5.8)	6 (4.3)	17 (21.2)	8 (21.1)	82 (17.7)	2 (2.9)	<0.0001
Cardiovascular Death	91 (5.8)	6 (6.9)	1 (2.8)	24 (3.7)	2 (1.4)	14 (17.5)	5 (13.2)	37 (8.0)	2 (2.9)	<0.0001
non-Cardiovascular Death	75 (4.8)	3 (3.4)	2 (5.6)	15 (2.3)	4 (2.9)	4 (5.0)	3 (7.9)	44 (9.5)	0 (0.0)	
Sudden Cardiac Death	34 (2.2)	2 (2.3)	1 (2.8)	9 (1.4)	1 (0.7)	3 (3.8)	3 (7.9)	15 (3.2)	0 (0.0)	<0.0001

Values were expressed as mean ± SD, median [IQR], or counts (%) as appropriate. T2D, type 2 diabetes; LVEF, left ventricular ejection fraction; BMI, body mass index; sysBP, systolic blood pressure; diaBP, diastolic blood pressure; BNP, B-type natriuretic peptide; %GHbA1C, percentage of glycated hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NYHA, New York Heart Association Classification; ARBs, Angiotensin II receptor blocker; ACEIs, Angiotensin-Converting Enzyme Inhibitors ; β-blockers, β-adrenergic blockers; CCBs, calcium channel blockers; MI, myocardial infarction; CABG, coronary artery bypass surgery; PCI, percutaneous coronary intervention. ET-1, endothelin-1.