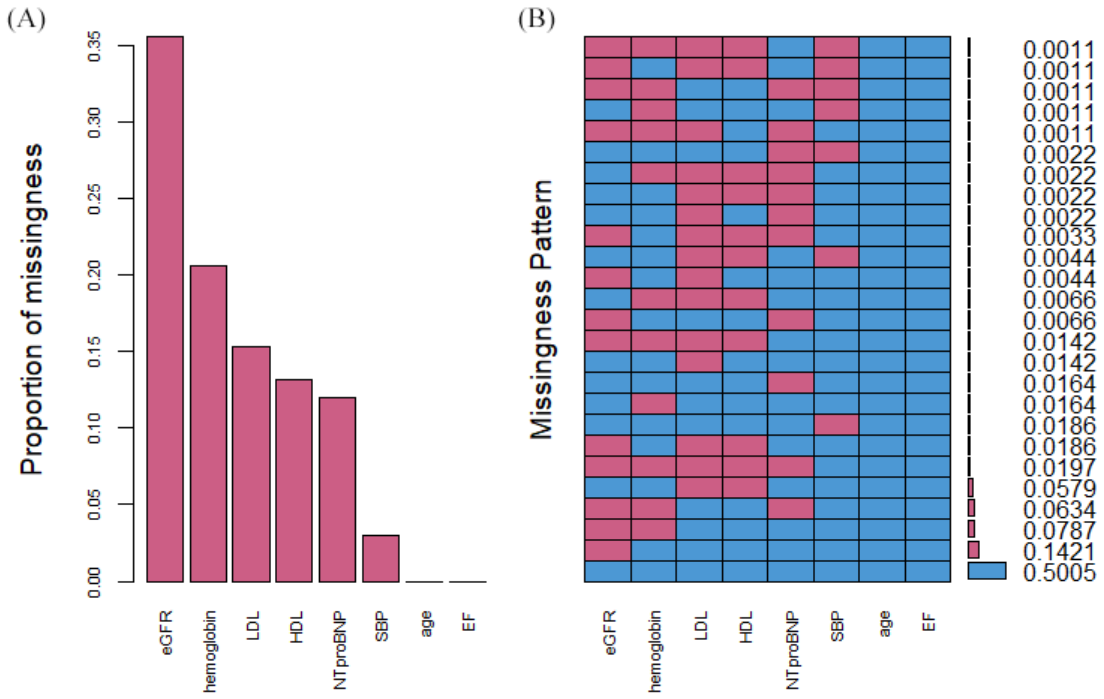

Fig. S1 The missing laboratory variables before data imputation. (A)The proportions of missing values. (B) the missing patterns. eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein; EF, left ventricular ejection fraction; NT-proBNP, N terminal pro B type natriuretic peptide; SBP, systolic blood pressure.

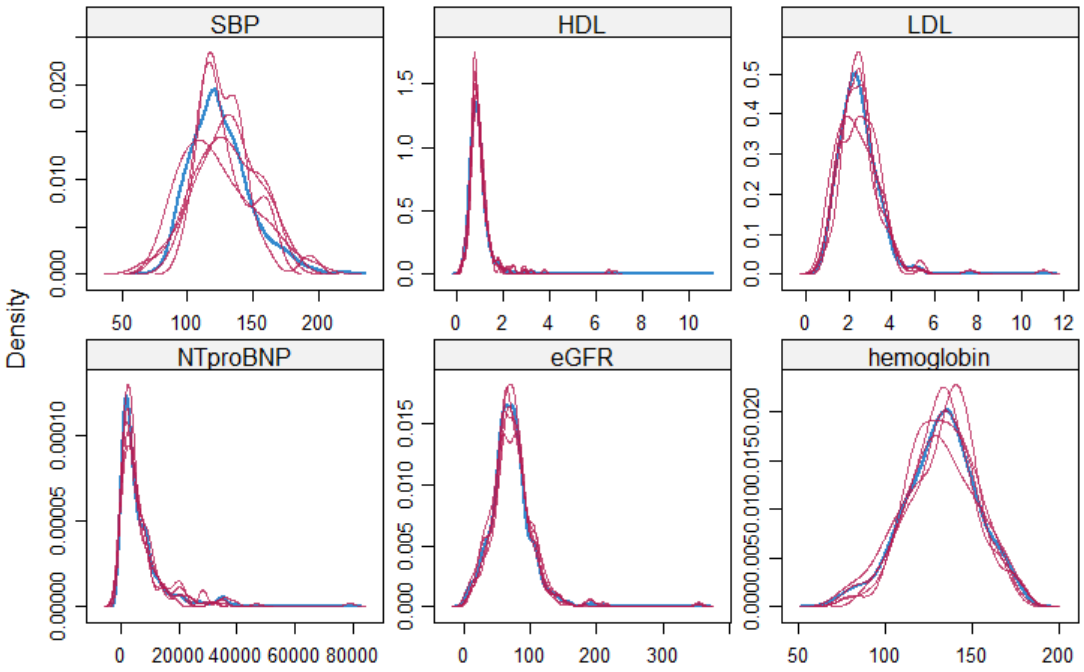

Fig. S2 The density plots illustrating the goodness of fit for missing data imputation with multiple imputation method. The blue curves are the observed variables and red ones are imputed variables. eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein; NT-proBNP, N terminal pro B type natriuretic peptide; SBP, systolic blood pressure.

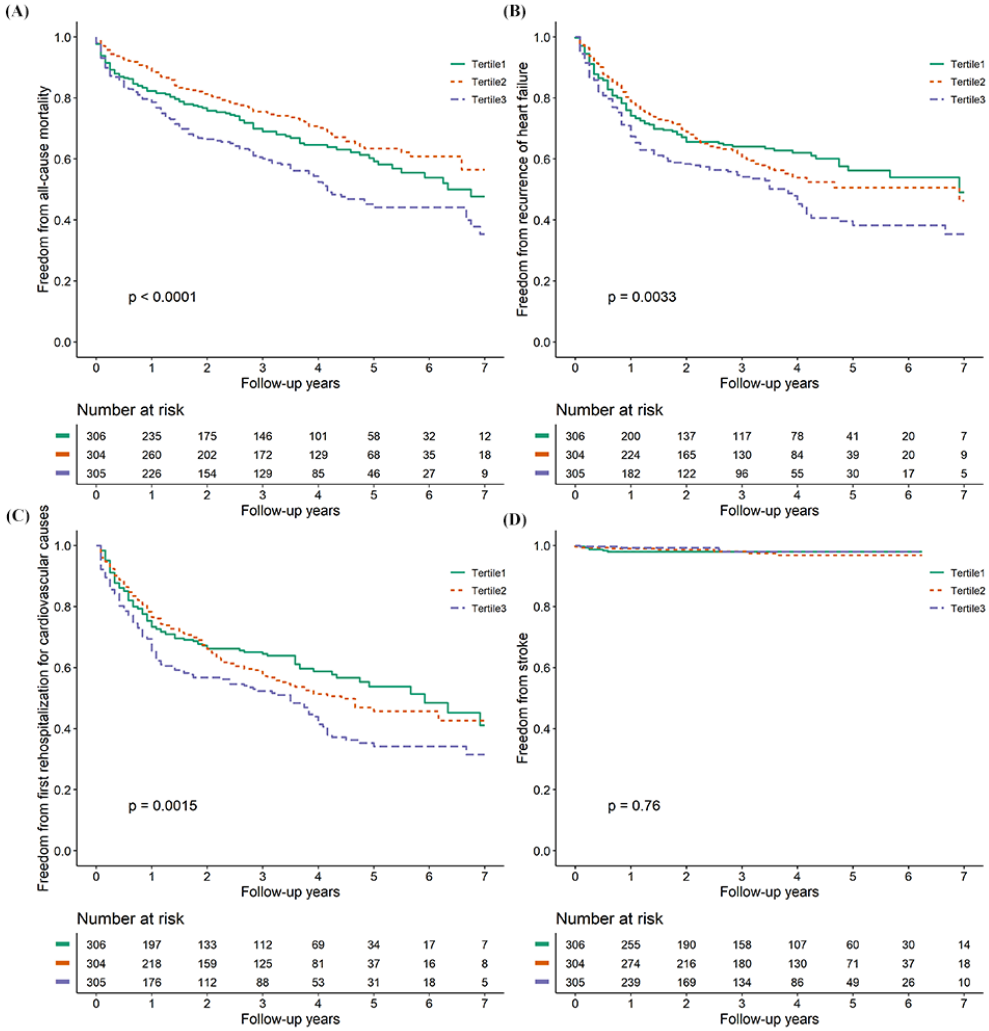

Fig. S3 The Kaplan-Meier curves for secondary outcome with TMAO stratified by tertiles. (A)The Kaplan-Meier curves for all-cause mortality with TMAO stratified by tertiles. (B) The Kaplan-Meier curves for recurrence of heart failure with TMAO stratified by tertiles. (C) The Kaplan-Meier curves for first rehospitalization for cardiovascular causes with TMAO stratified by tertiles. (D) The Kaplan-Meier curves for stroke with TMAO stratified by tertiles. The *p* value is calculated by log-rank test.

Table S1 Risk of primary outcome according to tertiles of TMAO levels and the effects of choline and carnitine

Choline	**Tertile 1** ⩽9.79	**Tertile 2** 9.79-13.88	**Tertile 3** > 13.88	***p* value**
Unadjusted	1	1.26 (0.95-1.67)	1.42 (1.08-1.87)	0.013
Adjusted with carnitine	1	1.28 (0.96-1.69)	1.44 (1.09-1.91)	0.033
Adjusted with TMAO	1	1.21 (0.92-1.61)	1.26 (0.95-1.68)	**0.109**
Carnitine	**Tertile 1** ⩽41.38	**Tertile 2** 41.38-58.70	**Tertile 3** > 58.70	***p* value**
Unadjusted	1	1.42 (1.05-1.916)	2.25 (1.70-2.99)	<0.001
Adjusted with choline	1	1.39 (1.03-1.88)	2.11 (1.57-2.84)	<0.001
Adjusted with TMAO	1	1.38 (1.02-1.86)	2.10 (1.57-2.79)	<0.001
TMAO	**Tertile 1** ⩽1.574	**Tertile 2** 1.574-3.770	**Tertile 3** > 3.770	***p* value**
Unadjusted	1	0.84 (0.63-1.12)	1.47 (1.13-1.91)	0.004
Adjusted with choline	1	0.83 (0.62-1.10)	1.35 (1.03-1.78)	0.023
Adjusted with carnitine	1	0.83 (0.62-1.11)	1.48 (1.13-1.92)	0.004

Hazard ratios and *p* values compare tertile 3 to tertile 1. Data was shown as hazard ratio (95% CI).

Table S2 Baseline characteristics of HFrEF cohort stratified by genotypes

	GG type (n=521)	GA type (n=263)	AA type (n=33)	p Value
Demographic characteristics				
Age (years)	57.0±14.2	56.9±13.8	56.9±13.3	0.994
Male (%)	68.8	70.7	72.7	0.797
Smoker (%)	42.1	39.9	42.4	0.841
Drinker (%)	27	27	36.4	0.495
SBP(mm Hg)	121 (108-137)	123 (109-140)	125 (108-140)	0.252
DBP(mm Hg)	79 (69-88)	81 (70-91)	80 (71-93)	0.740
Heart rate(beats per min)	85 (75-100)	87 (74-102)	96 (80-108)	0.250
NYHA class II/III/IV	24.5/44.2/31.4	24.3/42.6/33.1	21.2/45.5/33.3	0.980
Medical history, n (%)				
Hypertension	76.9	80.6	75.8	0.470
Diabetes	29.3	26.2	21.2	0.460
Dyslipidemia	19.3	11	15.2	0.012
Coronary artery disease	29.6	25.9	27.3	0.535
Laboratory measurements				
Fasting glucose (mmol/l)	5.63 (4.99-7.24)	5.78 (5.02-6.92)	5.34 (4.61-6.20)	0.525
Total cholesterol(mmol/L)	3.74 (3.13-4.49)	3.80 (3.20-4.64)	3.55 (3.12-4.22)	0.434
Triglycerides (mmol/L)	1.08 (0.78-1.58)	1.03 (0.81-1.48)	1.03 (0.92-1.39)	0.701
LDL cholesterol (mmol/L)	2.36 (1.86-3.01)	2.37 (1.86-2.85)	2.29 (1.88-2.71)	0.693

HDL cholesterol (mmol/L)	0.89 (0.72-1.10)	0.87 (0.69-1.12)	0.85 (0.60-1.05)	0.219
NT-proBNP (ng/L)	3710 (1734-8507)	3378 (1568-7900)	6400 (2340-15022)	0.002
hsCRP (mg/L)	6.00 (2.00-18.03)	4.35 (2.00-16.32)	6.30 (2.10-44.70)	0.363
eGFR (ml/min/1.73 m^2)	71.2 (55.2-85.5)	71.1 (54.9-88.4)	66.6 (42.8-84.2)	0.109
Hemoglobin (g/L)	134 (121-147)	135 (119-148)	124 (116-141)	0.141
Echocardiography				
LVEDD (mm)	64 (58-70)	63 (58-69)	64 (59-69)	0.378
LVEF (%)	31 (25-36)	31 (26-36)	31 (26-36)	0.863
Medication, (%)				
Diuretics	84.3	89.0	84.8	0.201
ACEI/ARB	85.8	84.0	90.9	0.531
Beta-blocker	65.5	60.1	66.7	0.315
Spironolactone	80.6	85.2	78.8	0.211

Variables are expressed in mean ± standard deviation or median (interquartile range). DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; hsCRP, high sensitivity C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NT-proBNP, N terminal pro B type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; TMAO, trimethylamine N-oxide. Dyslipidemia is defined according to lipid levels or use of anti-dyslipidemia medications two weeks prior to the experiment.