Table S1. The usage characteristics of supplements and drugs for other chronic diseases in different medication burden status.

Drug n (%)	Total n = 1761	Controls n= 123	Polypharmacy n = 661	Hyperpolypharmacy n = 632	Super hyperpolypharmacy n = 345
Supplements					
Vitamin B	107 (6.1)	1 (0.8)	16 (2.4)	39 (6.2)	51 (14.8)
Calcium	296 (16.8)	0 (0)	50 (7.6)	123 (19.5)	123 (35.7)
Iron	169 (9.6)	0 (0)	27 (4.1)	71 (11.2)	71 (20.6)
Glucosamine	48 (2.7)	0 (0)	10 (1.5)	16 (2.5)	22 (6.4)
COPD/Asthma					
Salbutamol	240 (13.6)	0 (0)	34 (5.1)	94 (14.9)	112 (32.5)
Montelukast	41 (2.3)	0 (0)	1 (0.2)	14 (2.2)	26 (7.5)
Ipratropium	77 (4.4)	0 (0)	12 (1.8)	26 (4.1)	39 (11.3)
Thyroid diseases					
Levothyroxine	277 (15.7)	2 (1.6)	73 (11.0)	131 (20.7)	71 (20.6)
Methimazole / Propylthiouracil	5 (0.3)	0 (0)	0 (0)	2 (0.3)	3 (0.9)

Table S2. Baseline Characteristics of the Echocardiography Cohort by total medication burden at baseline

	Controls n = 31	Polypharmacy n = 243	Hyperpolypharmacy n = 260	Super hyperpolypharmacy n = 120	*P*
Mean LV wall thickness, mm	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	0.08
LVMi, g/m^2	107 ± 33	109 ± 32	110 ± 30	113 ± 30	0.56
LVEDVi, ml/m^2	50 ± 18	47 ± 15	47 ± 13	48 ± 13	0.73
LVESVi, ml/m^2	22 ± 14	20 ± 9	19 ± 8	19 ± 7	0.26
LVEF, %	58 ± 10	59 ± 8	60 ± 8	62 ± 7	0.030
Longitudinal strain, %	-16.1 ± 4.2	-15.5 ± 3.6	-15.3 ± 3.5	-15.8 ± 3.0	0.73
RVFAC, %	49 ± 10	48 ± 8	49 ± 8	49 ± 8	0.84
LAVi, ml	29 ± 14	32 ± 13	31 ± 15	30 ± 12	0.40
MR jet area/LA area	0.13 (0.00-0.17)	0.06 (0.00-0.12)	0.04 (0.00-0.10)	0.09 (0.00-0.15)	0.08
TR jet velocity, m/s	2.8 ± 0.5	2.8 ± 0.5	2.9 ± 0.5	2.7 ± 0.4	0.26

Values are mean ± SD or median (interquartile range).

LA = left atrial; LAVi = left atrial volume index; LV = left ventricular; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end systolic volume index; LVMi = left ventricular mass index; MR = mitral regurgitation, RVFAC = right ventricular fractional area change; TR = tricuspid regurgitation.

Table S3. Event rates of the studied outcomes by total medication burden at baseline

	Events (n (%))	Event rates (per 100 person-yrs)
Primary Outcome*		
Controls (n=123)	20 (16.3)	6.3 (3.8-9.7)
Polypharmacy (n=661)	156 (23.6)	8.7 (7.4-10.2)
Hyperpolypharmacy (n=632)	207 (32.8)	12.5 (10.9-14.4)
Super hyperpolypharmacy (n=345)	138 (40.0)	16.8 (14.2-19.9)
Cardiovascular death		
Controls (n=123)	14 (11.4)	4.3 (2.4-7.2)
Polypharmacy (n=661)	78 (11.8)	4.0 (3.2-5.0)
Hyperpolypharmacy (n=632)	82 (13.0)	4.2 (3.3-5.2)
Super hyperpolypharmacy (n=345)	49 (14.2)	4.8 (3.5-6.3)
All-cause death		
Controls (n=123)	25 (20.3)	7.7 (5.0-11.3)
Polypharmacy (n=661)	128 (19.4)	6.6 (5.5-7.8)
Hyperpolypharmacy (n=632)	155 (24.5)	8.0 (6.7-9.3)
Super hyperpolypharmacy (n=345)	77 (22.3)	7.5 (5.9-9.4)
HF Hospitalization		
Controls (n=123)	8 (6.5)	2.5 (1.1-5.0)
Polypharmacy (n=661)	112 (16.9)	6.3 (5.2-7.6)
Hyperpolypharmacy (n=632)	166 (26.3)	10.0 (8.6-11.7)
Super hyperpolypharmacy (n=345)	113 (32.8)	13.7 (11.3-16.5)
All-cause Hospitalization		
Controls (n=123)	42 (34.1)	15.6 (11.3-21.1)
Polypharmacy (n=661)	356 (53.9)	28.0 (25.2-31.1)
Hyperpolypharmacy (n=632)	403 (63.8)	36.8 (33.3-40.5)
Super hyperpolypharmacy (n=345)	258 (74.8)	53.3 (47.0-60.2)
Myocardial infarction		
Controls (n=123)	3 (2.4)	0.9 (0.2-2.7)
Polypharmacy (n=661)	30 (4.5)	1.6 (1.1-2.3)
Hyperpolypharmacy (n=632)	31 (4.9)	1.7 (1.1-2.3)
Super hyperpolypharmacy (n=345)	29 (8.4)	3.0 (2.0-4.3)
Stroke		
Controls (n=123)	3 (2.4)	0.9 (0.2-2.7)
Polypharmacy (n=661)	31 (4.7)	1.6 (1.1-2.3)
Hyperpolypharmacy (n=632)	24 (3.8)	1.3 (0.8-1.9)
Super hyperpolypharmacy (n=345)	19 (5.5)	1.9 (1.1-3.0)

* Primary outcome was composite of cardiovascular disease death, aborted cardiac arrest, or heart failure hospitalization

Table S4. Adjusted HRs regarding medication burden in different EF strata.

	45 ≤ EF < 55 n = 484		55 ≤ EF < 65 n = 848			EF ≥ 65 n = 429			Global *P* for interaction
	Adjusted HRs*	*P*	Adjusted HRs*	*P*	*P* for interaction†	Adjusted HRs*	*P*	*P* for interaction†	
All-cause death									0.46
Polypharmacy vs. Controls	0.95 (0.42-2.15)	0.90	0.32 (0.17-0.61)	<0.001	0.20	0.87 (0.30-2.51)	0.79	0.66	
Hyperpolypharmacy vs. Controls	0.78 (0.33-1.84)	0.58	0.41 (0.22-0.77)	0.005	0.77	0.68 (0.23-2.05)	0.50	0.55	
Super hyperpolypharmacy vs. Controls	0.96 (0.38-2.47)	0.94	0.32 (0.16-0.63)	0.001	0.49	0.45 (0.13-1.55)	0.21	0.82	
HF hospitalization									0.08
Polypharmacy vs. Controls	3.03 (0.72-12.69)	0.13	0.99 (0.38-2.55)	0.98	0.32	3.54 (0.48-26.30)	0.22	0.71	
Hyperpolypharmacy vs. Controls	3.76 (0.88-16.05)	0.07	1.66 (0.65-4.22)	0.29	0.58	3.59 (0.48-26.96)	0.21	0.74	
Super hyperpolypharmacy vs. Controls	2.96 (0.66-13.34)	0.16	1.67 (0.64-4.39)	0.30	0.98	5.12 (0.66-39.54)	0.12	0.32	
All-cause hospitalization									0.42
Polypharmacy vs. Controls	1.53 (0.83-2.83)	0.18	1.59 (0.96-2.62)	0.07	0.71	1.29 (0.70-2.38)	0.41	0.95	
Hyperpolypharmacy vs. Controls	1.77 (0.93-3.36)	0.08	2.14 (1.30-3.54)	0.003	0.42	1.22 (0.65-2.28)	0.54	0.86	
Super hyperpolypharmacy vs. Controls	1.95 (0.98-3.87)	0.06	2.67 (1.58-4.49)	<0.001	0.28	1.96 (1.00-3.83)	0.05	0.48	

EF = ejection fraction; HF = heart failure; HRs = hazard ratios; CIs = confidence intervals.

*Adjusted for age, sex, race, diastolic blood pressure, smoking status, New York Heart Association functional class, hemoglobin, serum creatinine, history of HF hospitalization, arterial disease, diabetes mellitus, chronic obstructive pulmonary disease.

† Using group of 45≤EF<55 as reference.

Table S5. Predictors of using ≥5 medications, ≥10 medications and ≥15 medications in univariable models.

	≥ 5 medications		≥ 10 medications		≥ 15 medications	
	RRs (95% CIs)	***P* value**	**RRs (95% CIs)**	***P* value**	**RRs (95% CIs)**	***P* value**
Female	-	-	0.92 (0.84-1.00)	0.043	-	-
DBP <80 mmHg	1.09 (1.05-1.13)	<0.001	1.38 (1.24-1.54)	<0.001	1.80 (1.40-2.32)	<0.001
Heart Rate, beats/min *	0.98 (0.97-0.99)	0.001	-	-	-	-
BMI, kg/m2	1.002 (1.001-1.002)	<0.001	1.01 (1.01-1.02)	<0.001	1.02 (1.01-1.03)	<0.001
Waist circumference, cm *	1.009 (1.008-1.011)	<0.001	1.08 (1.08-1.09)	<0.001	1.15 (1.10-1.21)	<0.001
Smoking status						
Never *vs.* Ever	1.05 (1.03-1.08)	<0.001	1.25 (1.15-1.37)	<0.001	1.43 (1.15-1.76)	<0.001
NYHA functional class						
I & II *vs*. III & IV	1.05 (1.02-1.07)	<0.001	1.32 (1.22-1.43)	<0.001	1.62 (1.33-1.96)	<0.001
KCCQ Scores						
Self-efficacy score *	1.006 (1.001-1.012)	0.027	1.03 (1.01-1.05)	0.002	-	-
Quality of life score *	-	-	0.98 (0.96-0.99)	0.002	0.92 (0.89-0.96)	<0.001
Social limitation score *	-	-	0.97 (0.96-0.99)	<0.001	0.93 (0.90-0.96)	<0.001
Laboratory values						
Anemia†	1.06 (1.03-1.08)	<0.001	1.32 (1.21-1.42)	<0.001	1.66 (1.38-2.01)	<0.001
Serum K+, mg/dl	-	-	0.88 (0.80-0.97)	0.009	0.76 (0.61-0.95)	0.017
ALP, U/L *	0.993 (0.990-0.996)	<0.001	0.97 (0.96-0.98)	<0.001	0.96 (0.94-0.99)	0.002
Serum creatinine, mg/dl	1.04 (1.03-1.05)	<0.001	1.40 (1.36-1.43)	<0.001	1.95 (1.54-2.46)	<0.001
eGFR, ml/min *	0.984 (0.979-0.990)	<0.001	0.94 (0.92-0.96)	<0.001	0.90 (0.85-0.95)	<0.001
Comorbidities						
Previous HF hospitalization			-	-	1.29 (1.05-1.59)	0.014
Previous stroke	1.07 (1.04-1.09)	<0.001	1.28 (1.14-1.44)	<0.001	1.51 (1.15-1.99)	0.003
Previous MI	1.08 (1.06-1.10)	<0.001	1.40 (1.29-1.53)	<0.001	1.50 (1.21-1.85)	<0.001
CABG	1.08 (1.06-1.10)	<0.001	1.51 (1.40-1.64)	<0.001	1.85 (1.52-2.27)	<0.001
PCI	1.07 (1.05-1.09)	<0.001	1.49 (1.37-1.61)	<0.001	1.85 (1.52-2.26)	<0.001
Angina pectoris	1.08 (1.06-1.10)	<0.001	1.47 (1.36-1.59)	<0.001	2.21 (1.83-2.67)	<0.001
ICD	-	-	1.41 (1.18-1.67)	<0.001	-	-

Pacemaker	-	-	1.20 (1.08-1.34)	<0.001	-	-
Hypertension	1.09 (1.02-1.15)	0.008	1.31 (1.10-1.56)	0.003	1.82 (1.18-2.81)	0.007
Dyslipidemia	1.13 (1.09-1.18)	<0.001	1.82 (1.60-2.06)	<0.001	2.15 (1.63-2.83)	<0.001
PAD	1.06 (1.04-1.09)	<0.001	1.37 (1.25-1.51)	<0.001	1.66 (1.30-2.10)	<0.001
COPD	1.07 (1.05-1.10)	<0.001	1.34 (1.22-1.47)	<0.001	2.09 (1.71-2.55)	<0.001
Asthma	1.05 (1.03-1.08)	<0.001	1.47 (1.34-1.61)	<0.001	1.93 (1.54-2.42)	<0.001
Diabetes mellitus	1.09 (1.06-1.12)	<0.001	1.65 (1.52-1.80)	<0.001	2.24 (1.83-2.75)	<0.001
Thyroid diseases	1.07 (1.05-1.10)	<0.001	1.34 (1.23-1.46)	<0.001	1.37 (1.10-1.70)	0.006
Number of comorbidities	1.01 (1.01-1.02)	<0.001	1.12 (1.11-1.12)	<0.001	1.37 (1.34-1.40)	<0.001

* Calculated by per 10 units increase.

† Anemia is defined as hemoglobin (Hb) levels <12.0 g/dL in women and <13.0 g/dL in men.

TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist Trial); DBP = diastolic blood pressure; BMI = body mass index; NYHA = New York Heart Association; KCCQ = the Kansas City Cardiomyopathy Questionnaire; ALP = alkaline phosphatase; HF = heart failure; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; PCI = percutaneous coronary intervention; ICD = implanted cardioverter defibrillator; CABG = coronary artery bypass grafting; PAD = peripheral arterial disease; COPD = chronic obstructive pulmonary disease; RRs = Risk Ratios**;** CIs = confidence intervals.

Table S6. Dosage of drugs by total medication burden at baseline

	Controls	Polypharmacy	Hyperpolypharmacy	Super hyperpolypharmacy	*P* value
ENALAPRIL, mg	10 (10-20)	20 (10-30)	20 (20-40)	20 (20-40)	0.003
LISINOPRIL, mg	10 (5-12.5)	20 (10-40)	20 (10-40)	20 (10-40)	0.259
RAMIPRIL, mg	7.5 (4.2-10)	7.5 (5-10)	10 (8.8-10)	10 (10-15.5)	0.131
LOSARTAN, mg	50 (50-100)	100 (50-100)	100 (50-100)	100 (50-100)	0.785
VALSARTAN, mg	320 (160-320)	160 (80-320)	160 (100-320)	160 (160-320)	0.758
CARVEDILOL, mg	12.5 (7.2-25)	25 (12.5-42.5)	25 (25-50)	50 (14.4-50)	<0.001
METOPROLOL.SUCCINATE, mg	50 (37.5-50)	50 (50-100)	75 (50-150)	100 (50-100)	0.446
METOPROLOL.TARTRATE, mg	50 (50-100)	100 (50-175)	100 (50-100)	100 (50-150)	0.761
ATENOLOL, mg	50 (50-50)	50 (25-100)	50 (25-100)	50 (25-100)	0.955
FUROSEMIDE, mg	40 (40-40)	40 (40-80)	40 (40-80)	80 (40-100)	<0.001
HYDROCHLOROTHIAZIDE, mg	25 (25-25)	25 (12.5-25)	25 (12.5-25)	25 (12.5-25)	0.325
AMLODIPINE.BESYLATE, mg	10 (10-10)	10 (5-10)	10 (5-10)	10 (5-10)	0.382
HYDRALAZINE, mg	200 (200-200)	131 (75-206.2)	75 (50-150)	150 (75-225)	0.111
ASPIRIN, mg	100 (81-100)	81 (81-100)	81 (81-81)	81 (81-81)	<0.001
CLOPIDOGREL, mg	75 (75-75)	75 (75-75)	75 (75-75)	75 (75-75)	0.766
SIMVASTATIN, mg	30 (20-40)	20 (20-40)	40 (20-40)	40 (20-40)	0.004
LIPITOR, mg	20 (20-80)	20 (10-40)	20 (20-40)	40 (10-50)	0.139
CRESTOR, mg	5 (5-5)	10 (10-20)	10 (10-20)	10 (8.8-20)	0.246
WARFARIN, mg	5 (3.2-6.2)	5 (2.5-5)	5 (3-5)	5 (3-5)	0.901
DIGOXIN, mg	0.2 (0.2-0.2)	0.2 (0.1-0.2)	0.1 (0.1-0.2)	0.1 (0.1-0.2)	0.615
IMDUR, mg	-	30 (30-37.5)	60 (30-60)	60 (30-97.5)	0.19
METFORMIN, g	1 (0.8-1.8)	1 (0.8-1.7)	1.5 (1-2)	1.3 (1-2)	0.02
GLIPIZIDE, mg	-	5 (5-10)	10 (5-15)	20 (10-20)	0.058
LANTUS, iu	25 (25-25)	41.5 (32.2-52.5)	40 (26.2-59)	42.5 (25.8-95)	0.513

Values are median (interquartile range).