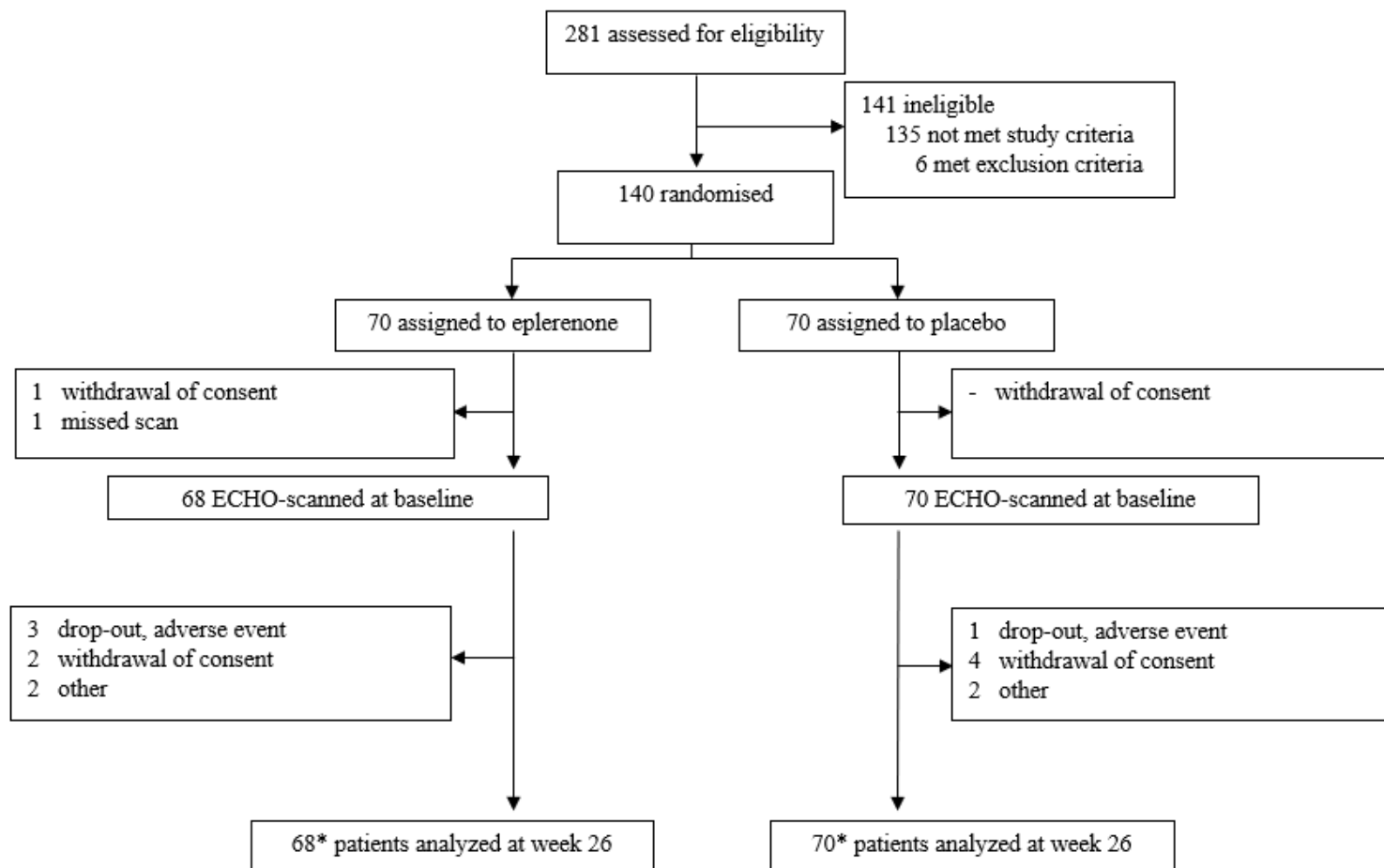


Supplementary Figure 1: Flowchart of patient participation in the trial



* All patients completing at least one scan (n = 138) included in an intention to treat analysis as missingness was deemed to be missing at random or missing completely at random.

Supplementary table 1: Additional echocardiographic measures at baseline

	Placebo	Eplerenone	
Structure			
IVSD, cm	1.2	(0.2)	1.2 (0.2)
LVID, cm	4.4	(0.6)	4.4 (0.6)
LVPW, cm	1.2	(0.2)	1.2 (0.2)
Left ventricular function			
<i>Systolic function</i>			
EDV, mL	84.2	(22.6)	90.7 (23.0)
ESV, mL	35.7	(13.9)	37.5 (12.8)
Heart rate, beat/min	72.0	(13.3)	69.5 (11.5)
<i>Diastolic function</i>			
e', cm/s	6.9	(1.7)	7.4 (1.7)
E-wave, m/s	0.7	(0.2)	0.8 (0.2)
A-wave, m/s	0.8	(0.2)	0.8 (0.2)
E/A-ratio	1.1	(0.6)	1.1 (0.4)
E-wave deceleration time, ms	260.9	(73.9)	268.3 (72.1)
Right ventricular function			
GLS, %	-16.1	(5.3)	-16.6 (5.6)
S', cm/s	12.2	(3.0)	12.0 (2.6)
TAPSE, mm/s	22.6	(3.8)	22.5 (4.8)

Additional echocardiographic values measured at baseline. Abbreviations: IVSD, intraventricular septal diameter at end-diastole; LVID, left ventricular internal diameter at end-diastole; LVPW, left ventricular posterior wall diameter at end-diastole; EDV end-diastolic volume; ESV, end-systolic volume; GLS, global longitudinal strain; TAPSE, tricuspid annular plane systolic excursion

Supplementary material – Paper III

	Baseline		Placebo		P	Eplerenone		P	Treatment effect		P
Structure											
IVSD, cm	1.2	[1.2 to 1.2]	0.0	[0.0 to 0.1]	0.370	0.0	[-0.1 to 0.0]	0.922	0.0	[-0.1 to 0.0]	0.445
LVID, cm	4.4	[4.3 to 4.5]	0.0	[-0.1 to 0.2]	0.543	0.0	[-0.1 to 0.1]	0.887	0.0	[-0.2 to 0.1]	0.728
LVPW, cm	1.2	[1.2 to 1.2]	0.0	[-0.1 to 0.0]	0.586	0.0	[-0.1 to 0.0]	0.135	0.0	[-0.1 to 0.0]	0.461
Systolic function											
LV SV, mL	50.8	[48.6 to 53.1]	1.5	[-1.3 to 4.2]	0.287	0.1	[-2.7 to 2.8]	0.971	-1.4	[-5.1 to 2.3]	0.445
Diastolic function											
A', cm/s	9.6	[9.2 to 10.0]	-0.3	[-0.8 to 0.2]	0.218	0.2	[-0.3 to 0.7]	0.444	0.5	[-0.2 to 1.1]	0.140
S', cm/s	7.1	[6.9 to 7.4]	0.0	[-0.3 to 0.4]	0.790	0.2	[-0.1 to 0.5]	0.188	0.2	[-0.3 to 0.6]	0.427
Right ventricular function											
GLS, %*	-16.6	[-17.6 to -15.6]	1.4	[0.0 to 2.8]	0.057	-1.2	[-2.7 to 0.3]	0.107	-2.6	[-4.5 to -0.7]	0.009
S', cm/s	12.1	[11.6 to 12.6]	-0.1	[-0.8 to 0.6]	0.790	0.0	[-0.7 to 0.8]	0.916	0.1	[-0.8 to 1.1]	0.774
TAPSE, mm/s	22.6	[21.9 to 23.4]	-0.4	[-1.6 to 0.8]	0.482	0.3	[-0.9 to 1.5]	0.636	0.7	[-0.9 to 2.3]	0.378

Supplementary table 2: Analyses of conventional echocardiographic measures of cardiac function

Treatment effects across additional measures of cardiovascular function measured at baseline and after 26 weeks. The analyses are performed using a constrained linear mixed model. Abbreviations: IVSD, intraventricular septal diameter at end-diastole; LVID, left ventricular internal diameter at end-diastole; LVPW, left ventricular posterior wall at end-diastole; LV SV, left ventricular stroke volume; GLS, global longitudinal strain; TAPSE, tricuspid annular plane systolic excursion.

Supplementary table 3: Complete case analyses of effect of high-dose eplerenone after 26 weeks of treatment

	Baseline		Placebo		P	Eplerenone		P	Treatment effect		P	
<i>Structure</i>												
LVMi, g/m ²	92.4	[88.4 to 96.4]	2.0	[-2.8 to 6.8]	0.401	-1.7	[-6.6 to 3.1]	0.481	-3.8	[-10.2 to 2.7]	0.247	
IVS, cm	1.2	[1.2 to 1.3]	0.0	[0.0 to 0.1]	0.459	0.0	[-0.1 to 0.0]	0.811	0.0	[-0.1 to 0.0]	0.444	
LVID, cm	4.4	[4.3 to 4.5]	0.0	[-0.1 to 0.2]	0.461	0.0	[-0.1 to 0.2]	0.784	0.0	[-0.2 to 0.1]	0.728	
LVPW, cm	1.2	[1.2 to 1.2]	0.0	[-0.1 to 0.0]	0.549	0.0	[-0.1 to 0.0]	0.124	0.0	[-0.1 to 0.0]	0.461	
<i>Left ventricular function</i>												
GLS, %*	-15.1	[-15.7 to -14.5]	0.5	[-0.3 to 1.3]	0.240	0.0	[-0.7 to 0.8]	0.905	-0.4	[-1.5 to 0.6]	0.427	
EF, %*	59.0	[57.7 to 60.4]	0.0	[-1.6 to 1.6]	0.972	0.9	[-0.7 to 2.5]	0.273	0.9	[-1.1 to 2.8]	0.382	
EDV, mL	87.4	[83.2 to 91.6]	1.9	[-2.3 to 6.1]	0.376	-2.1	[-6.3 to 2.1]	0.328	-3.9	[-9.6 to 1.7]	0.167	
ESV, mL	36.3	[34.0 to 38.5]	0.2	[-2.1 to 2.6]	0.837	-1.7	[-4.1 to 0.6]	0.145	-2.0	[-5.0 to 1.1]	0.201	
SV, mL	51.1	[48.7 to 53.6]	1.4	[-1.4 to 4.2]	0.330	-0.1	[-2.8 to 2.7]	0.965	-1.4	[-5.1 to 2.3]	0.445	
Heart rate, beat/min	70.3	[68.0 to 72.6]	1.3	[-1.1 to 3.7]	0.296	0.5	[-2.0 to 3.0]	0.671	-0.7	[-3.9 to 2.4]	0.643	
<i>Diastolic function</i>												
E-wave, m/s	0.8	[0.7 to 0.8]	0.0	[0.0 to 0.0]	0.563	0.0	[0.0 to 0.0]	0.897	0.0	[0.0 to 0.1]	0.749	
A-wave, m/s	0.8	[0.7 to 0.8]	0.0	[0.0 to 0.0]	0.484	0.0	[0.0 to 0.1]	0.158	0.0	[0.0 to 0.1]	0.129	
E/A-ratio	1.1	[1.0 to 1.2]	0.0	[-0.1 to 0.1]	0.719	-0.1	[-0.1 to 0.0]	0.152	-0.1	[-0.2 to 0.0]	0.193	
e', cm/s	7.1	[6.8 to 7.4]	0.0	[-0.3 to 0.4]	0.893	0.1	[-0.2 to 0.5]	0.483	0.1	[-0.4 to 0.6]	0.669	
E/e'-ratio	11.2	[10.4 to 12.0]	0.0	[-1.6 to 1.6]	0.972	0.9	[-0.7 to 2.5]	0.273	0.0	[-1.2 to 1.2]	0.991	
E-wave deceleration time	266.0	[252.5 to 279.4]	1.7	[-15.1 to 18.5]	0.844	13.3	[-3.6 to 30.3]	0.122	11.7	[-9.7 to 33.1]	0.283	
A', cm/s	9.6	[9.2 to 10.0]	-0.3	[-0.8 to 0.2]	0.198	0.2	[-0.3 to 0.6]	0.481	0.5	[-0.2 to 1.1]	0.140	
S', cm/s	7.1	[6.8 to 7.4]	0.0	[-0.3 to 0.4]	0.760	0.2	[-0.1 to 0.5]	0.178	0.2	[-0.3 to 0.6]	0.427	
LA volume, mL	53.1	[49.7 to 56.4]	-2.1	[-5.2 to 1.1]	0.195	-4.4	[-7.6 to -1.3]	0.006	-2.3	[-6.6 to 1.9]	0.279	
<i>Right ventricular function</i>												
GLS, %*	-16.5	[-17.6 to -15.4]	1.4	[0.0 to 2.9]	0.048	-1.1	[-2.6 to 0.3]	0.130	-2.6	[-4.5 to -0.7]	0.008	
S', cm/s	12.0	[11.5 to 12.6]	-0.1	[-0.8 to 0.6]	0.845	0.1	[-0.7 to 0.8]	0.861	0.1	[-0.8 to 1.1]	0.771	
TAPSE, mm/s	22.5	[21.7 to 23.4]	-0.4	[-1.6 to 0.8]	0.537	0.3	[-0.9 to 1.5]	0.583	0.7	[-0.9 to 2.3]	0.379	

Complete case analysis regarding effects of treatment on all reported endpoints. The analyses are performed using a constrained linear mixed model. Abbreviations: LVMi, left ventricular mass indexed to body surface area; IVSD, intraventricular septal diameter at end-diastole; LVID, left ventricular internal diameter at end-diastole; LVPW, left ventricular posterior wall diameter at end-diastole; GLS, global longitudinal strain; EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; LA, left atrial volume; TAPSE, tricuspid annular plane systolic excursion.

Supplementary table 4: Testing for effect medication of prescribed medication on diastolic function and left ventricular mass

	Treatment	Prescribed	P-value	Not prescribed	P-value	Interaction
LAI, mL/m ²	ACE-i	1.4 [-2.5 to 5.2]	0.485	-2.0 [-4.4 to 0.3]	0.094	0.142
	ARB	-2.3 [-5.1 to 0.5]	0.111	0.1 [-2.8 to 2.9]	0.953	0.248
	Beta-blockade	-3.1 [-6.4 to 0.2]	0.064	0.1 [-2.5 to 2.6]	0.965	0.132
E/e', %	ACE-i	1.0 [-1.3 to 3.2]	0.385	-0.4 [-1.8 to 1.0]	0.561	0.296
	ARB	0.1 [-1.6 to 1.8]	0.900	-0.1 [-1.8 to 1.6]	0.889	0.851
	Beta-blockade	0.6 [-1.3 to 2.6]	0.521	-0.4 [-1.9 to 1.1]	0.620	0.418
LVMi, g/m ²	ACE-i	-6.0 [-18.1 to 6.2]	0.332	-2.9 [-10.6 to 4.8]	0.455	0.676
	ARB	-5.7 [-14.9 to 3.5]	0.221	-1.7 [-10.9 to 7.5]	0.713	0.541
	Beta-blockade	-1.8 [-12.6 to 9.0]	0.742	-4.6 [-12.6 to 3.4]	0.254	0.677

Treatment effects of the primary focus are tested for the presence of effect modification of concurrent therapy prescribed at baseline, first according to the presence or absence and finally a formal test of interaction. The analyses are performed using a modified constrained linear mixed model expanded the primary analysis to include the fixed effects: ‘*time-prescribed interaction*’ and ‘*time-prescribed-treatment interaction*’. Abbreviations: LAi, left atrial volume indexed to body surface area; LVMi, left ventricular mass indexed to body surface area; ACE-i, angiotensin converting enzyme; ARB, angiotensin receptor blocker.