

Supplementary Material

Supplementary Table 1. HOMAGE trial inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<p>1. Ability to provide written informed consent prior to any study procedure</p> <p>2. Age >65years (<i>modified to >60 years during the trial</i>)</p> <p>3. Clinical risk factors for developing heart failure, either:</p> <p>A. Coronary artery disease (h/o myocardial infarction, angioplasty or coronary artery bypass)</p> <p style="text-align: center;"><u>Or</u></p> <p>B. At least two of the following:</p> <ul style="list-style-type: none"> • Diabetes Mellitus requiring Hypoglycaemic Pharmacotherapy • Receiving pharmacological treatment for Hypertension • Microalbuminuria • Abnormal ECG (left ventricular hypertrophy, QRS >120msec, abnormal Q-waves) <p>4. Biological risk: NT-pro-BNP values between 125 and 1,000 ng/L or BNP values between 35 and 280 pg/mL</p>	<p>1. Recent wound healing/inflammation:</p> <ul style="list-style-type: none"> • Surgical procedure, coronary, cerebral or peripheral vascular events or infection in the prior 3 months • Cancer (life limiting or less than 2 years in remission) • Autoimmune disease • Hepatic Disease <p>2. Pre-existing diagnosis of clinical HF</p> <p>3. Moderate/severe LV systolic ventricular dysfunction, i.e. LVEF <45%</p> <p>4. Moderate or severe valve disease (investigators opinion)</p> <p>5. Corrected eGFR < 30ml/min/1.73m², using the MDRD four-variable equation</p> <p>6. Serum potassium >5.0 mmol/L and serum sodium <125 mmol/L</p> <p>7. Treatment with an MRA or a loop diuretic (furosemide, bumetanide, ethacrynic acid or torasemide) in the previous three months</p> <p>8. Potassium supplements or potassium-sparing diuretic at time of enrolment.</p> <p>9. Atrial fibrillation within one month prior to inclusion</p> <p>10. History of hypersensitivity to spironolactone or to any of its excipients</p> <p>11. Patients who require treatment with prohibited medications according to the summary of product characteristics with the exception of ACE inhibitors or angiotensin receptor blockers – although not their combination</p> <p>12. Patients unable to give written informed consent</p> <p>13. Participation in another interventional trial in the preceding month</p> <p>14. Ability to walk is, in the investigators opinion, clearly limited by joint disease or other locomotor problems or lung diseases rather than by cardiorespiratory fitness</p>

Supplementary Table 2. Spironolactone dose adaptations

Serum potassium (mmol/l)	Action	Dose adjustment
<4.5	Increase	25 mg OD to 50 mg OD 25 mg EOD to 25 mg OD
4.5 – 5.4	Maintain	No dose adjustment
5.5 – 5.9	Decrease	50 mg OD to 25 mg OD 25 mg OD to 25 mg EOD 25 mg EOD to withhold
≥ 6.0	Withhold	N/A

Legend: EOD: Every Other Day; OD: Once daily. After withholding spironolactone due to high serum potassium, it can be re-started at a dose of 25 mg EOD when potassium levels have fallen below 4.5 mmol/L. Spironolactone must be discontinued if serum creatinine ≥ 220 $\mu\text{mol/L}$ (or eGFR ≤ 30 ml/min/1.73m²). Treatment may be restarted at the investigator's *discretion once serum* creatinine is < 220 $\mu\text{mol/L}$ and eGFR > 30 ml/min/1.73m².

Supplementary Table 3. Baseline characteristics of the screened and randomized patients

	Not Randomised		Randomised	
	N=350		N=527	
Centre				
Berlin	23	(6.6)	25	(4.7)
Cortona	29	(8.3)	120	(22.8)
Dublin	6	(1.7)	12	(2.3)
Glasgow	18	(5.1)	41	(7.8)
Hull	107	(30.6)	118	(22.4)
Maastricht	41	(11.7)	63	(12.0)
Manchester	20	(5.7)	36	(6.8)
Nancy	105	(30.0)	104	(19.7)
Toulouse / Corbeil	1	(0.3)	8	(1.5)
Demographics and Lifestyle				
Age-years	70.2	(66.9, 75.1)	72.9	(68.5, 78.5)
Women-N.(%)	70	(20.0)	135	(25.6)
Caucasian-N.(%)	346	(98.9)	518	(98.3)
Current smoker-N.(%)	39	(11.1)	44	(8.3)
Inclusion Criteria-N.(%)				
CAD	249	(71.1)	377	(71.5)
Diabetes	131	(37.4)	212	(40.2)
Hypertension	280	(80.0)	412	(78.2)
Microalbuminuria	79	(22.6)	108	(20.5)
Abnormal ECG	83	(23.7)	176	(33.4)
Medical History-N.(%)				
Hypertension	284	(81.1)	413	(78.4)
Diabetes mellitus	141	(40.3)	217	(41.2)
CAD	249	(71.1)	379	(71.9)
Angina	128	(36.6)	194	(36.8)
Positive coronary angiogram	124	(35.4)	222	(42.1)
Myocardial Infarction	136	(38.9)	214	(40.6)
PCI	176	(50.3)	265	(50.3)
CABG	72	(20.6)	136	(25.8)
Stroke/TIA	14	(4.0)	28	(5.3)
COPD	23	(6.6)	33	(6.3)
Cardiac device	12	(3.4)	22	(4.2)
Medications-N.(%)				
Thiazides	50	(14.3)	85	(16.1)
Beta Blocker	203	(58.0)	365	(69.3)
ACE Inhibitors	175	(50.0)	275	(52.2)
ARB	89	(25.4)	145	(27.5)
CCB	58	(16.6)	108	(20.5)
Statin/Lipid lowering drug	280	(80.0)	431	(81.8)
Anticoagulant	27	(7.7)	29	(5.5)
Aspirin	210	(60.0)	373	(70.8)

Antiplatelet (exc aspirin)	58	(16.6)	99	(18.8)
Clinical Assessment				
Visual Analogue Score (EQ5D)	80	(65, 90)	80	(70, 90)
Breathlessness on moderate exercise	3	(2, 6)	5	(2, 6)
Swollen ankles	0	(0, 1)	0	(0, 2)
Weight-kg	84.4	(74.8, 94.9)	82.0	(72.0, 91.6)
BMI-kg/msq	28.5	(26.2, 31.3)	28.1	(25.4, 31.6)
Systolic Blood Pressure-mmHg	141	(130, 153)	140	(128, 154)
140-159	121	(34.6)	175	(33.2)
160+	54	(15.4)	93	(17.6)
Diastolic Blood Pressure-mmHg	80	(74, 87)	78	(71, 85)
Heart Rate-bpm	64	(58, 71)	61	(55, 67)
ECG QRS-msec	94	(86, 104)	92	(84, 104)
Blood Results				
NT-pro BNP-ng/L	93	(49, 181)	214	(137, 356)
BNP-pg/mL	23	(15, 64)	68	(48, 111)
eGFR-MDRD-mL/min/1.73msq	76.8	(65.3, 90.7)	72.4	(61.6, 84.7)
<45	18	(5.1)	26	(4.9)
45-60	45	(12.9)	95	(18.0)
>60	277	(79.1)	405	(76.9)
Haemoglobin-g/dL	14.4	(13.4, 15.2)	14.0	(13.1, 14.9)
Sodium-mmol/L	139	(137, 141)	140	(138, 141)
Potassium-mmol/L	4.3	(4.0, 4.5)	4.3	(4.1, 4.6)
Creatinine-mg/dL	0.9	(0.8, 1.1)	1.0	(0.8, 1.1)

Supplementary Table 4

	Control	Spiro	P-value
All-Cause Mortality	2 (0.8)	2 (0.8)	1.00
CV Mortality	2 (0.8)	1 (0.4)	0.62
Heart Failure	6 (2.3)	4 (1.5)	0.54
Atrial Fibrillation	6 (2.3)	5 (1.9)	0.77
Stroke	0 (0.0)	2 (0.8)	0.50
Myocardial Infarction	0 (0.0)	0 (0.0)	1.00
Composite clinical endpoint*	11 (4.2)	9 (3.0)	0.50

* composite of CV death, AHF, AF, stroke. p-values from Fisher's exact test

Supplementary Figure 1

Distribution of duration of follow-up.

Nine months corresponds to approximately 275 days

