Early and late renal function changes with spironolactone in patients at risk of developing heart failure: findings from the HOMAGE trial

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Summary

Spironolactone reduces estimated glomerular filtration rate (eGFR) soon after initiating treatment, but mineralocorticoid receptor antagonists (MRA) may prevent longer-term decline in eGFR. We studied the effect of spironolactone (compared to usual care) on eGFR changes and its biomarker correlations in 527 people at risk of developing heart failure enrolled in the HOMAGE trial. eGFR was determined at baseline, one and nine months. Compared to usual care, spironolactone reduced eGFR from baseline to month one: -3 (-4 to -2) ml/min/1.73m^2, P <0.001 (corresponding to a -4% change on average). Spironolactone caused no further reduction in eGFR from month one to month nine: -1 (-3 to 0) ml/min/1.73m^2, P =0.085. eGFR decrease between baseline and one month was positively correlated with brain natriuretic peptide and kidney injury molecule 1. Thus, spironolactone induces a small, early eGFR decrease without evidence of renal tubular injury, suggesting an early hemodynamic effect.

Key-words: estimated glomerular filtration rate; tubular injury; spironolactone; heart failure risk.

Background

Mineralocorticoid receptor antagonists (MRA) induce hemodynamic changes that reduce estimated glomerular filtration rate (eGFR), which usually occurs early after treatment initiation and then stabilises and is generally of small magnitude, and not associated with a decrease of clinical benefit from MRA therapy.[1-3] However, clinicians may withhold or stop spironolactone (and other RAAS inhibitors) when eGFR decreases (even if transient), which may increase the risk of subsequent events.[4]

In the HOMAGE (Heart OMics in AGEing; NCT02556450) trial enrolling patients with risk factors for developing heart failure (HF), spironolactone (compared to usual care) reduced markers of collagen synthesis, blood pressure, natriuretic peptides, and improved cardiac structure and function, while decreasing eGFR by ~5 ml/min/1.73m^2 from baseline to month 9.[5]

The factors associated with early and late eGFR decrease and respective biomarker correlations have not been studied in this population.

Methods

The HOMAGE clinical trial was a prospective, randomized, open-label, blinded-endpoint (PROBE) study comparing spironolactone vs. usual care in people at increased risk of developing HF. The protocol and design of HOMAGE have been previously described.[6] In short, the main inclusion criteria were age greater than 60 years, plasma concentrations of natriuretic peptides above the normal range, coronary artery disease or at least two of the following: diabetes mellitus,

hypertension, microalbuminuria, or abnormal ECG. The key exclusion criteria were an eGFR <30 ml/min/1.73 m^2, serum potassium >5.0 mmol/L, left ventricular ejection fraction <45%, atrial fibrillation, a prior diagnosis of HF, or treatment with loop diuretics. After randomization, eGFR was assessed at one and nine months. Spironolactone was initiated at a dose of 25 mg/day. Doses could be increased up to 50 mg/day or reduced to 25 mg every other day or stopped with or without re-initiation according to serum potassium.[6,7] Furthermore, spironolactone had to be discontinued if eGFR fell to or below 30ml/min/1.73m^2. Treatment could be restarted at the investigator's discretion if eGFR rose above 30ml/min/1.73m^2.

Worsening renal function (WRF) >20% from baseline was a prespecified secondary outcome.

In this analysis, eGFR was determined using the CKD-EPI 2009 creatinine-based formula. The effect of spironolactone on early and late eGFR changes was assessed by analysis of covariance. Patients' characteristics were compared across tertiles of early and late eGFR changes. Associations between eGFR changes and changes in biomarkers of cardiac stretch (BNP, brain natriuretic peptide), tubular kidney injury (KIM1, kidney injury molecule-1), mineralocorticoid receptor blockade feedback (renin), and systolic blood pressure (SBP) were assessed with linear regression models. Analyses were performed using Stata® version 17.1 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC).

Results

Spironolactone effect on early and late eGFR changes

A total of 527 participants (265 spironolactone and 262 usual care) were included in the analysis. *Supplementary Table 1*. Compared to usual care, spironolactone decreased eGFR from baseline to month one: -3 (-4 to -2) ml/min/1.73m^2, P <0.001 (corresponding to a -4% change on average). This effect was similar in patients with baseline eGFR above or below 60 ml/min/1.73m^2, interactionP =0.63. On the other hand, spironolactone did not decrease eGFR between months one and nine: -1 (-3 to 0) ml/min/1.73m^2, P =0.085. No significant interaction was found by eGFR above or below 60 ml/min/1.73m^2 measured at one month, interactionP =0.11. *Figure 1*.

The proportion of patients with eGFR decrease ≥20% from baseline was small and not significantly different between spironolactone and usual care: any timepoint: spironolactone =36 (14.0%) vs. usual care =25 (9.9%), P =0.15; baseline to month one spironolactone =14 (5.5%) vs. usual care =6 (2.4%), P =0.074; month one to month nine, spironolactone =22 (8.9%) vs. usual care =19 (7.6%), P =0.60. The proportion of patients with eGFR drop ≥30% from baseline was also small and not significantly different between spironolactone and usual care: any timepoint: spironolactone =16 (6.2%) vs. usual care =8 (3.2%), P =0.10; baseline to month 1, spironolactone =5 (1.9%) vs. usual care =1 (0.4%), P =0.11; month 1 to month 9, spironolactone =11 (4.5%) vs. usual care =7 (2.8%), P =0.32.

Patient's characteristics across tertiles of eGFR change

Compared to patients in whom eGFR increased from baseline to month one, those in whom eGFR decreased had higher eGFR at baseline and were more often randomized to spironolactone (P <0.01 for both). *Supplementary Tables 2 & 3*.

Association between eGFR and circulating biomarker changes

eGFR decrease from baseline to month one was caused by spironolactone initiation (without differences in the usual care group) and these were negatively correlated (i.e., eGFR decrease/biomarker increase) with renin, and positively correlated (i.e., eGFR decrease/biomarker decrease) with BNP, KIM-1, and SBP ($P<0.01$ for all). No biomarker predicted the occurrence of WRF >20%.

Conclusion

This analysis shows that spironolactone exerted a small decrease in eGFR from baseline to month one, without a significant difference thereafter compared to a control group, suggesting that the eGFR decrease associated with spironolactone is caused by early hemodynamic changes without renal injury; findings that are furtherly supported by a positive correlation with BNP, KIM-1 and SBP decrease. *Graphical abstract*.

These findings expand those from RALES, EMPHASIS-HF and TOPCAT in patients with chronic HF with reduced or preserved ejection fraction, where steroid-based MRAs induced a mild eGFR decrease (from -2 to -4 ml/min/1.73m^2) that was apparent within weeks of treatment initiation, but thereafter participants assigned to MRA experienced eGFR trajectories similar to those observed with placebo in the following years. Together these data suggest that steroid-based MRAs cause an early eGFR decrease but do not accelerate long-term, age-related decline in renal function in patients at risk for or with chronic HF.

In HOMAGE the early eGFR decrease was negatively correlated with the increase in plasma renin concentration, which is occurs as a feedback mechanism to the blockade of the mineralocorticoid receptor by spironolactone.[8] The positive

correlation between eGFR decrease and BNP, KIM-1, and SBP supports the hypothesis that the early eGFR decrease after initiating spironolactone is hemodynamic in origin rather than reflecting structural renal damage or tubular injury.[9,10]

In summary, among patients at risk of developing heart failure enrolled in HOMAGE, spironolactone induced an early and mild eGFR decrease due to hemodynamic changes in the kidney, without evidence of tubular injury. After 1 month, changes in eGFR were similar between spironolactone and usual care.

Ethics approval and consent to participate

The study was approved by all relevant ethics committees and regulatory bodies. All participants provided written informed consent prior to study specific procedures.

Consent for publication

There is no data of individual persons included in the manuscript.

Competing interests

The authors have no relevant conflicts of interest to disclose regarding the content of this manuscript.

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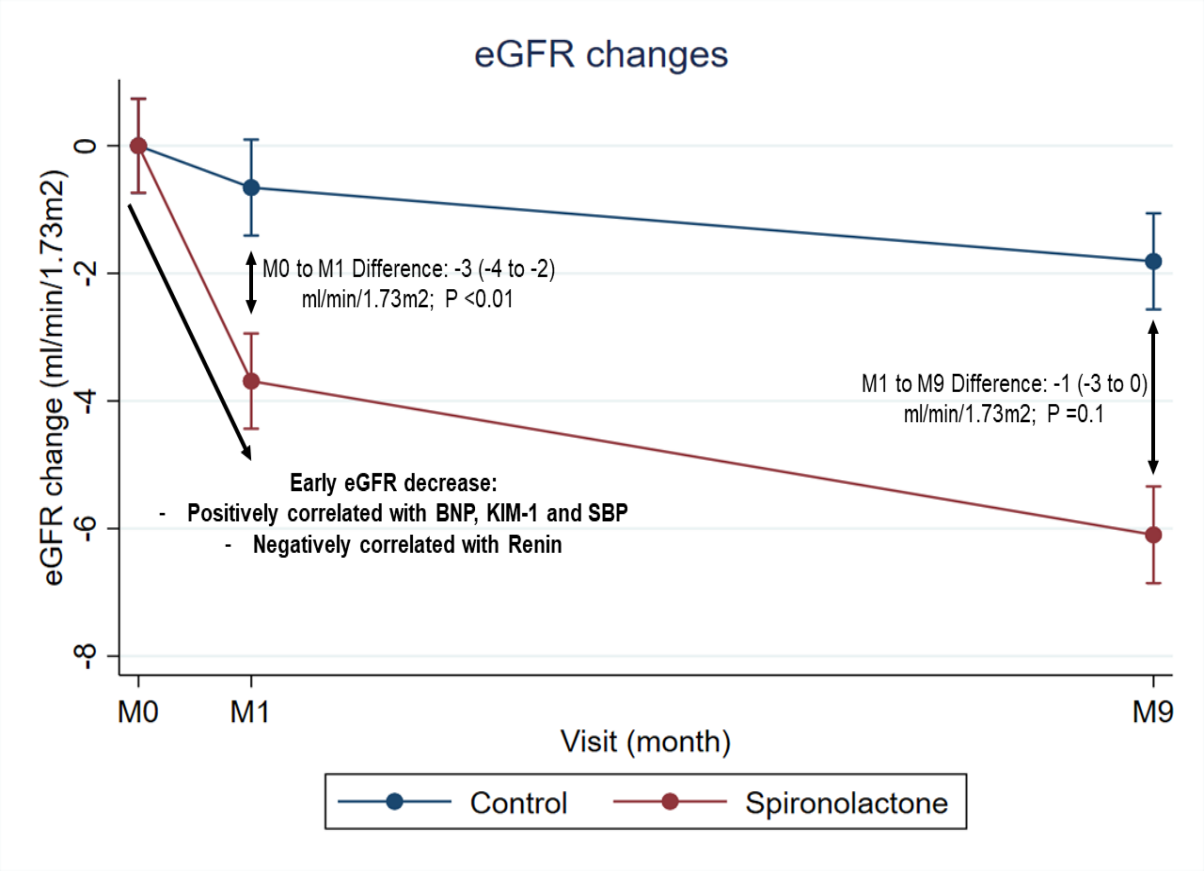
Renal Function in Patients With Acute Heart Failure Undergoing Aggressive Diuresis Is Not Associated With Tubular Injury. *Circulation*. 2018;137:2016-2028. doi: 10.1161/circulationaha.117.030112

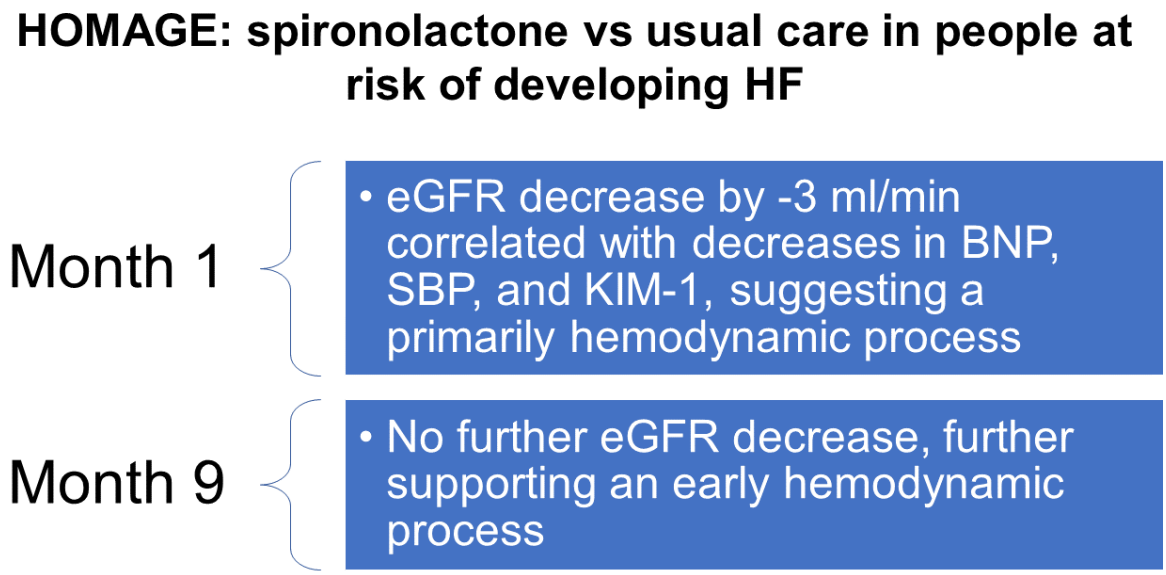
Figure 1. eGFR change from baseline to month 1 and month 1 to month 9 in spironolactone and usual care ("control") groups



Caption: Compared to usual care, spironolactone decreased eGFR from baseline to month 1 by -3 (-4 to -2) ml/min/1.73m^2, P <0.001; spironolactone did not significantly change eGFR from month 1 to month 9: -1 (-3 to 0) ml/min/1.73m^2, P =0.085. Early eGFR decrease with spironolactone was positively correlated with BNP (β =1.1 per Log_2 decrease), KIM-1 (β =2.3 per Log_2 decrease), and SBP (β =1.2 per 10 mmHg decrease), and negatively correlated with Renin (β =-2.5 per Log_2 increase); all P <0.01.

Legend: eGFR, estimated glomerular filtration rate; M0, month 0/baseline; M1, month 1; M9, month 9; BNP, brain natriuretic peptide; KIM-1, kidney injury molecule-1; SBP, systolic blood pressure.

Graphical abstract. Spironolactone induces an early hemodynamic eGFR decrease



Legend: eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; KIM-1, kidney injury molecule-1; SBP, systolic blood pressure.

Supplementary Table 1. Baseline characteristics

	Control		Spironolactone	
	N=262		N=265	
Demographics and Lifestyle				
Age-years	72.9	(68.4, 78.4)	72.9	(68.6, 78.5)
Female-N.(%)	75	(28.6)	60	(22.6)
Caucasian-N.(%)	260	(99.2)	258	(97.4)
Current smoker-N.(%)	20	(7.6)	24	(9.1)
Inclusion risk factors-N.(%)				
CAD	188	(71.8)	189	(71.3)
Diabetes	105	(40.1)	107	(40.4)
Hypertension	198	(75.6)	214	(80.8)
Microalbuminuria	53	(20.2)	55	(20.8)
Abnormal ECG	84	(32.1)	92	(34.7)
NT-pro BNP-pg/ml	209.0	(133.5, 339.5)	218.0	(138.0, 385.0)
BNP-pg/ml	65.0	(47.0, 108.0)	69.5	(48.0, 118.0)
Medical History-N.(%)				
Hypertension	199	(76.0)	214	(80.8)
Diabetes mellitus	109	(41.6)	110	(41.5)
CAD	190	(72.5)	190	(71.7)
Angina	97	(37.0)	98	(37.0)
Positive coronary angiogram	118	(45.0)	107	(40.4)
Myocardial Infarction	103	(39.3)	113	(42.6)
PCI	138	(52.7)	129	(48.7)
CABG	69	(26.3)	67	(25.3)
Stroke/TIA	13	(5.0)	15	(5.7)
COPD	13	(5.0)	21	(7.9)
Cardiac device	10	(3.8)	12	(4.5)
Medications-N.(%)				
Aspirin	181	(69.1)	195	(73.6)
Beta Blocker	180	(68.7)	186	(70.2)
Thiazides	41	(15.6)	46	(17.4)
ACEi	140	(53.4)	135	(50.9)
ARB	71	(27.1)	74	(27.9)
CCB	51	(19.5)	59	(22.3)
Statin/Lipid lowering drug	217	(82.8)	218	(82.3)
Anticoagulant	12	(4.6)	18	(6.8)
Antiplatelet (excl. aspirin)	51	(19.5)	48	(18.1)
Antiplatelet (incl. aspirin)	205	(78.2)	209	(78.9)
Anthropometrics				
Weight-kg	81.7	(71.0, 91.0)	82.0	(73.0, 92.3)
BMI-kg/msq	27.6	(25.3, 31.4) [1]	28.4	(25.4, 31.7) [1]
Vital Signs				

SBP-mmHg	140.0	(128.0, 155.0) [5]	140.0	(126.0, 155.0) [4]
<120	30	(11.5)	34	(12.8)
120-139	95	(36.3)	90	(34.0)
140-159	87	(33.2)	92	(34.7)
160+	45	(17.2)	45	(17.0)
DBP-mmHg	77.0	(71.0, 84.0) [5]	78.0	(71.0, 85.0) [4]
Heart Rate-bpm	61.0	(54.0, 67.0) [5]	60.0	(55.0, 67.0) [4]
ECHO results				
ECG QRS-msec	92.0	(84.0, 102.0) [0]	92.0	(84.0, 108.0) [2]
LVEF (%)	63.1	(56.5, 66.1) [75]	62.8	(58.5, 66.7) [88]
LVM (g/m^2)	94.7	(80.5, 113.5) [23]	94.5	(81.1, 110.9) [29]
LAV (ml/m^2)	31.4	(26.2, 37.2) [42]	30.4	(25.9, 35.3) [54]
E/e´ ratio (average)	9.4	(7.5, 11.8) [31]	9.2	(7.6, 11.3) [31]
E/A ratio	0.8	(0.7, 1.0) [17]	0.8	(0.7, 1.0) [15]
TAPSE-mm	22.4	(16.7, 26.6) [29]	21.7	(17.5, 26.2) [30]
MAPSE-mm	15.5	(13.5, 17.9) [19]	15.1	(13.1, 17.4) [19]
Blood Results				
eGFR-ml/min/1.73msq	71.6	(60.7, 81.0) [1]	73.4	(61.7, 87.5) [0]
<45	13	(5.0)	18	(6.8)
45-60	50	(19.1)	37	(14.0)
>60	199	(76.0)	210	(79.2)
Haemoglobin-g/dl	14.1	(13.2, 14.9) [0]	14.0	(13.1, 14.9) [2]
Creatinine-mg/dl	84.4	(74, 98) [1]	84.0	(71, 100) [0]
Sodium-mmol/l	139.0	(138.0, 141.0) [1]	140.0	(138.0, 141.0) [0]
Potassium-mmol/l	4.3	(4.1, 4.6) [4]	4.3	(4.0, 4.6) [1]
Urea-mmol/l	8.9	(5.8, 13.6)	8.5	(5.9, 14.6)

Numbers are frequency (percentage) or median (interquartile range).
[N] indicates missing values.
Legend: CAD, coronary artery disease; ECG, electrocardiogram; NT-pro BNP, N-terminal pro brain natriuretic peptide; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; LVEDV, left ventricular end-diastolic volume indexed to the body surface area; LVM, left ventricular mass indexed to the body surface area; LAV, left atrial volume indexed to the body surface area; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate calculated using MDRD formula; PICP, carboxy-terminal propeptide procollagen type I; PIIINP, procollagen type III N-terminal peptide; CITP, carboxy-terminal type-I telopeptide; MMP-1, matrix metalloproteinase-1; SQ, symptom questionnaire; QoL, quality of life.
*raw values ratio; **adjusted by molarity ratio.

Supplementary Table 2. Patient's characteristics across tertiles of eGFR change from baseline to month 1

Characteristic	**eGFR change tertiles in ml/min/1.73m²**			P-value
	Tertile 1: -8.1 (-11.8 to -5.8)	Tertile 2: -2.0 (-3.1 to -0.9)	Tertile 3: 3.2 (1.8 to 6.9)	
N.	170	170	170	
Age, years	73.6 (69.2, 79.2)	72.8 (68.5, 77.7)	72.0 (67.9, 78.5)	0.44
Men	122 (71.8%)	135 (79.4%)	126 (74.1%)	0.25
Current smoker	18 (10.6%)	17 (10.0%)	8 (4.7%)	0.06
CAD	114 (67.1%)	131 (77.1%)	124 (72.9%)	0.12
Angina	60 (52.6%)	67 (51.1%)	61 (49.2%)	0.87
MI	62 (54.4%)	71 (54.2%)	75 (60.5%)	0.53
PCI	84 (73.7%)	86 (65.6%)	89 (71.8%)	0.35
CABG	42 (36.8%)	47 (35.9%)	45 (36.3%)	0.99
Hypertension	138 (81.2%)	126 (74.1%)	134 (78.8%)	0.28
Diabetes	73 (42.9%)	68 (40.0%)	67 (39.4%)	0.78
Stroke	5 (2.9%)	12 (7.1%)	7 (4.1%)	0.18
Antiplatelet	131 (77.1%)	137 (80.6%)	130 (76.5%)	0.61
Beta-Blocker	118 (69.4%)	120 (70.6%)	117 (68.8%)	0.94
ACEi	84 (49.4%)	89 (52.4%)	92 (54.1%)	0.68
ARB	55 (32.4%)	35 (20.6%)	49 (28.8%)	0.05
CCB	40 (23.5%)	40 (23.5%)	28 (16.5%)	0.18
Thiazides	31 (18.2%)	22 (12.9%)	31 (18.2%)	0.32
Statin	138 (81.2%)	145 (85.3%)	137 (80.6%)	0.46
BMI, Kg/m^2	28.4 (25.5, 31.6)	27.8 (25.2, 31.6)	28.1 (25.4, 31.6)	0.71
SBP, mmHg	143.5 (128.0, 157.0)	140.0 (128.0, 154.0)	139.0 (128.0, 154.0)	0.12
DBP, mmHg	79.0 (72.0, 85.0)	78.0 (71.0, 84.0)	78.0 (70.0, 84.0)	0.55
Heart rate, bpm	61.0 (56.0, 68.0)	58.0 (53.0, 66.0)	63.0 (56.0, 67.0)	0.05
LVEF, %	63.3 (57.4, 67.1)	63.4 (59.2, 66.6)	62.8 (58.1, 65.8)	0.60
LVMi, g/m^2	94.2 (82.4, 108.2)	93.5 (78.2, 113.2)	96.0 (82.8, 115.5)	0.50
LAVi, ml/m^2	29.4 (24.8, 34.9)	30.0 (25.6, 35.6)	31.6 (26.3, 37.7)	0.19
eGFR, ml/min/1.73m^2	74.5 (64.5, 83.1)	78.9 (61.0, 89.1)	70.5 (59.9, 82.3)	0.007
Urea, mmol/l	9.3 (6.1, 14.6)	7.8 (5.3, 13.2)	8.9 (5.9, 14.6)	0.11
Hemoglobin, g/dL	13.9 (13.0, 14.9)	14.1 (13.1, 14.8)	14.0 (13.2, 15.2)	0.33
Sodium, mmol/l	140.0 (137.0, 141.0)	139.0 (138.0, 141.0)	140.0 (138.0, 141.0)	0.62
Potassium, mmol/l	4.3 (4.1, 4.6)	4.3 (4.0, 4.6)	4.3 (4.1, 4.6)	0.26
Spiro. rand.	105 (61.8%)	86 (50.6%)	66 (38.8%)	<0.001

Legend: CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass indexed; LAVi, left atrial volume indexed; eGFR, estimated glomerular filtration rate; Spiro. rand., randomization to spironolactone.

Supplementary Table 3. Patient's characteristics across tertiles of eGFR change from month 1 to month 9

Characteristic	**eGFR change tertiles in ml/min/1.73m^2**			P-value
	Tertile 1: -8.8 (-12.0 to -6.0)	Tertile 2: -1.0 (-2.5 to 0.0)	Tertile 3: 5.3 (3.1 to 8.2)	
N.	166	166	165	
Age, years	73.1 (69.1, 79.4)	71.7 (67.3, 77.5)	73.1 (69.0, 78.1)	0.15
Men	121 (72.9%)	127 (76.5%)	125 (75.8%)	0.72
Current smoker	14 (8.4%)	9 (5.4%)	17 (10.3%)	0.24
CAD	105 (63.3%)	130 (78.3%)	124 (75.2%)	0.005
Angina	52 (49.5%)	64 (49.2%)	68 (54.8%)	0.61
MI	59 (56.2%)	77 (59.2%)	66 (53.2%)	0.63
PCI	83 (79.0%)	85 (65.4%)	83 (66.9%)	0.051
CABG	33 (31.4%)	52 (40.0%)	47 (37.9%)	0.38
Hypertension	142 (85.5%)	119 (71.7%)	127 (77.0%)	0.009
Diabetes	74 (44.6%)	68 (41.0%)	61 (37.0%)	0.37
Stroke	5 (3.0%)	6 (3.6%)	11 (6.7%)	0.22
Antiplatelet	119 (71.7%)	136 (81.9%)	131 (79.4%)	0.066
Beta-Blocker	106 (63.9%)	122 (73.5%)	118 (71.5%)	0.13
ACEi	86 (51.8%)	79 (47.6%)	91 (55.2%)	0.39
ARB	55 (33.1%)	42 (25.3%)	41 (24.8%)	0.17
CCB	33 (19.9%)	34 (20.5%)	37 (22.4%)	0.84
Thiazides	33 (19.9%)	23 (13.9%)	26 (15.8%)	0.32
Statin	129 (77.7%)	147 (88.6%)	133 (80.6%)	0.028
BMI, Kg/m^2	28.5 (25.9, 32.2)	27.8 (25.0, 31.5)	27.7 (25.0, 30.7)	0.061
SBP, mmHg	142.0 (132.0, 157.0)	140.0 (126.5, 154.5)	138.0 (126.0, 154.0)	0.037
DBP, mmHg	79.0 (72.0, 86.0)	78.0 (71.0, 84.0)	78.0 (71.0, 85.0)	0.58
Heart rate, bpm	61.0 (55.0, 66.0)	62.0 (55.0, 67.0)	60.0 (55.0, 69.0)	1.00
LVEF, %	63.0 (58.0, 66.5)	62.5 (59.3, 66.2)	63.5 (57.5, 66.9)	0.83
LVMi, g/m^2	97.2 (84.9, 115.7)	94.8 (81.8, 111.2)	91.6 (77.3, 108.4)	0.068
LAVi, ml/m^2	31.4 (25.7, 41.3)	30.1 (25.4, 34.5)	29.7 (25.3, 35.2)	0.15
eGFR, ml/min/1.73m^2	74.3 (61.0, 83.5)	78.2 (62.8, 88.6)	71.6 (60.6, 80.6)	0.011
Urea, mmol/l	11.1 (6.1, 15.4)	7.7 (5.6, 12.5)	8.4 (5.8, 14.6)	0.008
Hemoglobin, g/dL	14.0 (13.0, 14.9)	14.0 (13.2, 14.6)	14.1 (13.1, 15.0)	0.50
Sodium, mmol/l	140.0 (138.0, 141.0)	139.0 (137.0, 141.0)	140.0 (138.0, 142.0)	0.018
Potassium, mmol/l	4.3 (4.1, 4.5)	4.3 (4.1, 4.5)	4.4 (4.2, 4.6)	0.067
Spiro. rand.	96 (57.8%)	74 (44.6%)	77 (46.7%)	0.034

Legend: CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass indexed; LAVi, left atrial volume indexed; eGFR, estimated glomerular filtration rate; Spiro. rand., randomization to spironolactone.