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ORIGINAL ARTICLE

Heart rate reactivity, recovery, and endurance of the incremental shuttle walk test in patients prone to heart failure

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Abstract

Aims Few randomized trials assessed the changes over time in the chronotropic heart rate (HR) reactivity (CHR), HR recovery (HRR) and exercise endurance (EE) in response to the incremental shuttle walk test (ISWT). We addressed this issue by analysing the open HOMAGE (Heart OMics in Aging) trial.

Methods In HOMAGE, 527 patients prone to heart failure were randomized to usual treatment with or without spironolactone (25–50 mg/day). The current sub-study included 113 controls and 114 patients assigned spironolactone (~70% on beta-blockers), who all completed the ISWT at baseline and at Months 1 and 9. Within-group changes over time (follow-up minus baseline) and between-group differences at each time point (spironolactone minus control) were analysed by repeated measures ANOVA, unadjusted or adjusted for sex, age and body mass index, and additionally for baseline for testing 1 and 9 month data.

Results Irrespective of randomization, the resting HR and CHR did not change from baseline to follow-up, with the exception of a small decrease in the HR immediately post-exercise (−3.11 b.p.m.) in controls at Month 9. In within-group analyses, HR decline over the 5 min post-exercise followed a slightly lower course at the 1 month visit in controls and at the 9 month visits in both groups, but not at the 1 month visit in the spironolactone group. Compared with baseline, EE increased by two to three shuttles at Months 1 and 9 in the spironolactone group but remained unchanged in the control group. In the between-group analyses, irrespective of adjustment, there were no HR differences at any time point from rest up to 5 min post-exercise or in EE. Subgroup analyses by sex or categorized by the medians of age, left ventricular ejection fraction or glomerular filtration rate were confirmatory. Combining baseline and Months 1 and 9 data in both treatment groups, the resting HR, CHR and HRR at 1 and 5 min averaged 61.5, 20.0, 9.07 and 13.8 b.p.m. and EE 48.3 shuttles.

Conclusions Spironolactone on top of usual treatment compared with usual treatment alone did not change resting HR, CHR, HRR and EE in response to ISWT. Beta-blockade might have concealed the effects of spironolactone. The current findings demonstrate that the ISWT, already used in a wide variety of pathological conditions, is a practical instrument to measure symptom-limited exercise capacity in patients prone to developing heart failure because of coronary heart disease.

Keywords heart failure; heart rate; incremental shuttle walk test; mineralocorticoid receptor antagonism; spironolactone

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The HOMAGE investigators are listed in Reference [28].

Introduction

The reliable assessment of exercise capacity provides important diagnostic and prognostic information in patients with cardiac[1] and pulmonary disease[2] and is also widely used to evaluate the efficacy of new therapies. Changes in heart rate (HR) and blood pressure provide important diagnostic and prognostic information.[3,4] Conventionally, symptom-limited, graded, bicycle or treadmill exercise tests are used to determine maximum exercise capacity.[5] This requires a substantial amount of equipment and is an unfamiliar type of exercise for many patients. The incremental shuttle walk test (ISWT) is an alternative symptom-limited test that requires little equipment and involves a more familiar type of exercise (walking), which has been used to assess the exercise capacity of patients with chronic heart failure (HF).[6] The ISWT is designed to provoke symptoms and assess maximum exercise capacity.[6,7] The 6 min walking test (6MWT) is designed to assess submaximal exercise capacity.[7]

The chronotropic HR reactivity (CHR) in response to exercise, the delayed HR recovery (HRR) after exercise or exercise endurance (EE) are independent predictors of a worse prognosis, cardiovascular endpoints, post-surgical complications and all-cause mortality in a variety of settings, including older adults,[8–10] patients with pulmonary arterial hypertension,[11–13] patients with obstructive[14–16] or interstitial[17,18] pulmonary disease, cancer patients undergoing lung[19,20] or abdominal[21] surgery, patients with a history of myocardial infarction,[7] HF[22–24] or chronic kidney disease[25] or patients referred for exercise testing.[26,27] However, few randomized trials assessed the changes over time in CHR, HRR and EE. To address the consistency of the results of exercise testing over time, we analysed CHR, HRR and EE in response to the ISWT in the HOMAGE (Heart OMics in Aging) trial, in which patients at risk of HF were randomized to usual treatment or spironolactone on top of usual treatment.[28] The trial design allowed for the assessment of between-group differences in addition to within-group changes over time and to evaluate the reproducibility of the ISWT results as validation in the absence of within-trial validation by state-of-the-art treadmill or bicycle tests.

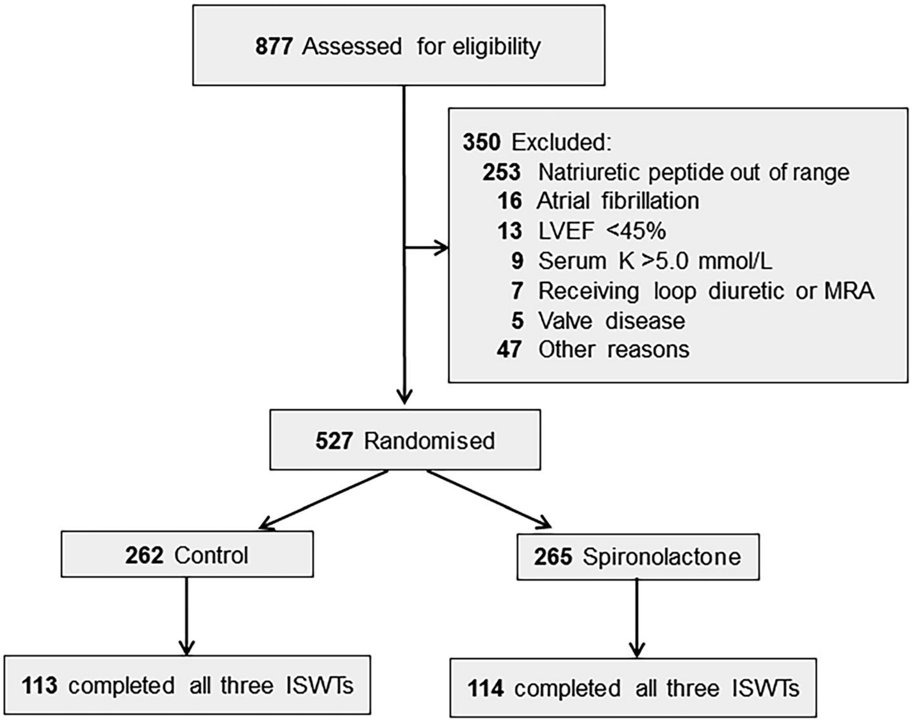
Methods

Study participants

HOMAGE is a multicentre open-label trial with blinded endpoint evaluation (Registration Number: NCT02556450),[28] conducted in nine centres in the United Kingdom, France, Italy, Ireland, Germany and the Netherlands. Each centre had its own recruitment strategies. The protocol was approved by the Greater Manchester Central Research Ethics Committee (Reference Number: 16/NW/0012; EudraCT Number: 2015-000413-48) as well as by each centre's local Ethics Committee. Patients of either sex, aged $\geq$60 years, were eligible provided that they were at increased risk of developing HF because they already had or were likely to develop coronary heart disease. Additionally, eligible patients had to have a plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) of 125–1000 ng/L or a plasma brain natriuretic peptide (BNP) of 35–280 ng/L. These ranges excluded patients at low HF risk as well as those with advanced disease requiring further investigation and treatment. The main exclusion criteria were an estimated glomerular filtration rate (eGFR)[29] of $<$30 mL/min/1.73 m^2, serum potassium of $>$5.0 mmol/L, left ventricular ejection fraction of $<$45%, atrial fibrillation, a diagnosis of HF prior to randomization and treatment with loop diuretics.

Of the 877 screened patients (Figure 1), 527 were randomized to spironolactone 25–50 mg/day (n = 265) on top of usual treatment or usual treatment alone (n = 262).[28] Of all patients randomized and followed up in the HOMAGE trial, 450/527 (85.4%), 324/516 (62.8%) and 400/506 (79.1%) completed the ISWT at baseline and at Months 1 and 9. The current analyses included 227 patients who completed the ISWTs at each of these three time points, the justification being that evaluating the same patients at each time point increases the comparability of the data over time. Of the 227 patients, 113 were randomized to control and 114 to spironolactone. NT-proBNP and high-sensitivity troponin T were assessed by electro-chemiluminescent assays (Roche Diagnostics).

Figure 1 Consort diagram showing patient disposition, including screening, randomization, follow-up and selection of patients for inclusion in the current analysis. All patients completed the incremental shuttle walk test (ISWT) at Months 0, 1 and 9. LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist.



Incremental shuttle walk test

Exercise capacity was measured by the ISWT.[6] Investigators were asked to conduct a familiarization test for each participant prior to the baseline assessment. As explained in detail in the supporting information, skilled personnel conducted the ISWT using a 10 m course (*the shuttle*) marked by two cones. The walking speed was determined by bleeps played from a compact disc. After every minute, walking speed increased. There are up to 12 levels of speed and, potentially, 102 shuttles. HR was measured at rest and immediately after the ISWT, and 1, 2, 3 and 5 min after completion of the ISWT. The test was performed at baseline and at Months 1 and 9. CHR was the difference between the HR immediately after the ISWT and the resting HR. Early and late HRR was the maximal HR immediately post-exercise minus the HR at 1 and 5 min post-exercise. An impaired HRR is the difference between the maximal and the 1 min HR of $<$12 b.p.m.[30] EE was assessed by the number of completed shuttles.

Statistical analysis

For database management and statistical analysis, SAS software, Version 9.4 (SAS Institute Inc., Cary, NC, USA), was used. For comparison of means, we used a paired or unpaired *t*-test, as appropriate, or a Wilcoxon–Mann–Whitney test depending on the distribution. Unpaired and pairwise comparisons of proportions were done by the χ^2-statistic and the McNemar test, respectively. The significance was a two-sided α level of $\leq$0.05. NT-proBNP was logarithmically transformed (base 10) to approximate the normal distribution.

The analyses focused on within-group changes over time (follow-up minus baseline) and on the between-group differences (spironolactone minus placebo) in CHR, HRR and EE. Changes in the ISWT-related variables from baseline to follow-up were given as signed differences and as percentage changes, using the baseline value as the denominator. The differences in the serial HR values during ISWT were implemented by repeated measures ANOVA with time point (within-group changes over time) or time point and treatment (between-group comparisons) as class variables and with the individual patient modelled as a random effect. In sensitivity analyses, the data were stratified by sex and the medians of age, left ventricular ejection fraction and eGFR. For the computation of the intraclass correlation coefficient (ICC), we used a published SAS macro.[31] ICC values of 0.5–0.6 indicate moderate, 0.7–0.8 strong and $>$0.8 perfect agreement between two ISWTs.[31]

Results

Patient characteristics

Descriptive data for the 227 analysed HOMAGE patients are shown in Table 1. No patients had a history of hospitalized HF prior to randomization. Most patients were receiving antihypertensive agents (*n* = 163; 71.8%), lipid-lowering drugs (*n* = 203; 89.4%), mainly statins (*n* = 197; 86.8%) and antiplatelet agents (*n* = 168; 74.0%), and 81 (35.7%) were on treatment with hypoglycaemic agents. Over time, there was no change in the use of antihypertensive drugs in either treatment group (Table S2). At any time during randomized follow-up, only 18 patients (7.93%) were on thiazide diuretics, but 159 (70.0%) were taking beta-blockers. The mean left ventricular ejection fraction was 62.8% (interquartile range: 59.3%–66.9%). At baseline and at the 1 and 9 month visits, 10 (4.41%), 6 (2.64%) and 12 (5.29%) patients used a walking aid: 10 (4.41%) only on one occasion, 6 (2.64%) twice and 2 (0.88%) at each test. Patients, randomized to control or spironolactone, were well balanced with regard to risk factors, clinical characteristics and routine biochemistry (Table 1). The 227 patients included in the present sub-study had broadly similar characteristics compared with the 300 HOMAGE patients not included (Table S1). However, the patients reported here were younger, had a higher eGFR, were less likely to smoke (5.73% vs. 10.3%; $P = 0.040$) but had a higher prevalence of ischaemic heart disease (79.3% vs. 66.3%; $P = 0.001$).

Changes over time on usual treatment

Over the first month (Table 2), the resting HR and the HR immediately post-exercise did not change ($P \geq 0.10$), but during the recovery period, the HR decline followed a lower course at Month 1 compared with baseline, reaching significance at 3 and 5 min ($P = 0.014$). The signed within-group changes (Month 1 minus baseline) in CHR and the early and late HRR were 0.08 ($P = 0.94$), 0.25 ($P = 0.77$) and 0.64 b.p.m. ($P = 0.52$), respectively (Table 3). From baseline to the last follow-up (Table 2), the resting HR did not change ($P = 0.55$), while HR decreased immediately and 2 and 5 min after exercise ($P \leq 0.037$). At last follow-up compared with baseline, the signed within-group changes (Month 9 minus baseline) in CHR and the early and late HRR were -2.51 ($P = 0.075$), -1.62 ($P = 0.24$) and -1.12 b.p.m. ($P = 0.37$), respectively (Table 3). The percentage of control patients with impaired HRR at baseline was 69.0%, and at the 1 and 9 month visits, it was 68.1% ($P > 0.99$) and 66.4% ($P = 0.72$). The mean number of completed shuttles on usual treatment was 48.5 at baseline and 48.3 and 49.0 at Months 1 and 9 (Table 2). None of the within-group changes in the number of completed shuttles reached significance ($P \geq 0.61$).

Changes over time on spironolactone

Over the first month (Table 4), the resting and the HRs immediately after exercise and during the HRR period up to 5 min

Table 1 Baseline characteristics of patients by trial arm.

Characteristic	Control	Spironolactone	*P*-value
Number with characteristic	113	114	
Women	26 (23.0)	23 (20.2)	0.60
Caucasian	112 (99.1)	109 (96.5)	0.50
Current smoking	8 (7.08)	5 (4.39)	0.56
Hypertension	84 (74.3)	87 (76.3)	0.73
Treated hypertension	81 (96.4)	82 (94.3)	0.97
Diabetes	45 (39.8)	42 (36.8)	0.64
Treated diabetes	40 (88.9)	41 (97.6)	0.93
History of coronary artery disease	90 (79.7)	90 (79.0)	0.90
History of myocardial infarction	46 (51.1)	47 (52.2)	0.88
Clinical characteristics			
Age (years)	72.4 ± 5.93	72.0 ± 6.16	0.61
BMI (kg/m^2)	28.7 ± 4.96	29.6 ± 5.42	0.18
Waist-to-hip ratio	0.97 ± 0.07	0.98 ± 0.07	0.15
Biochemistry			
Serum sodium (mmol/L)	139 (138–141)	138 (136–139)	0.40
Serum potassium (mmol/L)	4.3 (4.1–4.6)	4.5 (4.2–4.7)	0.42
eGFR (mL/min/1.73 m^2)	72 (61–82)	76 (61–89)	0.074
Plasma hsTnT (ng/L)	12.2 (8.7–17.4)	11.7 (8.4–15.0)	0.064
Plasma NT-proBNP (ng/L)	204 (118–289)	170 (120–331)	0.61

Note: Values are expressed as the arithmetic mean ± SD and median (interquartile range), and categorical variables are expressed as numbers and percentages.
Abbreviations: BMI, body mass index; eGFR, glomerular filtration rate estimated from serum creatinine according to the Chronic Kidney Disease Epidemiology equation; hsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 2 Changes over time in resting and post-exercise heart rate and walking distance in the control group.

Characteristic	Baseline	Follow-up	*P*-value	Differences		ICC (95% CI)
				Signed (95% CI)	Percentage (95% CI)	
Baseline vs. Month 1						
Resting HR, b.p.m.	62.1 ± 9.46	60.8 ± 9.10	0.10	−1.26 (−2.78 to 0.26)	−1.23 (−3.51 to 1.06)	0.61 (0.48 to 0.71)
Post-exercise HR						
Immediate, b.p.m.	83.1 ± 21.1	81.9 ± 20.2	0.33	−1.18 (−3.56 to 1.20)	0.15 (−3.04 to 3.34)	0.81 (0.73 to 0.86)
1 min, b.p.m.	73.7 ± 14.5	72.2 ± 14.8	0.16	−1.43 (−3.41 to 0.55)	−1.02 (−3.80 to 1.76)	0.74 (0.64 to 0.81)
2 min, b.p.m.	70.6 ± 12.5	69.1 ± 12.5	0.075	−1.55 (−3.26 to 0.16)	−1.46 (−3.91 to 0.99)	0.73 (0.63 to 0.81)
3 min, b.p.m.	69.6 ± 11.9	67.7 ± 11.6	0.014	−1.95 (−3.52 to −0.39)	−2.10 (−4.35 to 0.16)	0.73 (0.64 to 0.81)
5 min, b.p.m.	68.8 ± 11.2	67.0 ± 10.5	0.014	−1.81 (−3.24 to −0.38)	−1.95 (−4.02 to 0.11)	0.74 (0.65 to 0.82)
Shuttle number	48.5 ± 22.1	48.3 ± 22.2	0.83	−0.17 (−1.73 to 1.40)	2.57 (−2.57 to 7.71)	0.93 (0.90 to 0.95)
Baseline vs. Month 9						
Resting HR	62.1 ± 9.46	61.5 ± 11.4	0.55	−0.59 (−2.54 to 1.36)	−0.18 (−3.31 to 2.94)	0.50 (0.35 to 0.63)
Post-exercise HR						
Immediate	83.1 ± 21.1	80.0 ± 19.9	0.037	−3.11 (−6.02 to −0.19)	−1.72 (−5.26 to 1.82)	0.70 (0.60 to 0.78)
1 min	73.7 ± 14.5	72.2 ± 15.8	0.29	−1.49 (−4.28 to 1.31)	−0.34 (−4.85 to 4.16)	0.51 (0.36 to 0.64)
2 min	70.6 ± 12.5	68.5 ± 11.7	0.016	−2.18 (−3.94 to −0.42)	−2.15 (−4.65 to 0.35)	0.68 (0.57 to 0.77)
3 min	69.6 ± 11.9	68.0 ± 15.1	0.21	−1.59 (−4.11 to 0.92)	−1.39 (−5.07 to 2.29)	0.50 (0.35 to 0.63)
5 min	68.8 ± 11.2	66.8 ± 10.8	0.014	−1.99 (−3.55 to −0.42)	−2.12 (−4.40 to 0.17)	0.70 (0.59 to 0.78)
Shuttle number	48.5 ± 22.1	49.0 ± 22.5	0.61	0.49 (−1.42 to 2.39)	6.69 (−0.01 to 13.4)	0.90 (0.85 to 0.93)

Note: Baseline and follow-up values are means ± SD. Signed differences (follow-up minus baseline) are means given with a 95% confidence interval (CI). The percentage difference was obtained by dividing the signed difference by the baseline value and multiplying the quotient by 100.
Abbreviations: HR, heart rate; ICC, intraclass correlation coefficient.

Table 3 Changes over time in the chronotropic heart rate reactivity and recovery in response to exercise.

Characteristic	Baseline	Follow-up	*P*-value	Differences		ICC (95% CI)
				Signed (95% CI)	Percentage (95% CI)	
Control group						
Baseline vs. 1 month						
CHR, b.p.m.	21.1 ± 19.8	21.1 ± 19.3	0.94	0.08 (−1.88 to 2.04)	−13.5 (−57.0 to 29.9)	0.86 (0.80 to 0.90)
HRR vs. maximal HR						
1 min, b.p.m.	9.46 ± 11.4	9.72 ± 10.6	0.77	0.25 (−1.43 to 1.93)	15.9 (−27.6 to 59.4)	0.67 (0.55 to 0.76)
5 min, b.p.m.	14.3 ± 14.8	15.0 ± 14.1	0.52	0.64 (−1.33 to 2.61)	9.60 (−57.4 to 76.6)	0.73 (0.64 to 0.81)
Impaired HRR, *n* (%)	78 (69.0)	77 (68.1)	>0.99	0.88 (−7.15 to 8.92)	…	…
Baseline vs. 9 months						
CHR, b.p.m.	21.1 ± 19.8	18.5 ± 20.0	0.075	−2.51 (−5.28 to 0.25)	−14.1 (−50.5 to 22.4)	0.72 (0.62 to 0.80)
HRR vs. maximal HR						
1 min, b.p.m.	9.46 ± 11.4	7.84 ± 16.2	0.24	−1.62 (−4.33 to 1.09)	37.0 (−11.5 to 85.5)	0.46 (0.30 to 0.59)
5 min, b.p.m.	14.3 ± 14.8	13.2 ± 14.8	0.37	−1.12 (−3.59 to 1.35)	42.4 (−12.4 to 97.2)	0.60 (0.47 to 0.70)
Impaired HRR, *n* (%)	78 (69.0)	75 (66.4)	0.72	2.65 (−7.87 to 13.2)	…	…
Spironolactone group						
Baseline vs. 1 month						
CHR, b.p.m.	19.2 ± 18.9	20.4 ± 19.2	0.34	1.22 (−1.31 to 3.75)	−15.3 (−51.7 to 21.1)	0.74 (0.65 to 0.82)
HRR vs. maximal HR						
1 min, b.p.m.	8.64 ± 10.5	8.82 ± 10.1	0.87	0.17 (−1.88 to 2.23)	−53.6 (−109.8 to 2.58)	0.43 (0.27 to 0.56)
5 min, b.p.m.	13.2 ± 13.0	13.3 ± 14.2	0.91	0.13 (−2.05 to 2.32)	−57.5 (−112.4 to −2.50)	0.63 (0.50 to 0.73)
Impaired HRR, *n* (%)	75 (65.8)	76 (66.7)	>0.99	−0.88 (−12.5 to 10.7)	…	…
Baseline vs. 9 months						
CHR, b.p.m.	19.2 ± 18.9	19.5 ± 19.3	0.84	0.30 (−2.72 to 3.31)	9.29 (−39.2 to 57.8)	0.64 (0.52 to 0.74)
HRR vs. maximal HR						
1 min, b.p.m.	8.64 ± 10.5	9.95 ± 10.4	0.24	1.31 (−0.89 to 3.50)	−21.9 (−92.2 to 48.3)	0.35 (0.18 to 0.50)
5 min, b.p.m.	13.2 ± 13.0	14.0 ± 14.0	0.55	0.76 (−1.74 to 3.26)	−30.2 (−91.4 to 30.9)	0.50 (0.36 to 0.63)
Impaired HRR, *n* (%)	75 (65.8)	71 (62.3)	0.64	3.51 (−8.22 to 15.2)	…	…

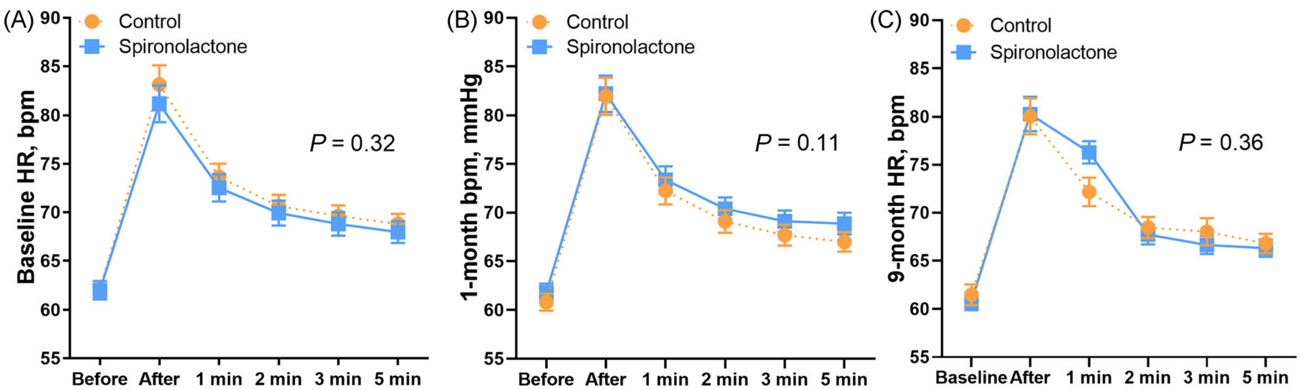
Note: Baseline and follow-up values are means ± SD. Signed differences (follow-up minus baseline) are means given with a 95% confidence interval (CI). The percentage difference was obtained by dividing the signed difference by the baseline value and multiplying the quotient by 100. An ellipsis indicates that it is not applicable. Chronotropic heart rate (HR) reactivity (CHR) is the difference between the maximal post-exercise HR and the resting HR. Early and late HR recovery (HRR) are the differences between the maximal HR and the HR at 1 and 5 min post-exercise. An impaired HRR is the difference of the maximal post-exercise HR and the 1 min HR of <12 b.p.m. ICC indicates the intraclass correlation coefficient.

Table 4 Changes over time in resting and post-exercise heart rate and walking distance in the spironolactone group.

Characteristic	Baseline	Follow-up	*P*-value	Differences		ICC (95% CI)
				Absolute (95% CI)	Percentage (95% CI)	
Baseline vs. Month 1						
Resting HR, b.p.m.	62.0 ± 9.79	61.8 ± 9.54	0.79	−0.19 (−1.59 to 1.21)	0.44 (−1.75 to 2.63)	0.70 (0.59 to 0.78)
Post-exercise HR						
Immediate, b.p.m.	81.2 ± 20.1	82.2 ± 20.0	0.45	1.03 (−1.68 to 3.74)	2.85 (−0.50 to 6.20)	0.74 (0.64 to 0.81)
1 min, b.p.m.	72.5 ± 15.0	73.4 ± 14.8	0.46	0.85 (−1.44 to 3.15)	2.51 (−0.35 to 5.37)	0.66 (0.54 to 0.75)
2 min, b.p.m.	69.9 ± 13.7	70.4 ± 12.5	0.59	0.48 (−1.29 to 2.25)	1.86 (−0.61 to 4.32)	0.74 (0.64 to 0.81)
3 min, b.p.m.	68.8 ± 12.8	69.1 ± 11.9	0.73	0.29 (−1.38 to 1.97)	1.44 (−0.86 to 3.73)	0.74 (0.64 to 0.81)
5 min, b.p.m.	68.0 ± 12.1	68.9 ± 12.0	0.32	0.90 (−0.87 to 2.66)	2.27 (−0.27 to 4.82)	0.69 (0.58 to 0.77)
Shuttle number	46.4 ± 21.7	48.3 ± 23.1	0.025	1.93 (0.25 to 3.61)	7.35 (1.53 to 13.2)	0.92 (0.88 to 0.94)
Baseline vs. Month 9						
Resting HR, b.p.m.	62.0 ± 9.79	60.8 ± 9.38	0.12	−1.20 (−2.71 to 0.31)	−1.09 (−3.41 to 1.23)	0.64 (0.51 to 0.73)
Post-exercise HR						
Immediate, b.p.m.	81.2 ± 20.1	80.3 ± 19.0	0.58	−0.90 (−4.12 to 2.32)	1.31 (−2.71 to 5.33)	0.61 (0.48 to 0.71)
1 min, b.p.m.	72.5 ± 15.0	70.3 ± 12.4	0.091	−2.21 (−4.78 to 0.36)	−0.89 (−4.29 to 2.50)	0.49 (0.33 to 0.61)
2 min, b.p.m.	69.9 ± 13.7	67.7 ± 11.1	0.042	−2.19 (−4.30 to −0.08)	−1.47 (−4.27 to 1.34)	0.57 (0.44 to 0.68)
3 min, b.p.m.	68.8 ± 12.8	66.6 ± 10.0	0.021	−2.17 (−4.00 to −0.34)	−1.68 (−4.19 to 0.82)	0.62 (0.49 to 0.72)
5 min, b.p.m.	68.0 ± 12.1	66.3 ± 9.69	0.076	−1.66 (−3.50 to 0.18)	−1.01 (−3.56 to 1.54)	0.59 (0.45 to 0.69)
Shuttle number	46.4 ± 21.7	49.3 ± 25.3	0.030	2.89 (0.28 to 5.50)	13.5 (3.89 to 23.2)	0.82 (0.75 to 0.87)

Note: Baseline and follow-up values are means ± SD. Differences (follow-up minus baseline) are means given with a 95% confidence interval (CI). The percentage difference was obtained by dividing the signed difference by the baseline value and multiplying the quotient by 100.
Abbreviations: HR, heart rate; ICC, intraclass correlation coefficient.

Figure 2 The pre- and post-exercise heart rate (HR) and heart recovery at 1, 2, 3 and 5 min after exercise at baseline and at Months 1 and 9. Data points are unadjusted means ± SE recorded at (A) baseline and at the (B) 1 and (C) 9 month visits. *P*-values for the between-group difference were computed by repeated measures ANOVA.



post-exercise did not change ($P \geq 0.32$). The signed within-group changes (1 month minus baseline) in CHR and in the early and late HRR were 1.22 ($P = 0.34$), 0.17 ($P = 0.87$) and 0.13 b.p.m. ($P = 0.91$), respectively (Table 3). At the last follow-up compared with baseline, the signed within-group changes (Month 9 minus baseline) in CHR and in the early and late HRR were 0.30 ($P = 0.84$), 1.31 ($P = 0.24$) and 0.76 b.p.m. ($P = 0.55$), respectively (Table 3). The percentage of patients assigned spironolactone with an impaired HRR at baseline was 65.8%, and at the 1 and 9 month visits, it was 66.7% ($P > 0.99$) and 62.3% ($P = 0.64$; Table 3). The number of completed shuttles averaged 46.4, 48.3 and 49.3 at baseline and at Months 1 and 9, respectively (Table 4). The within-group changes from baseline to the follow-up visits were significant ($P \leq 0.030$). The ICCs showed moderate to strong agreement between the baseline and the follow-up data, irrespective of treatment assignment (Tables 2–4).

Between-group differences

Figure 2 shows the time course of HR from rest to 5 min post-exercise. There were no significant between-group differ-

Table 5 Heart rate reactivity, recovery and exercise endurance by randomization group.

Variable	Control		Difference (95% confidence interval)			
	Control (n = 113)	Spironolactone (n = 114)	Unadjusted	P-value	Adjusted	P-value
CHR, b.p.m.						
Baseline	21.1 ± 19.8	19.2 ± 18.9	−1.86 (−6.93 to 3.21)	0.47	−2.03 (−6.87 to 2.82)	0.41
Month 1	21.1 ± 19.3	20.4 ± 19.2	−0.72 (−5.76 to 4.32)	0.78	0.58 (−2.44 to 3.59)	0.71
Month 9	18.5 ± 20.0	19.5 ± 19.3	0.95 (−4.19 to 6.10)	0.72	2.11 (−1.67 to 5.90)	0.27
Early HRR, b.p.m.						
Baseline	9.46 ± 11.4	8.64 ± 10.5	−0.82 (−3.68 to 2.05)	0.57	−0.84 (−3.64 to 1.97)	0.56
Month 1	9.72 ± 10.6	8.82 ± 10.1	−0.89 (−3.61 to 1.81)	0.51	−0.45 (−2.73 to 1.83)	0.70
Month 9	7.84 ± 16.2	9.95 ± 10.4	2.11 (−1.45 to −5.67)	0.24	2.51 (−0.71 to 5.73)	0.13
Late HRR, b.p.m.						
Baseline	14.3 ± 14.8	13.2 ± 13.0	−1.12 (−4.76 to 2.52)	0.55	−1.13 (−4.69 to 2.43)	0.53
Month 1	15.0 ± 14.1	13.3 ± 14.2	−1.62 (−5.32 to 2.08)	0.39	−0.85 (−3.58 to 1.88)	0.54
Month 9	13.2 ± 14.8	14.0 ± 14.0	0.76 (−3.01 to 4.53)	0.69	1.24 (−1.92 to 4.41)	0.44
EE, n						
Baseline	48.5 ± 22.1	46.4 ± 21.7	−2.11 (−7.84 to 3.63)	0.47	−1.93 (−6.88 to 3.02)	0.44
Month 1	48.3 ± 22.2	48.3 ± 23.1	−0.01 (−5.94 to 5.92)	>0.99	2.15 (−0.10 to 4.40)	0.061
Month 9	49.0 ± 22.5	49.3 ± 25.3	0.30 (−5.96 to 6.56)	0.93	2.49 (−0.75 to 5.74)	0.13

Note: Chronotropic heart rate (HR) reactivity (CHR) is the difference between the maximal HR immediately post-exercise and the resting HR. Early and late HR recovery (HRR) is the maximal HR immediately post-exercise minus the HR at 1 and 5 min post-exercise. Exercise endurance (EE) refers to the number of completed shuttles. Between-group differences (spironolactone minus control) were analysed by a two-factor (time and treatment) repeated measures ANOVA with the patients modelled as random effects. Models were adjusted for sex, age and body mass index, and additionally for baseline for testing 1 and 9 month data.

ences, irrespective of the time point in the trial ($P \geq 0.11$). Subgroup analyses stratified for sex (Figure S1) or median age (<71 vs. ≥71 years; Figure S2), left ventricular ejection fraction (<63% vs. ≥63%; Figure S3), eGFR (<73 vs. ≥73 mL/min/1.73 m^2; Figure S4) or use of beta-blockers (Figure S5) produced results similar to those shown in Figure 2 without significant subgroup-by-time point interactions ($P \geq 0.059$). However, at baseline, in women (Figure S1), age < 71 years (Figure S2) or eGFR < 73 mL/min/1.73 m^2 (Figure S4), HR followed a slightly higher course in the control group compared with the spironolactone group ($P \leq 0.033$). Unadjusted and adjusted analyses (Table 5) did not reveal any between-group differences at baseline or Months 1 and 9.

Discussion

The HOMAGE trial offered the opportunity to assess in patients randomized to usual treatment with or without spironolactone the within-group changes over time and the between-group differences in the ISWT-related key variables, that is, CHR, HRR and EE. In the within-group analyses, the main findings were as follows: First, irrespective of randomization, resting HR and CHR did not change from baseline to follow-up, with the exception of a small decrease in HR immediately post-exercise (−3.11 b.p.m.) in controls at Month 9. HR decline over the 5 min post-exercise followed a slightly lower course at the 1 month visit in control patients and at the 9 month visits in both groups, but not at the 1 month visit in the spironolactone group. Finally, compared with baseline, EE increased by two to three shuttles at Months 1 and 9 in the spironolactone group but remained unchanged in the control group. In unadjusted between-group analyses, there were no HR differences at any time point from rest up to 5 min post-exercise. In subgroups dichotomized by sex or the medians of age or eGFR, at baseline, HR followed a slightly higher course in the controls compared with patients assigned spironolactone. At the 9 month visit, this was still the case in women and participants aged <71 years, but the time point-by-subgroup interactions were not significant (P-values 0.40 and 0.059 for sex and age group, respectively).

Heart rate responses

Exercise increases sympathetic tone via circulating adrenaline and the neural release of noradrenaline. The initial HR decline within 30 s post-exercise is predominantly mediated by vagal reactivation, with sympathetic withdrawal playing a lesser role. However, starting from 2 min post-exercise, the decline in HR is mainly associated with sympathetic withdrawal.[30]

The literature does not provide a consistent definition of impaired post-exercise HRR.[30] The causes of the inconsistency are the variability in exercise protocols, varying ways to characterize HRR, the widely diverse characteristics of the examined individuals and differences in endpoint definitions and follow-up duration. As reviewed elsewhere,[30] across studies, the definition of a deficient HRR ranged from 12 to 30 b.p.m. at the first minute post-exercise and from 22 to 42 b.p.m. at the second minute. In the current study, we applied the most commonly applied definition, that is, a difference between the post-exercise HR and the 1 min post-exercise HR of <12 b.p.m. HOMAGE included patients

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likely to have or have coronary heart disease as a cause of subsequent HF.[28] Given the limited number of primary endpoints in the whole trial (control vs. spironolactone: n = 11 vs. 9; P = 0.50)[28] over the 9 month follow-up, the prediction of adverse health outcomes was not within the scope of the current subgroup analysis. However, multiple studies,[32–35] albeit not all,[36] using classic treadmill exercise protocols,[32,35] treadmill exercise with nuclear myocardial perfusion imaging[36] or treadmill echocardiographic exercise[33,36] demonstrated the accuracy of an impaired HRR in the prediction of mortality[32,33,36] or in the association of HRR with coronary heart disease[34,35] or high-risk features on myocardial perfusion imaging[34] over and beyond other risk indicators.

Reproducibility or repeatability refers to the probability of getting the same results when a variable is measured under similar conditions by different methods, by different observers applying the same method or after a short interval that does not include biological or pharmacologically induced variability. In our current study, we did not assess reproducibility in the proper sense of the word, but rather within-group changes over time and the between-group differences in these changes. However, two studies described HRR reproducibility.[37,38] In a retrospective study of 90 patients undergoing treadmill exercise testing twice at an interval of 18 weeks or less, none of the abnormal HRR definitions provided more than 55% concordance between tests.[37] However, a second study applying the same treadmill protocol demonstrated that resting HR (ICC = 0.92), CHR (ICC = 0.88) and HRR measured from 1 to 5 min post-exercise are reproducible in healthy adults when tests are repeated after 1 week and 1 month.[38] Our 1 month observations are in line with the second study referred to above,[38] and the ICC at Month 9 still indicates moderate (ICC = 0.5–0.6) or strong (ICC = 0.7–0.8) reproducibility, thereby providing a surrogate validation of the ISWT in the absence of state-of-the-art validation by treadmill or bicycle exercise tests. Given that there were no or only minimal within- or between-group differences in CHR and HRR, our current study extends the above observations to 9 months in patients with underlying coronary heart disease who are therefore prone to HF.

Exercise endurance

An assessment of exercise capacity is widely used to grade the severity of chronic HF. Until recently, the 6MWT, a measure of submaximal EE, has most frequently been used for the assessment of interventions in HF patients,[39] but results have often been disappointing.[40] The ISWT is designed to provoke symptoms, such as breathlessness, and assess maximum symptom-limited exercise capacity.[7,41] In a systematic review including 13 studies in patients with chronic lung disease and 8 in patients with cardiac disease,[42] the correlations between distance covered in the ISWT and peak oxygen consumption ranged from 0.67 to 0.95 ($P < 0.01$). The ICCs for test–retest reliability ranged from 0.76 to 0.99. Moreover, the ISWT was responsive to interventions including pulmonary rehabilitation and bronchodilator administration. The minimum clinically important difference in the distance covered in patients with lung disease was approximately 48 m.[42,43] For cardiac rehabilitation, the minimum clinically important difference was 70 m, but smaller estimates may apply for those with comorbid lung disease (39 m), obesity (29 m) or depression (52 m).[42,43]

In the current study, the ISWT improved with spironolactone at 9 months (P = 0.030), but in between-group analyses, significance was lost, irrespective of adjustment. The ISWT was used as the primary endpoint in a single-centre trial including 76 men comparing testosterone substitution to placebo over 12 months. Testosterone improved ISWT by 25 m (P = 0.006) as well as symptoms.[44] EE did not improve with spironolactone compared with placebo in older people with reduced functional status.[45] The Aldosterone Receptor Blockade in Diastolic Heart Failure Trial (ALDO-DHF) also failed to show an improvement in bicycle exercise capacity with spironolactone compared with placebo in a population similar to HOMAGE.[46] However, another placebo-controlled trial suggested an improvement in treadmill exercise capacity with spironolactone.[47] By and large, the small effects of spironolactone on the ISWT responses in HOMAGE are fairly consistent with the majority of trials of mineralocorticoid receptor antagonists in patients with cardiovascular disease.

Study limitations

This study has several limitations. First, we excluded patients who did not complete the three ISWTs, that is, at baseline and at Months 1 and 9. The rationale for this decision was the primary focus of our analyses of the change over time in CHR, HRR and EE. Not having the same patients at each time interval during the course of the trial would have precluded direct comparisons between the short- and long-term within- and between-group changes in these variables. Second, approximately 70% of patients were on treatment with beta-blockers, which have a negative chronotropic effect on the resting HR and the HR responses to exercise.[48,49] Beta-blockade might have masked potential changes in CHR, HRR or EE produced by spironolactone. Third, women were underrepresented in our study, as in many other trials. Few patients had musculoskeletal dysfunction requiring the use of a walking aid during the ISWT. These observations limit the generalizability of the current findings. Fourth, the HOMAGE trial protocol did not include a comparison of the exercise responses to ISWT with state-of-the-art endurance tests

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by bicycle or treadmill exercise.[5] Finally, given the relatively small sample size and the short follow-up, we could not relate the ISWT results to clinical events. However, as reviewed in detail above,[32–35] a multitude of studies showed that HRR and EE predict mortality and cardiovascular endpoints.

Conclusions

Spironolactone on top of usual treatment compared with usual treatment alone does not change resting HR, CHR, HRR or EE in response to the ISWT. Beta-blockade might have concealed the effects of spironolactone. However, the current findings demonstrate that the ISWT, already used in a variety of pathological conditions ranging from apparently healthy individuals[8,9] to patients with advanced pulmonary,[11–18] malignant,[19–21] cardiovascular[7,22–24] or renal[25] disease, is a practical instrument to measure symptom-limited exercise capacity in patients with comorbidities, such as coronary heart disease. In these patients, ISWT might replace the more complex state-of-the-art symptom-limited bicycle or treadmill exercise tests when such diagnostic resources are not readily available or when complex exercise testing is not indicated or difficult to repeat at short time intervals.

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Conflict of interest statement

None of the authors reported a conflict of interest.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics of included and excluded patients.
Table S2. Antihypertensive drug treatment at months 1 and 9 by treatment group.
Figure S1. The pre-and post-exercise heart rate and heart recovery at baseline and month 9 categorised by sex.
Figure S2. The pre-and post-exercise heart rate and heart recovery at baseline and month 9 categorised by median age.
Figure S3. The pre-and post-exercise heart rate and heart recovery at baseline and month 9 categorised by median left ventricular ejection fraction.
Figure S4. The pre-and post-exercise heart rate and heart recovery at baseline and month 9 categorised by median eGFR.
Figure S5. The pre-and post-exercise heart rate and heart recovery at months 1 and 9 categorised by the use vs non-use of β-blockers.

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Data Supplement

Heart rate reactivity, recovery, and endurance of the incremental shuttle walk test in patient prone to heart failure

Wei FF, Mariottoni B, An DW, Pellicori P, Yu YL, Verdonschot JAJ, Liu C, Ahmed FZ, Petutschnigg J, Rossignol P, Heymans S, Cuthbert J, Girerd N, Li Y, Clark AL, Nawrot TS, Ferreira JP, Zannad F, Cleland JGF, Staessen JA, on behalf of the HOMAGE investigators

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Protocol of the ISWT

Introduction

Exercise requires more oxygen to be delivered to skeletal muscles. This is achieved by an increase in heart rate and stroke volume, resulting in greater cardiac output, a redistribution of blood flow from other vascular beds, an increase in oxygen uptake achieved by faster respiratory rate, higher pulmonary blood flow and ventilation. The incremental shuttle walk-test (ISWT) is designed to provoke symptoms and assess maximum exercise capacity. The 6-minute walking test (6MWT) is often a longer test better designed to assess sub-maximal exercise capacity. The ISWT is a better method for grading the cardiorespiratory performance and to engage in physical effort. The symptoms and signs of heart failure are often only manifest during exercise. Many patients with cardiac dysfunction avoid provoking symptoms by reducing or avoiding physical exertion. Some form of exercise testing should be a routine part of the assessment of any person with, or at risk of developing, heart failure.

The ISWT is a standardised externally-paced, progressive, incremental field walking test for patients comprising up to 12 levels and 102 shuttles. Patients walk around a 10-metre shuttle course marked by cones in time with a series of bleeps played from a CD. The ISWT is a valid and reproducible measure of exercise capacity in patients with chronic obstructive pulmonary disease. It produces a higher peak heart-rate and Borg dyspnoea score as well as a more graded cardiorespiratory response to exercise compared to the 6MWT. It is used as an outcome measure of exercise capacity in pulmonary rehabilitation but also to assess patients with heart failure.[1,2] Changes of 50-70 metres are considered clinically significant.[3] There is a learning effect. When using the ISWT as a trial endpoint, the patient should have at least one test prior to the baseline test.

Required equipment

The required equipment consists of two cones, two chairs, stopwatch, CD player with ISWT CD, typed ISWT instructions, typed instructions, and an assessment sheet.

Contraindications and precautions

Unstable angina or myocardial infarction during the previous month are absolute contra-indications for the ISWT, while a resting heart rate of more than 120 beats per minute and a systolic blood pressure of more than 180 mm Hg are relative contraindications. Patients with any of these findings should be referred to the physician ordering or supervising the test for individual clinical assessment and a decision about the conduct of the test. The results from a resting electrocardiogram done during the previous 6 months should also be reviewed before testing. Stable exertional angina is not an absolute contraindication for an ISWT, but patients with these symptoms should perform the test, after using their anti-angina medication and rescue nitrate medication should be readily available.

Testing should be performed in a location where a rapid, appropriate response to an emergency is possible. The appropriate location of the crash trolley should be determined by the assessor undertaking the test. At least one other person should be within earshot should an emergency arise. Oxygen must be available. If applicable, the patient's sublingual nitro-glycerine and or salbutamol, must also be accessible. A telephone or other means of calling help should be available. The person doing the test should have training in cardiopulmonary resuscitation and at least one other trained individual should be in the vicinity. The assessor should be completely familiar with the ISWT procedures and have had one or more practice runs before administering the test to a patient.

Before the test

The observer should clearly explain and demonstrate all procedures prior to testing and ensure the patient understands the instructions. If a patient is uncomfortable performing a test or if the observer feels that it is not safe for an individual to continue, the test should not be performed. The reason for not performing the test should be documented.

- If this is the patient's initial assessment, document the past-medical history.
- Identify and record if the patient will do the test using a walking aid.
- Measure blood pressure, heart-rate, resting oxygen saturations and Borg dyspnoea level.
- If at the initial assessment the patients resting oxygen saturations is less than 92% consider assessment for respiratory disease.
- Set-up the course: two cones placed 9 metres apart on flat, straight flooring with a chair 1 metre behind each cone (**figure**).
- Show the patient the course and play the standardised instructions on the CD player or read the typed standardised instructions to the patient.
- Ask the patient if she/he understands the instructions and answer any questions asked.
- Before the test starts remind the patient that "*this is a maximal test, by the end of the test you should walk or run as fast as you can*".

During the test

- Walk with the patient for the first level (3 shuttles) to ensure correct pacing.
- The standardised instructions should be administered as appropriate and the patient should not be encouraged. It is aal right to advise the patient to slow her/his walking speed to ensure a continuous walk.

- At each new level (triple bleep) instruct the patient "*to increase your speed now*".
- Record each completed shuttle
- If the patient is less than 0.5 metre from the cone do not say anything.
- If the patient is greater than 0.5 metre from the cone advise the patient that "*You're not going fast enough, try to make up the speed now*".

The test can be terminated by the patient

- The patient feels unable to keep up.
- Limiting symptoms may be breathlessness, fatigue, claudication, chest pain, dizziness or other reasons that concern the test supervisor.
- The person supervising the test is concerned about patient safety.
- The patient is greater than 2 metres from the cone two shuttles in a row, i.e., the observer has given the patient a chance to increase her/his speed, but she/he is still not within 2.0 meters of the cone.

After the test

- Sit the patient on a chair − if patient is able to walk to one of the chairs behind the cones or if the patient is unable to walk bring a chair to the patient.
- Immediately record heart and respiratory rate and Borg dyspnoea level.
- Immediately begin timing recovery for five minutes.
- Record completed shuttles only, excluding the last shuttle it was terminated because the patient was more than 2.0 metres from the cone.
- Record why the test was stopped.

Verbal instructions for the ISWT

- The object of the progressive shuttle walking test is to walk for as long as possible back and forth along the 10-metre course keeping to the speed indicated by the beeps on the CD. You will hear these beeps at regular intervals. You should walk at a steady pace aiming to turn around the cone at one end of the course when you hear the first beep and at the other end when you hear the next.

- At first your walking speed will be very slow but you will need to speed up at the end of each minute. Your aim should be to follow the set rhythm for as long as you can. Each single beep signals the end of a shuttle and each triple beep signals an increase in walking speed. You should stop walking only when you become too breathless to maintain the required speed or can no longer keep up with the set pace.
- The test is maximal and progressive, in other words, it is easier at the start and harder at the end. Your walking speed for the first minute is very slow and you have 20 seconds to complete each 10-metre shuttle, so do not go too fast.
- Level one starts with a triple beep after the 4 second count down.
- Note to the assessor: before you start the ISWT remind patient that *"this is a maximal test, by the end of the test you should walk or run as fast as you can".*

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Table S1 Baseline characteristics of included and excluded patients.

Characteristic	Included	Not included	*p*
Number with characteristics	227	300	
Women	49 (21.6)	86 (28.7)	0.065
Caucasian	221 (97.8)	298 (99.3)	0.35
Current smoking	13 (5.73)	31 (10.3)	0.040
Hypertension	171 (75.3)	242 (80.7)	0.14
Treated hypertension	163 (95.3)	226 (93.4)	0.36
Diabetes	87 (38.3)	130 (43.3)	0.25
Treated diabetes	81 (93.1)	107 (82.3)	0.99
Ischaemic heart disease	180 (79.3)	199 (66.3)	0.001
History of myocardial infarction	93 (51.7)	121 (60.5)	0.083
Clinical characteristics			
Age (years)	72.9±6.07	75.2±6.79	<0.001
BMI (kg/m^2)	29.2±5.20	28.7±4.91	0.26
Waist-to-hip ratio	0.98±0.07	0.98±0.06	0.73
Biochemistry			
Serum sodium (mmol/L)	138.8±2.72	139.7±2.74	<0.001
Serum potassium (mmol/L)	4.33±0.36	4.31±0.36	0.53
eGFR (mL/min/1.73 m^2)	73.1±16.3	68.8±15.5	0.002

Values are number of patients (%) or mean± SD. The glomerular filtration rate was derived from serum creatinine by the Chronic Kidney Disease Epidemiology Collaboration equation.

Table S2 Antihypertensive drug treatment at months 1 and 9 by treatment group

Variable	Controls			Spironolactone		
	Month 1	**Month 9**	***p***	**Month 1**	**Month 9**	***p***
Thiazides, %	7 (6.19)	7 (6.19)	>0.99	8 (7.02)	7 (6.14)	0.56
β-blockers, %	83 (73.4)	82 (72.6)	0.32	76 (66.7)	77 (67.5)	0.32
CCBs, %	4 (3.54)	5 (4.42)	0.56	1 (0.88)	2 (1.75)	0.32
ACEIs, %	54 (47.8)	54 (47.8)	>0.99	52 (45.6)	53 (46.5)	0.56
ARBs, %	36 (31.9)	35 (31.0)	0.56	34 (29.8)	31 (27.2)	0.18

Abbreviations: CCB, Calcium-channel blocker; ACEIs, angiotensin-converting enzyme inhibitors; and ARBs, angiotensin II type-1 receptor blockers. *p*-values were calculated by McNemar's test.

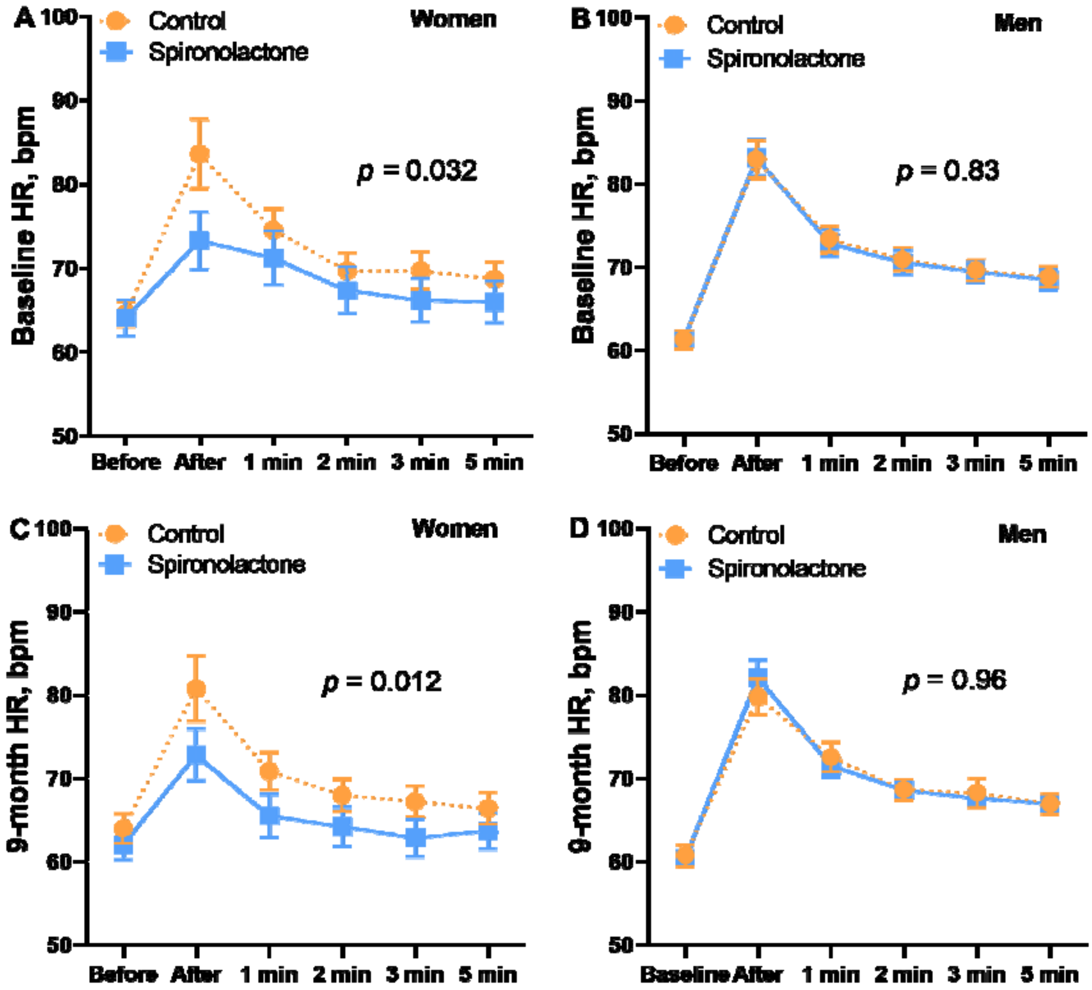

Figure S1

The pre-and post-exercise heart rate and heart recovery at 1, 2, 3 and 5 minutes after exercise at baseline and 9-months in women (A, C) and men (B, D).

Data points are unadjusted means ± SE. *p*-values for the between-group difference were computed by repeated measures ANOVA. The sex-by-time point interactions were not significant ($p \geq 0.40$).

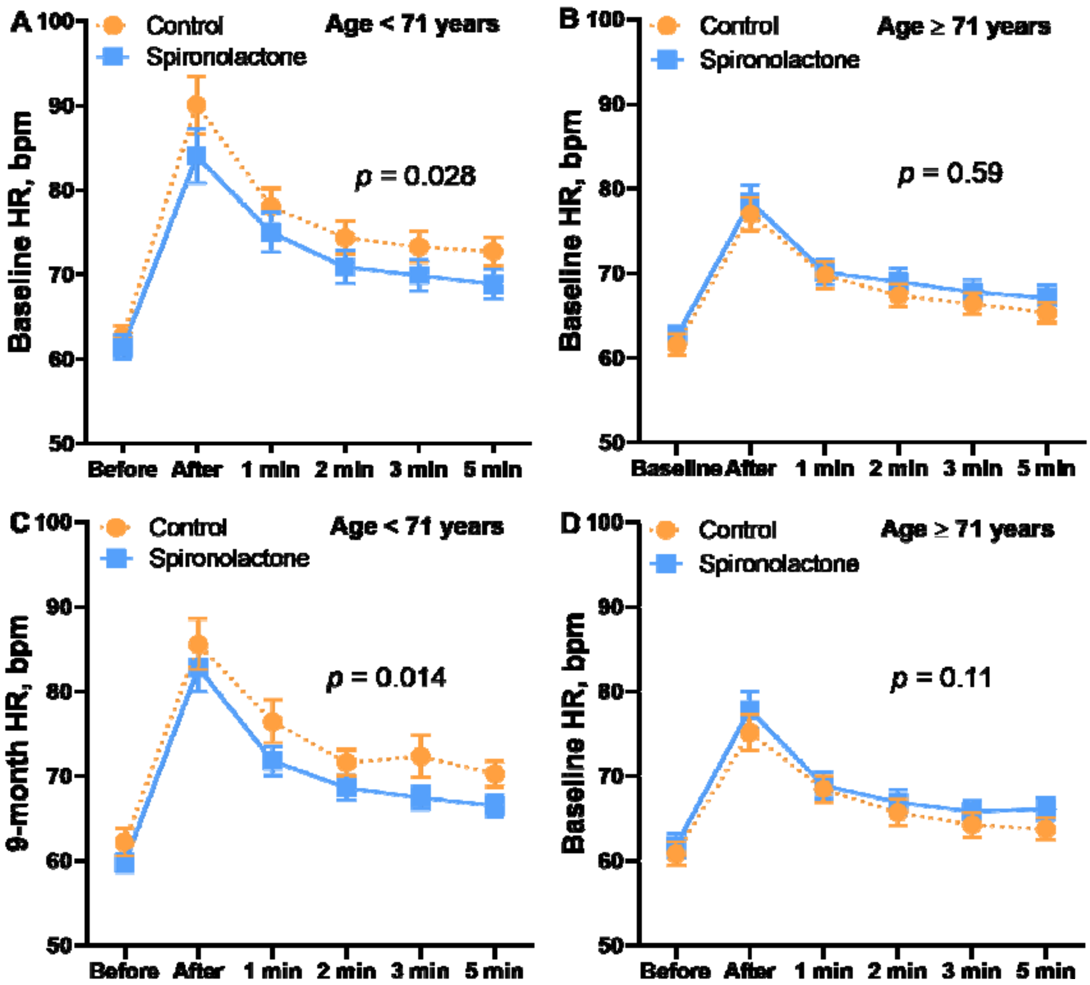

Figure S2

The pre-and post-exercise heart rate and heart recovery at 1, 2, 3 and 5 minutes after exercise at baseline and 9-months categorised by median age: < 71 years (A, C) *vs* ≥ 71 years (B, D).

Data points are unadjusted means ± SE. *p*-values for the between-group difference were computed by repeated measures ANOVA. The age-by-time point interactions were not significant ($p \geq 0.059$).

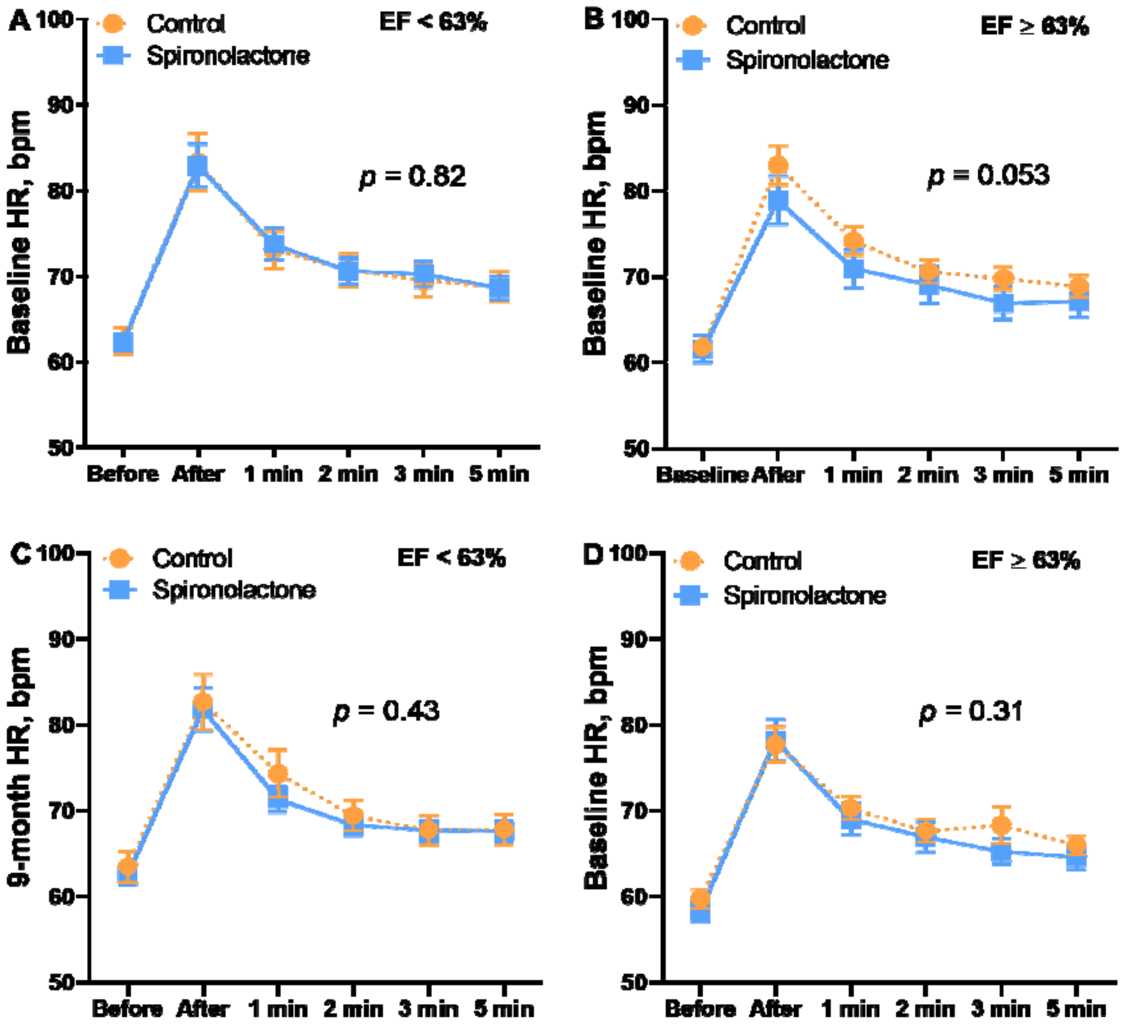

Figure S3

The pre-and post-exercise heart rate and heart recovery at 1, 2, 3 and 5 minutes after exercise at baseline and 9-months categorised by median left ventricular ejection fraction: < 63% (A, C) *vs* ≥ 63% (B, D).

Data points are unadjusted means ± SE. *p*-values for the between-group difference were computed by repeated measures ANOVA. The EF-by-time point interactions were not significant (*p* ≥ 0.22).

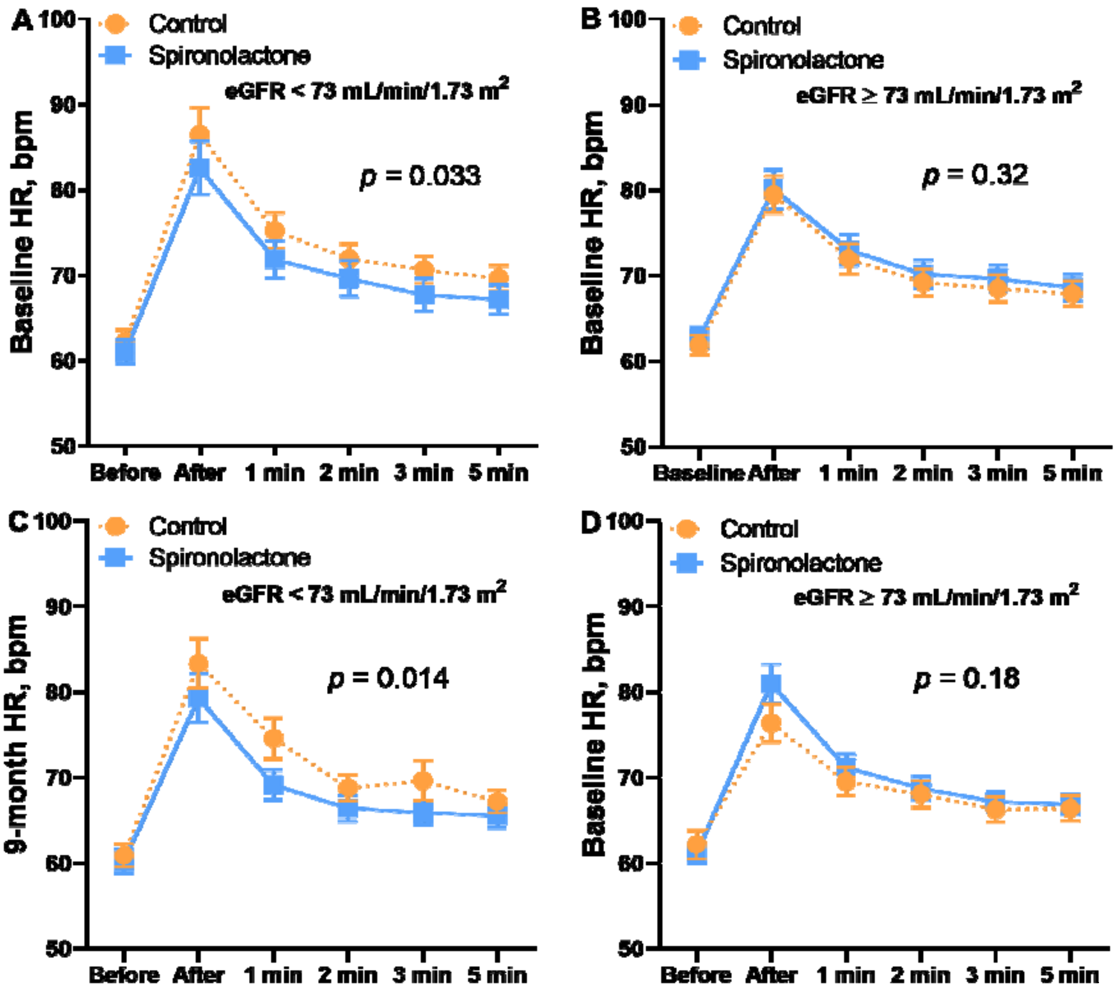

Figure S4

The pre-and post-exercise heart rate and heart recovery at 1, 2, 3 and 5 minutes after exercise at baseline and 9-months categorised by median glomerular filtration rate estimated from serum creatinine: < 73 mL/min/1.73 m^2 (A, C) *vs* ≥ 73 mL/min/1.73 m^2 (B, D).

Data points are unadjusted means ± SE. *p*-values for the between-group difference were computed by repeated measures ANOVA. The eGFR-by-time point interactions were not significant ($p \geq 0.58$).

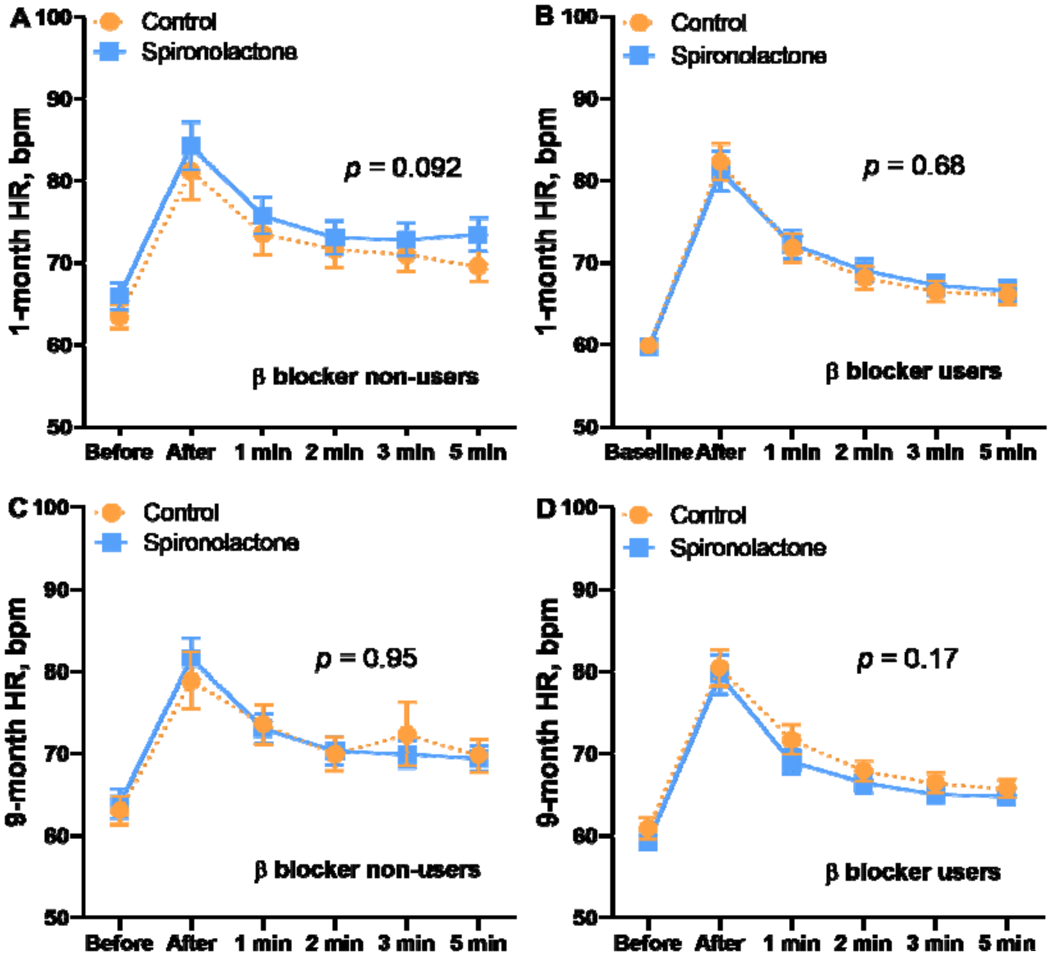

Figure S5

The pre-and post-exercise heart rate and heart recovery at 1, 2, 3 and 5 minutes after exercise at baseline and 9-months categorised by the use of β-blockers (A, C) *vs* non-use of β-blockers (B, D) at month 1 (A, B) and month 9 (C, D).

Data points are unadjusted means ± SE. *p*-values for the between-group difference were computed by repeated measures ANOVA. The β-blocker use-by-time point interactions are not significant ($p \geq 0.28$).