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Effect of spironolactone on QRS duration in patients at risk for heart failure: findings from the HOMAGE trial

João Pedro Ferreira[1,2]; John G. F. Cleland[3]; Nicolas Girerd[2]; Pierpaolo Pellicori[3]; Mark R. Hazebroek[4]; Job Verdonschot[5]; Timothy J. Collier[6]; Johannes Petutschnigg[7]; Andrew L. Clark[8]; Jan A. Staessen[9]; Stephane Heymans[4]; Patrick Rossignol[2]; Faiez Zannad[2]

[1] UnIC@RISE, Cardiovascular Research and Development Center, Department of Surgery and Physiology, Faculty of Medicine, University of Porto, Porto, Portugal.

[2] INSERM, Centre d'Investigations Cliniques - Plurithématique 14-33, Université de Lorraine, and INSERM U1116, CHRU Nancy, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France.

[3] British Heart Foundation Centre of Research Excellence, School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, United Kingdom.

[4] Department of Cardiology, CARIM, Maastricht University Medical Centre, Maastricht, The Netherlands.

[5] Department of Clinical Genetics, Maastricht University Medical Centre, Maastricht, The Netherlands.

[6] London School of Hygiene and Tropical Medicine, London, UK.

[7] Department of Internal Medicine and Cardiology, Campus Virchow Klinikum, Charité University Medicine Berlin and German Centre for Cardiovascular Research (DZHK), Berlin, Germany.

[8] Department of Cardiology, University of Hull, Castle Hill Hospital, Cottingham, UK.

[9] Research Institute Alliance for the Promotion of Preventive Medicine, Mechelen, Belgium.

Contact to:

Dr João Pedro Ferreira

CIM - Centro de Investigação Médica

Faculdade de Medicina UP - Piso 6 - DCF

Rua Plácido da Costa, s/n

4200-450 Porto, Portugal

Tel : +351 22 551 3600

Mail: jpferreira@med.up.pt

The QRS duration can be easily obtained from a 12-lead electrocardiogram. Increased QRS duration reflects greater ventricular activation times. Increases in left ventricular (LV) mass and volume cause subtle increases in the QRS duration, which may explain why men have a longer QRS duration than women.1 Delayed ventricular activation because of bundle branch block or right ventricular pacing can cause a much greater prolongation of the QRS complex, leading to ventricular dyssynchrony.

Dyssynchrony causes an impairment of the global cardiac function and adversely affects the prognosis of patients with heart failure (HF) and a dilated left ventricle, which might be improved by cardiac resynchronization therapy.2, 3, 4, 5, 6, 7, 8 For patients with HF with preserved ejection fraction (HFpEF), there is a linear relation between increasing QRS and worsening prognosis.3 However, little is known about the impact of pharmacologic therapies on the QRS duration, particularly for patients with presymptomatic HF with a preserved LV ejection fraction (LVEF) (i.e., stage B HFpEF).

HOMAGE (Heart OMics in AGEing; ClinicalTrials.gov identifier: NCT02556450) was a prospective randomized, open-label, blinded end point trial, enrolling patients at risk factors for developing HF, randomly assigned to either spironolactone or the usual care (without spironolactone or any other mineralocorticoid receptor antagonist) for approximately 9 months.9 Spironolactone reduced markers of collagen synthesis, blood pressure, natriuretic peptide levels, improved cardiac structure and function, and shortened QRS duration.10

This analysis reports the effect of spironolactone on the QRS duration in greater detail. Patient characteristics were compared across tertiles of QRS duration. The

effect of spironolactone on the changes in the QRS duration was studied with analysis of covariance. The associations between changes in the QRS duration and the changes in N-terminal pro-brain natriuretic peptide (NT-proBNP), echocardiographic measurements, systolic blood pressure (SBP), and procollagen type I carboxy-terminal propeptide (PICP) were assessed with linear regression models. A $p < 0.05$ was considered statistically significant. The analyses were performed using Stata version 17.1 (2021 StataCorp LLC, College Station, Texas).

A total of 525 patients was included in the analysis. The median (percentile25-75) QRS duration at baseline was 92 (84 to 106) ms, without differences between the randomized groups ($p = 0.33$). The baseline QRS duration tertiles were: tertile 1 (n = 191): 80 (79 to 85) ms, tertile 2 (n = 163): 92 (90 to 98) ms, and tertile 3 (n = 171): 120 (106 to 130) ms. Patients with a wider QRS were taller (median 166 cm in tertile 1 vs 171 cm in tertile 3), more often men (60% in tertile 1 vs 84% in tertile 3), had a larger indexed LV end-diastolic volume (median 40 ml/m2 in tertile 1 vs 43 ml/m2 in tertile 3), lower ejection fraction (64% in tertile 1 vs 61% in tertile 3), and higher indexed LV mass (median 91 g/m2 in tertile 1 vs 99 g/m2 in tertile 3). A total of 22 participants had a pacemaker, most of whom (n = 17, 77%) had a wide QRS (tertile 3). No significant differences in age, SBP, NT-proBNP, or PICP were observed between the groups/tertiles (Table 1).

Spironolactone reduced the QRS duration at month 9 by −2.8, 95% confidence interval −4.6 to −1.0 ms, $p = 0.003$. By 9 months, the QRS increased by 1 ms in the control group and decreased by 2 ms in the spironolactone group, without significant between-group differences at month 1 (Figure 1). The reduction in the QRS duration

was consistent across tertiles (interaction p = 0.79), and the effect remained similar after excluding the 22 patients with a pacemaker (β = −2.9, 95% confidence interval −4.6 to −1.2 ms, p = 0.001). No significant associations were found between the month 9 changes in the QRS duration and the corresponding changes in the LVEF, LV mass, LV end-diastolic volume, SBP, NT-proBNP, and PICP (all p >0.05).

This analysis shows that for patients with a stage B HFpEF, a longer QRS duration is associated with greater height (and therefore the male gender), LV mass, and LV end-diastolic volume and a lower LVEF. Therapy with spironolactone for 9 months shortened the QRS duration, an effect that was not associated with reductions in the LV mass or volume, supporting the hypothesis that spironolactone has direct beneficial effects to improve the myocardial electrical activation in patients with stage B HFpEF.

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

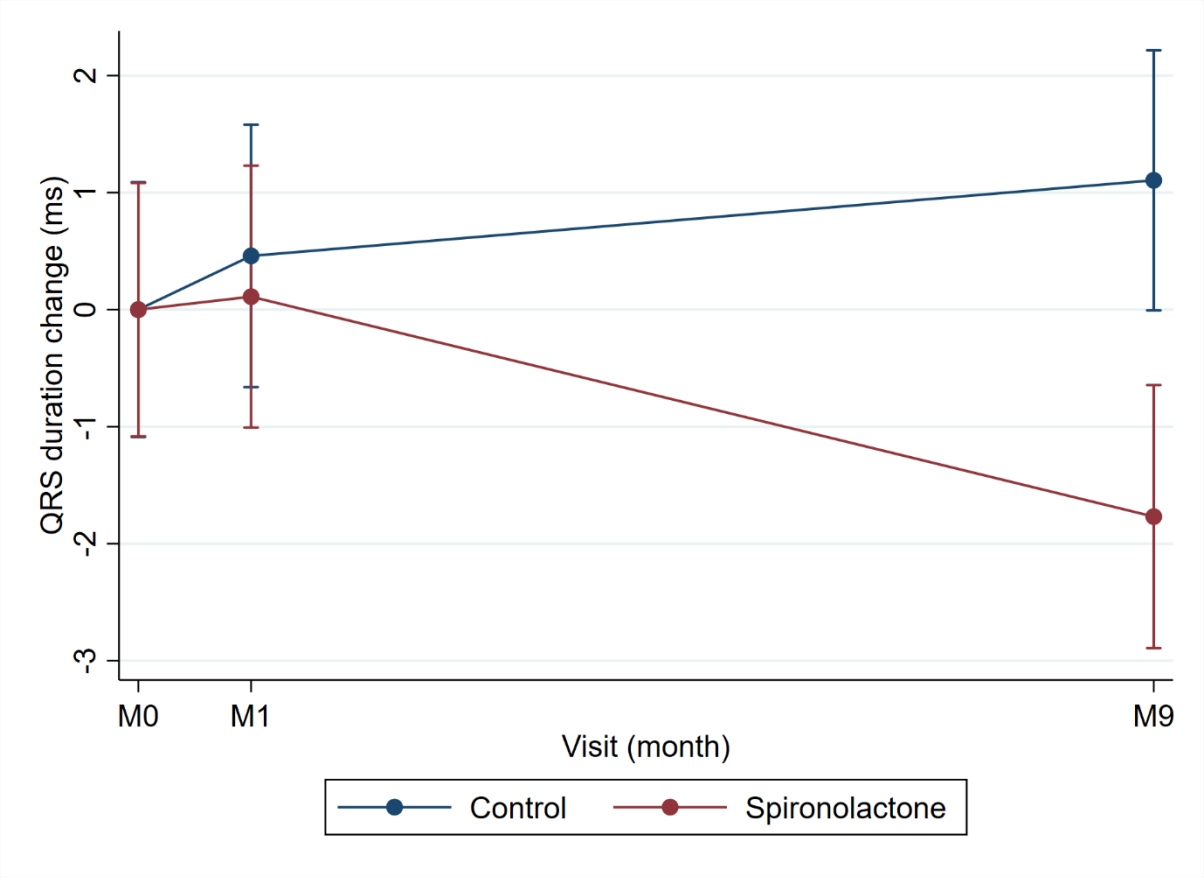
The authors have no relevant conflicts of interest to disclose regarding the content of this manuscript.

Table 1. Patient's characteristics by QRS tertiles

Characteristic	Lowest Third	Middle Third	Upper Third	P-value
N.	191	163	171	
QRS duration, ms	80 (79, 85)	92 (90, 98)	120 (106, 130)	-
Age, years	73 (68, 78)	73 (68, 78)	73 (69, 79)	0.55
Men	115 (60%)	132 (81%)	143 (84%)	<0.001
Height, cm	166 (161, 172)	171 (166, 176)	171 (166, 175)	<0.001
Weight, Kg	78 (67, 87)	83 (74, 92)	83 (75, 96)	<0.001
BMI, Kg/m^2	28 (25, 32)	28 (26, 31)	29 (26, 32)	0.23
Hypertension	152 (80%)	116 (71%)	144 (84%)	0.013
Diabetes mellitus	85 (45%)	63 (39%)	68 (40%)	0.49
Myocardial Infarction	79 (59%)	71 (56%)	63 (54%)	0.76
Stroke	13 (7%)	6 (4%)	9 (5%)	0.43
Pacemaker	1 (1%)	4 (3%)	17 (10%)	<0.001
Beta-blocker	131 (69%)	114 (70%)	119 (70%)	0.96
ACEi/ARB	150 (79%)	120 (74%)	144 (84%)	0.060
Thiazides	35 (18%)	22 (14%)	30 (18%)	0.44
Statin	156 (82%)	144 (88%)	133 (78%)	0.037
SBP, mmHg	140 (127, 156)	140 (128, 156)	140 (129, 154)	0.95
Heart rate, bpm	62 (56, 69)	60 (55, 66)	60 (54, 68)	0.16
LVEF, %	64 (60, 67)	64 (59, 67)	61 (55, 65)	0.002
LVM index, g/m^2	91 (77, 102)	94 (81, 114)	99 (85, 119)	0.001
LVH	43 (24%)	41 (29%)	55 (36%)	0.060
LVEDV index, ml/m^2	40 (34, 46)	42 (36, 52)	43 (36, 49)	0.007
LAVi, ml/m^2	30 (26, 36)	31 (26, 38)	30 (25, 35)	0.23
eGFR, ml/min	73 (62, 84)	77 (63, 86)	72 (59, 85)	0.23
Hemoglobin, g/dl	13.8 (12.9, 14.7)	14.2 (13.3, 15.0)	14.0 (13.1, 15.1)	0.023
Sodium, mmol/L	139 (138, 141)	140 (138, 142)	139 (138, 141)	0.071
Potassium, mmol/L	4.3 (4.1, 4.6)	4.3 (4.1, 4.6)	4.3 (4.1, 4.6)	0.87
NT-proBNP, pg/mL	208 (133, 308)	222 (137, 384)	208 (137, 358)	0.35
PICP, ng/ml	79 (65, 97)	81 (66, 98)	79 (64, 97)	0.74

Legend: ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; LVM index, left ventricular mass indexed to body surface area; LVEDV index, left ventricular end-diastolic volume indexed to body surface area; LVH, left ventricular hypertrophy; LAVi, left atrial volume indexed; eGFR, estimated glomerular filtration rate; NT-proBNP, N terminal-pro brain natriuretic peptide; PICP, procollagen type I carboxy-terminal propeptide.

Figure 1. Spironolactone effect on QRS duration



Legend: M, month.
Caption: Spironolactone reduced QRS duration at month 9 by -2.8, 9%CI -4.6 to -1.0 ms, P =0.003, without significant between-group differences at month 1 (β =-0.3, 95%CI -1.9 to 1.2, P =0.66).

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