Effect of Spironolactone on QRS Duration in Patients at Risk for Heart Failure - findings from the HOMAGE trial

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Abstract

QRS duration can be easily obtained from a 12-lead ECG. Increased QRS duration reflects greater ventricular activation times and often ventricular dyssynchrony. Dyssynchrony causes impairment of global cardiac function and adversely affects prognosis in patients with heart failure (HF). Little is known about the impact of pharmacologic therapies on QRS duration, particularly for patients with pre-symptomatic HF with a preserved LV ejection fraction (i.e., stage B HFpEF). The HOMAGE (Heart OMics in AGEing) trial, enrolled patients with risk factors for developing HF and assigned them to receive either spironolactone or usual care for approximately 9 months in a randomized manner. This analysis reports the effect of spironolactone on QRS duration. A total of 525 patients was included in the analysis. The median (percentile$_{25\text{-}75}$) QRS duration at baseline was 92 (84-106) ms. Spironolactone reduced QRS duration at month 9 by -2.8, 95%CI -4.6 to -1.0 ms, P =0.003. No significant associations were found between month 9 changes in QRS duration and corresponding changes in left ventricular (LV) ejection fraction, LV mass, LV end-diastolic volume, blood pressure, NT-proBNP, and procollagen type I carboxy-terminal propeptide (all P >0.05). This analysis shows that for patients with stage-B HFpEF, therapy with spironolactone for 9 months shortened QRS duration, an effect that was not associated with reductions in LV mass or volume, supporting the hypothesis that spironolactone has direct beneficial effects to improve myocardial electrical activation in patients with stage B HFpEF.

Key-words: spironolactone; ECG; QRS duration; heart failure.

QRS duration can be easily obtained from a 12-lead ECG. Increased QRS duration reflects greater ventricular activation times. Increases in left ventricular (LV) mass and volume cause subtle increases in QRS duration, which may explain why men have a longer QRS duration than women.[1] Delayed ventricular activation due to bundle-branch block or right ventricular pacing can cause much greater prolongation of the QRS complex, leading to ventricular dyssynchrony. Dyssynchrony causes impairment of global cardiac function and adversely affects prognosis in patients with heart failure (HF) and a dilated left ventricle, which might be improved by cardiac resynchronisation therapy.[2-8] For patients with heart failure and a 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 QRS duration, particularly for patients with pre-symptomatic HF with a preserved LV ejection fraction (i.e., stage B HFpEF).

HOMAGE (Heart OMics in AGEing; ClinicalTrials.gov Identifier: NCT02556450) was a prospective randomized open-label blinded endpoint (PROBE) trial, enrolling patients with risk factors for developing HF randomly assigned to either spironolactone or 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 QRS duration in greater detail. Patient characteristics were compared across tertiles of QRS duration. The effect of spironolactone on changes in QRS duration was studied with analysis of covariance (ANCOVA). Associations between changes in QRS duration and changes in NT-proBNP, echocardiographic measurements, systolic blood pressure

(SBP), and procollagen type I carboxy-terminal propeptide (PICP) were assessed with linear regression models. A P-value <0.05 was considered statistically significant. Analyses were performed using Stata® version 17.1 (StataCorp. 2021).

A total of 525 patients was included in the analysis. The median (percentile$_{25\text{-}75}$) QRS duration at baseline was 92 (84-106) ms without differences between randomized groups (P =0.33). The baseline QRS duration tertiles were: tertile 1 (n =191): 80 (79-85) ms, tertile 2 (n =163): 92 (90-98) ms, and tertile 3 (n =171): 120 (106-130) ms. Patients with 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 larger indexed LV end-diastolic volume (median 40 ml/m^2 in tertile 1 vs. 43 ml/m^2 in tertile 3), lower ejection fraction (64 % in tertile 1 vs. 61 % in tertile 3), and higher indexed LV mass (median 91 g/m^2 in tertile 1 vs. 99 g/m^2 in tertile 3). 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 groups/tertiles. *Table 1*.

Spironolactone reduced QRS duration at month 9 by -2.8, 95%CI -4.6 to -1.0 ms, P =0.003. By 9 months, QRS increased by 1 ms in control group and decreased by 2 ms in spironolactone group, without significant between-group differences at month 1. *Figure 1*. The reduction in 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%CI -4.6 to -1.2 ms, P =0.001). No significant associations were found between month 9 changes in QRS duration and corresponding changes in LV ejection fraction, LV mass, LV end-diastolic volume, SBP, NT-proBNP, and PICP (all P >0.05).

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

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Table 1. Patient's characteristics by QRS tertiles

Characteristic	Tertile 1	Tertile 2	Tertile 3	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.