disease and randomization treatment assignment.

Table S3. Impact of randomized treatment allocation (spironolactone vs. placebo) on outcomes in patients without pulmonary disease (668 on spironolactone and 681 on placebo) and with pulmonary disease (218 on spironolactone and 198 on placebo).

Table S4. Baseline clinical characteristics among TOPCAT Americas patients in the echocardiographic substudy stratified by the presence of pulmonary disease.

Table S5. Cardiac structure and function among TOPCAT Americas patients in the echocardiographic substudy, overall and stratified by the presence of pulmonary disease.

Acknowledgements

The authors wish to thank the staff and participants of the TOPCAT study for their important contributions.

Funding

TOPCAT was funded by National Heart, Lung, and Blood Institute, National Institutes of Health (Bethesda, MD), Contract Number HHSN268200425207C. The content of this paper does not necessarily represent the views of the sponsor or of the Department of Health and Human Services. The work for this manuscript was also supported by NIH/NHLBI grants K08HL116792, R01HL135008, and R01HL143224 (Dr. Shah), and a Watkins Discovery Award from the Brigham and Women's Heart and Vascular Center (Dr. Shah).

Conflict of interest: A.M.S. has received research support from Novartis and consulting fees from Philips Ultrasound and Bellerophon. All other authors have nothing to disclose.

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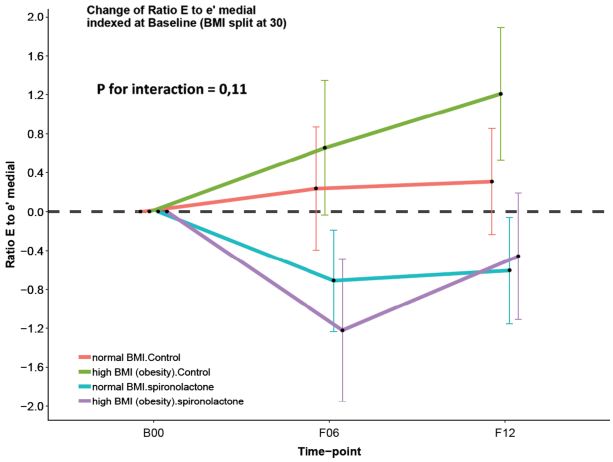
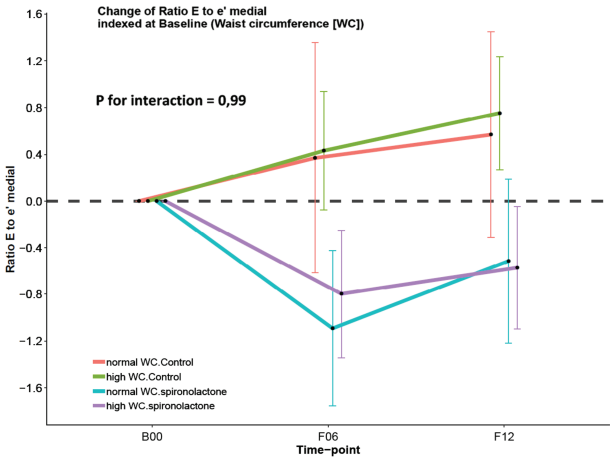
doi:10.1002/ejhf.1723
Online publish-ahead-of-print 7 January 2020

Body fat phenotypes and treatment response to spironolactone in ambulatory patients with heart failure and preserved ejection fraction: a post-hoc analysis of the Aldo-DHF trial

Obesity and heart failure (HF) with preserved ejection fraction (HFpEF) often co-exist, are increasingly prevalent and with rising incidence.[1] Recent reports have suggested that the development of HFpEF is associated with a systemic proinflammatory state related to commonly coexisting conditions such as obesity, diabetes, hypertension, and the habit of smoking.[2]

In patients enrolled in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial, those with abdominal obesity had higher event rates, including cardiovascular death.[3] In TOPCAT, spironolactone reduced the primary outcome of HF hospitalization or cardiovascular death in the reliable patient cohort from the 'Americas', who showed unquestioned HF signs and symptoms (and event rates compatible with HFpEF) as well as detectable serum levels of spironolactone metabolites.[4,5] In consequence, spironolactone received a class IIa indication for the treatment of HFpEF in the updated American College of Cardiology/American Heart Association/Heart Failure Society of America guidelines.[6] In TOPCAT, no treatment effect modification (i.e. 'interaction') was found between spironolactone and the obesity parameters, including body mass index (BMI) and waist circumference (WC), with regard to the study outcomes (P for interaction >0,1).[3] In a post-hoc analysis of the EMPHASIS-HF (Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms) trial that enrolled patients with HF and a reduced ejection fraction (HFrEF), eplerenone might have been more effective in patients with abdominal obesity.[7] The 'effect modification' by abdominal obesity could have been specific of HFrEF in comparison to HFpEF patients but needs further validation in different cohorts. To clarify these observations we studied the relationship





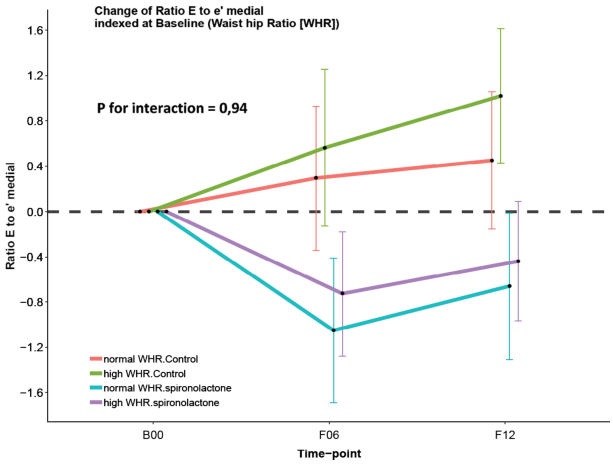


Figure 1 Changes of E/e' for the four subgroups composed by treatment arm and obesity. BMI, body mass index.

between the treatment effect of spironolactone in the prospective Aldo-DHF (Effect of Spironolactone on Diastolic Function and Exercise Capacity in Patients With Heart Failure With Preserved Ejection Fraction) trial,[8] and the potential spironolactone effect modification using mixed-effects models with an interaction term with several obesity parameters: BMI (<30 vs. ≥30 kg/m^2), WC (<88/102 vs. ≥88/102 cm) and waist-to-hip ratio (<0.86 vs. ≥0.86), with regard to the outcomes of N-terminal pro-B-type natriuretic peptide (NT-pro BNP), E/e', and left ventricular mass index (LVMI) measured at baseline, 6 and 12 months of follow-up.

The ALDO-DHF trial enrolled 422 patients [mean age, 67 (standard deviation, 8) years; 52% female] with chronic New York Heart Association class II or III HF, preserved left ventricular ejection fraction of 50% or greater and evidence of diastolic dysfunction in nine sites in Germany and Austria. Over a follow-up of 11.6 months [95% confidence interval (CI) 11.4–11.8 months] patients received a mean daily dose of spironolactone of 21.6 mg (95% CI 20.8–22.3 mg) and had a mean BMI of 28.9 (standard deviation, 3.6) kg/m^2. The intention-to-treat effects have been previously reported[8]; here we report the obesity parameters adjusted analysis and the subgroup analyses below and above the referenced cutoffs of the obesity parameters. The full results are presented in the online supplementary *Tables S1–S3*.

Obese patients (by any of the considered parameters) were more often diabetic, had lower baseline NT-proBNP levels and to a greater extent a reduced maximal oxygen consumption. No significant differences (between obese and non-obese) were present with regard to the echocardiographic parameters at baseline. In online supplementary *Table S4* we present the results of linear mixed models for the change of the Aldo-DHF endpoints. Fixed effects are treatment arm, obesity characteristic, an interaction term and time. A random intercept for patient ID is included. In the first and second line each, the estimated main effects of arm and obesity are shown. The third line contains the interaction effect 'arm × obesity parameter'. The meaning of the numbers is explained, e.g. for change of E/e' medial and BMI: the overall effect of spironolactone compared to placebo on change of E/e' from baseline to the 12-month follow-up visit was estimated −0.61 (95% CI −1.03;-0.21; $P = 0.005$). The estimate of 0.43 (95% CI −0.06;0.88; $P = 0.07$) corresponds to the effect of a high BMI (using the World Health Organization split) from baseline to the 12-month follow-up visit. Finally, the interaction 'arm × BMI' shows the potential effect modification by BMI and is estimated as −0.55 (95% CI −1.25;0.13) and not significant ($P = 0.11$).

In *Figure 1*, similarly to BMI, no significant interactions were found for WC and waist-to-hip ratio.

Hence, we conclude that in Aldo-DHF, spironolactone reduced E/e', LVMI and NT-proBNP, supporting the favorable effects of

this drug in improving cardiac function and potentially cardiovascular outcomes.[8] The overall effect of spironolactone was slightly reduced when adjusting for the obesity parameters and no effect modification of the treatment effects (i.e. 'interaction') was found by obesity, suggesting that spironolactone may be efficient both in obese and lean patients.

Supplementary Information

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

Table S1. Patient baseline characteristics: body mass index.

Table S2. Patient baseline characteristics: waist circumference.

Table S3. Patient baseline characteristics: waist-to-hip ratio.

Table S4. Analysis of Aldo-DHF endpoints adjusted for trial medication and obesity parameters. Main effects and interaction.

Funding

J.P., T.D.T., D.H., G.H., B.P. and F.E. are supported by DZHK (German Centre for Cardiovascular Research). C.H.L. has received research funding from the German Ministry of Education and Research. B.P. reports research funding from EU and German government funding instruments, as well as personal and Charité payments for advisory board, steering committee, and lecture services from Novartis, Bayer Healthcare, MSD, Daiichi-Sankyo, and BMS. J.P.F. and F.Z. are supported by the French National Research Agency Fighting Heart Failure (ANR-15-RHU-0004), by the French PIA project 'Lorraine Université d'Excellence' GEENAGE (ANR-15-IDEX-04-LUE) programmes, and the Contrat de Plan Etat Région Lorraine and FEDER IT2MP.

Conflict of interest: none declared.

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doi:10.1002/ejhf.1736
Online publish-ahead-of-print 18 February 2020

Index of microcirculatory resistance assessment in patients with new diagnosis of left ventricular dilatation without significant coronary artery lesions: IMPAIRED pilot trial

According to Camici and Crea[1] coronary microvascular dysfunction can exist in the presence of myocardial diseases, particularly in patients with a new diagnosis of left ventricular (LV) dilatation without coronary artery lesions. The aim of the present study was to evaluate the index of microcirculatory resistance (IMR), coronary flow reserve (CFR) and fractional flow reserve (FFR) and their mutual interaction in patients with dilated cardiomyopathy. The study protocol was approved by the local Institutional Review Board, registered on ClinicalTrials.gov (NCT02705170), and all patients provided informed consent. Major inclusion criteria for the study were recent diagnosis of LV dilatation and absence of significant coronary artery stenosis (<40%) at coronary artery angiography. After coronary angiography, coronary physiological measurements (IMR, CFR, FFR) were performed on the left anterior descending artery (LAD). IMR and CFR were obtained according to the method described previously.[2,3] Cut-off values of abnormality were ≥25 for IMR, ≤2.5 for CFR and ≤0.80 for FFR. Coronary angiograms were reviewed by S.B., blinded to functional evaluation findings. Values were presented as median (interquartile range) and compared by Mann–Whitney U and Kruskal–Wallis tests. Data analysis was carried out by M.T. and A.M.L. Between March 2016 and November