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Title: Cardiopulmonary functional capacity: Another piece of the puzzle of SGLT2 inhibition in heart failure?

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ejhf.2672

The glifozins have become an integral part of the treatment of heart failure [1]. Following the results of the DAPA-HF trial [2] which were soon followed by EMPEROR-Reduced trial [3], they firmly established themselves as a core therapy for heart failure with reduced ejection fraction, even upending decades of sequential treatment initiation algorithms in guidelines. Ever since the glifozins were shown to be beneficial in patients with type 2 diabetes, there has been immense interest in their mechanism of action and this has only intensified since the discovery that they improved outcomes in patients with heart failure with multiple studies speculating on potential mechanisms of action that underlie the benefits in heart failure [4]. It is possible that there is no single mechanism as the benefit of these drugs also extends to patients with chronic kidney disease as well as patients with type 2 diabetes. It is difficult to imagine that in every disease area there is only one single mechanism of action. Indeed, secondary analysis of many of these trials suggest multiple benefits for patients. One of the major findings from the trials of glifozins and heart failure with reduced ejection fraction is a very consistent benefit on symptoms and health-related quality of life [5,6]. This is as important if not more important often to patients than reductions in morbidity and mortality. Understanding why patients feel better may also help us understand the mechanisms that lead to a reduction in morbidity and mortality that are observed in the randomised trials. There have been other trials that have used health-related quality of life as an outcome [7, 8,9]. These have been very consistent with the randomised trials that examined morbidity and mortality outcomes. A consistent finding of all of these trials is an improvement in health-related quality of life in all domains. The Kansas City Cardiomyopathy Questionnaire (KCCQ) is commonly used to assess health-related quality of life. This questionnaire is a patient reported metric that quantifies symptoms, physical function, quality of life, and social function over the prior 2 weeks. In DAPA-HF dapagliflozin caused more patients to improve their KCCQ score and less to suffer a deterioration in their score [6]. One remaining question has been how does dapagliflozin do this? In this issue of the Journal Palau and colleagues present the results of a small, randomised trial looking at the effect of dapagliflozin on functional capacity as measured by cardiopulmonary exercise testing [10].

In their study patients were randomised either to dapagliflozin or placebo (with 45 patients in each group) and in this double-blinded trial patients who had heart failure with a reduced ejection fraction underwent maximal cardiopulmonary exercise testing at baseline, 1 and 3 months. The primary outcome of the trial was a change in peak VO_2 at 1 and 3 months. Several secondary endpoints were also examined, these included changes at 1 and 3 months in the 6-minute walk test distance and health related quality of life measured by the Minnesota Living with Heart Failure Questionnaire. Echocardiographic parameters (left ventricular ejection fraction, E/e' and left ventricular and atrial volumes) were also measured to look for signs of cardiac remodelling. The cohort that they enrolled was very representative of patients with heart failure with reduced ejection fraction. However, there was one characteristic that merits special attention. This was an extremely well treated population. Of the randomized patients, 89% of were receiving sacubitril/valsartan, 91% were receiving a beta blocker and 74% of patients were receiving a mineralocorticoid receptor antagonist. This is much better than many clinical trials and registries of patients with heart failure with reduced ejection fraction. Despite this excellent baseline therapy, the investigators reported that peak VO_2 increased in patients who were randomised to dapagliflozin at 1-month and at 3 months. There was no difference in 6-minute walk test distance or with the health-related quality of life questionnaire. There was no statistically significant difference in echocardiographic parameters either. At first sight this may seem to be at odds with the results of trials like DEFINE-HF [7] or the sub studies of the large randomised trials of SGLT2 inhibitors which have shown a benefit on health-related quality of life [5,6]. However, this sample was relatively small and the time period over which the change was examined was also fairly short in comparison to other trials or analyses. Although neither the 6-minute walk distance or scores from the Minnesota Living with Heart Failure Questionnaire were statistically significantly different between the two groups the change and each of these parameters was in favour of dapagliflozin. As might be expected

in a trial of such short duration there was no difference in structural measures of cardiac function such as ejection fraction or volumes or indeed filling pressures is measured by E/e'. Previous studies of remodelling in patients with heart failure have required longer periods of follow up to show any effect on cardiac structure [11]. How important is the improvement in peak VO_2 that we have seen in this trial? An analysis of the HF-ACTION trial which collected information and peak VO_2 in 1620 patients with heart failure with reduced ejection fraction, reported that a 6% increase in peak VO_2, when adjusted for other significant predictors was associated with a 5% lower risk of the composite of all-cause mortality or all-cause hospitalisation [12]. There was 8% lower risk of cardiovascular mortality or heart failure hospitalisation associated with this 6% increase of peak VO_2 at 3 months. Therefore peak VO_2 is clearly related to outcomes in this population. In the study by Palau et al the baseline peak VO_2 was 13.4 mL/kg/min and at 3-months this was 13.7 mL/kg/min. The significant difference between the dapagliflozin and placebo groups arose because the peak VO^2 fell from 12.9 to 12.7 mL/kg/min on average. This led to a greater difference between the two groups at 3 months compared to baseline and dapagliflozin appeared to preserve and improve peak VO_2 in a short period of time. This preservation phenomenon also follows the pattern that we have seen with other biological parameter such as renal function and health related quality of life where less people deteriorated with dapagliflozin. Returning to the question of how do glifozins work in heart failure, the findings of Palau et al take us further forward in our understanding of the many potential mechanisms that may be at play. While the findings do not complete the puzzle, they add an important piece to the picture.

References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2022 Jan;24(1):4-131. doi: 10.1002/ejhf.2333.

2. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde AM; DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381(21):1995-2008.

3. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F; EMPEROR-Reduced Trial Investigators. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020 Oct 8;383(15):1413-1424.

4. Zelniker TA, Braunwald E. Mechanisms of Cardiorenal Effects of Sodium-Glucose Cotransporter 2 Inhibitors: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020 Feb 4;75(4):422-434. Erratum in: J Am Coll Cardiol. 2020 Sep 22;76(12):1505.

5. Butler J, Anker SD, Filippatos G, Khan MS, Ferreira JP, Pocock SJ, Giannetti N, Januzzi JL, Piña IL, Lam CSP, Ponikowski P, Sattar N, Verma S, Brueckmann M, Jamal W, Vedin O, Peil B, Zeller C, Zannad F, Packer M; EMPEROR-Reduced Trial Committees and Investigators. Empagliflozin and health-related quality of life outcomes in patients with heart failure with reduced ejection fraction: the EMPEROR-Reduced trial. Eur Heart J. 2021 Mar 31;42(13):1203-1212.

6. Kosiborod MN, Jhund PS, Docherty KF, Diez M, Petrie MC, Verma S, Nicolau JC, Merkely B, Kitakaze M, DeMets DL, Inzucchi SE, Køber L, Martinez FA, Ponikowski P, Sabatine MS, Solomon SD, Bengtsson O, Lindholm D, Niklasson A, Sjöstrand M, Langkilde AM, McMurray JJV. Effects of Dapagliflozin on Symptoms, Function, and Quality of Life in Patients With Heart Failure and Reduced Ejection Fraction: Results From the DAPA-HF Trial. Circulation. 2020 Jan 14;141(2):90-99.

7. Nassif ME, Windsor SL, Tang F, Khariton Y, Husain M, Inzucchi SE, McGuire DK, Pitt B, Scirica BM, Austin B, Drazner MH, Fong MW, Givertz MM, Gordon RA, Jermyn R, Katz SD, Lamba S, Lanfear DE, LaRue SJ, Lindenfeld J, Malone M, Margulies K, Mentz RJ, Mutharasan RK, Pursley M, Umpierrez G, Kosiborod M. Dapagliflozin Effects on Biomarkers, Symptoms, and Functional Status in Patients With Heart Failure With Reduced Ejection Fraction: The DEFINE-HF Trial. Circulation. 2019 Oct 29;140(18):1463-1476.

8. Nassif ME, Windsor SL, Borlaug BA, Kitzman DW, Shah SJ, Tang F, Khariton Y, Malik AO, Khumri T, Umpierrez G, Lamba S, Sharma K, Khan SS, Chandra L, Gordon RA, Ryan JJ, Chaudhry SP, Joseph SM, Chow CH, Kanwar MK, Pursley M, Siraj ES, Lewis GD, Clemson BS, Fong M, Kosiborod MN. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. Nat Med. 2021 Nov;27(11):1954-1960.

9. Kosiborod MN, Angermann CE, Collins SP, Teerlink JR, Ponikowski P, Biegus J, Comin-Colet J, Ferreira JP, Mentz RJ, Nassif ME, Psotka MA, Tromp J, Brueckmann M, Blatchford JP, Salsali A, Voors AA. Effects of Empagliflozin on Symptoms, Physical Limitations, and Quality of Life in Patients Hospitalized for Acute Heart Failure: Results From the EMPULSE Trial. Circulation. 2022 Jul 26;146(4):279-288.

10. Palau P, Amiguet M, Domínguez E, Sastre C, Mollar A, Seller J, Garcia Pinilla JM, Larumbe A, Valle A, Gómez Doblas JJ, de la Espriella R, Miñana G, Mezcua AR, Santas E, Bodí V, Sanchis J, Pascual-Figal D, Górriz JL, Baýes-Genís A, Núñez J; DAPA-VO2 Investigators (see Appendix). Short-term effects of dapagliflozin on maximal functional capacity in heart failure with reduced ejection fraction (DAPA-VO2): a randomized clinical trial. Eur J Heart Fail. 2022 May 23. doi: 10.1002/ejhf.2560. Epub ahead of print.

11. Lee MMY, Brooksbank KJM, Wetherall K, Mangion K, Roditi G, Campbell RT, Berry C, Chong V, Coyle L, Docherty KF, Dreisbach JG, Labinjoh C, Lang NN, Lennie V, McConnachie A, Murphy CL, Petrie CJ, Petrie JR, Speirits IA, Sourbron S, Welsh P, Woodward R, Radjenovic A, Mark PB, McMurray JJV, Jhund PS, Petrie MC, Sattar N. Effect of Empagliflozin on Left Ventricular Volumes in Patients With Type 2 Diabetes, or Prediabetes, and Heart Failure With Reduced Ejection Fraction (SUGAR-DM-HF). Circulation. 2021 Feb 9;143(6):516-525.

12. Swank AM, Horton J, Fleg JL, Fonarow GC, Keteyian S, Goldberg L, Wolfel G, Handberg EM, Bensimhon D, Illiou MC, Vest M, Ewald G, Blackburn G, Leifer E, Cooper L, Kraus WE; HF-ACTION Investigators. Modest increase in peak VO2 is related to better clinical outcomes in chronic heart failure patients: results from heart failure and a controlled trial to investigate outcomes of exercise training. Circ Heart Fail. 2012 Sep 1;5(5):579-85.