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Response by Lee et al to Letter Regarding Article, “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)”

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In Response:

The trial conducted by Singh et al included only 56 patients and as pointed out by the authors, the patients enrolled had a much smaller left ventricular end- systolic volume index (52 vs 77 mL/m² in our trial).^{1,2} As a result of these differences, their trial had substantially less power to show an effect on left ventricular volumes, reduction of which has now been confirmed in 2 further, larger trials in patients with heart failure and dilated left ventricles.^{3,4} We think these differences in trial size and baseline left ventricular volumes are much more important than any difference in use of diuretics which are not known to affect left ventricular remodeling. Furthermore, diuretic use at baseline did not modify the response to empagliflozin in our trial and baseline diuretic use did not modify the effect of sodium-glucose cotransporter 2 inhibitors in the large outcome trials in heart failure.^{5,6}

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Disclosures

Dr Lee’s employer, the University of Glasgow, has received grant support from Boehringer Ingelheim. Dr McMurray’s employer, the University of Glasgow, has been paid by AbbVie, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, DalCor, GSK, Merck Sharp and Dohme, Novartis, Resverlogix, and Theracos for his participation in clinical trials and by Alnylam, AstraZeneca, Cardurion, Novartis, and Pfizer for consultancy, advisory board membership, or lectures. Dr Jhund’s employer, the University of Glasgow, is paid by AstraZeneca for involvement in the DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients with Chronic Heart Failure) and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved

Ejection Fraction Heart Failure) trials. He has also received consulting, advisory board, and speaker's fees from Novartis and AstraZeneca, advisory board fees from Cytokinetics, and a grant from Boehringer Ingelheim. Dr Petrie has received research grants or consultancy fees from SQ Innovations, AstraZeneca, Roche, Boehringer Ingelheim, Eli Lilly, Napp Pharmaceuticals, Novartis, and Novo Nordisk, and has served on clinical events committees for AbbVie, Alnylam, AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Resverlogix, and Novo Nordisk. Dr Sattar has consulted for or received lecture fees from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp and Dohme, Novartis, Novo Nordisk, Pfizer, and Sanofi. He has received grant support from Boehringer Ingelheim through his institution, the University of Glasgow.

References

1. Singh JSS, Mordi IR, Vickneson K, Fathi A, Donnan PT, Mohan M, Choy AMJ, Gandy S, George J, Khan F, et al. Dapagliflozin versus placebo on left ventricular remodeling in patients with diabetes and heart failure: the REFORM trial. *Diabetes Care*. 2020;43:1356–1359. doi: 10.2337/dc19-2187
2. Lee MMY, Brooksbank KJM, Wetherall K, Mangion K, Roditi G, Campbell RT, Berry C, Chong V, Coyle L, Docherty KF, et al. 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;143:516–525. doi: 10.1161/CIRCULATIONAHA.120.052186
3. Santos-Gallego CG, Vargas-Delgado AP, Requena-Ibanez JA, Garcia-Ropero A, Mancini D, Pinney S, Macaluso F, Sartori S, Roque M, Sabatel-Perez F, et al; EMPA-TROPISM (ATRU-4) Investigators. Randomized trial of empagliflozin in nondiabetic patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol*. 2021;77:243–255. doi: 10.1016/j.jacc.2020.11.008
4. Omar M, Jensen J, Ali M, Frederiksen PH, Kistorp C, Videbæk L, Poulsen MK, Tuxen CD, Möller S, Gustafsson F, et al. Associations of empagliflozin with left ventricular volumes, mass, and function in patients with heart failure and reduced ejection fraction: a substudy of the Empire HF randomized clinical trial. *JAMA Cardiol*. 2021;e206827. doi: 10.1001/jamacardio.2020.6827
5. Jackson AM, Dewan P, Anand IS, Bělohávek J, Bengtsson O, de Boer RA, Böhm M, Boulton DW, Chopra VK, DeMets DL, et al. Dapagliflozin and diuretic use in patients with heart failure and reduced ejection fraction in DAPA-HF. *Circulation*. 2020;142:1040–1054. doi: 10.1161/CIRCULATIONAHA.120.047077
6. Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, Sattar N, Brueckmann M, Jamal W, Cotton D, Iwata T, Zannad F; EMPERORReduced Trial Committees and Investigators. Empagliflozin in patients with heart failure, reduced ejection fraction, and volume overload: EMPERORReduced trial. *J Am Coll Cardiol*. 2021;77:1381–1392. doi: 10.1016/j.jacc.2021.01.033