# Dapagliflozin Improves Left Ventricular Myocardial Longitudinal Function in Patients with Type 2 Diabetes

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**Dapagliflozin Improves Left Ventricular Myocardial Longitudinal Function in Patients with Type 2 Diabetes**
**Echocardiographic Substudy of the DAPA-LVH Trial**

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Subclinical left ventricular dysfunction (LVD) is highly prevalent in people with type 2 diabetes mellitus (T2DM) and is independently associated with poor cardiovascular outcome (1). Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have been shown to reduce hospitalisations for heart failure in patients with T2DM (2). The effect of SGLT2 inhibitors on subclinical LVD that includes LV diastolic function and myocardial longitudinal function assessed using global longitudinal strain (GLS) remains unknown.

Our recent DAPA-LVH study showed that the SGLT2i, dapagliflozin, significantly reduced LV mass compared to placebo in people with T2DM (3). Given the heart failure benefits seen in DECLARE-TIMI 58 trial, the objective of this echo sub-study of the DAPA-LVH trial was to assess whether dapagliflozin treatment improves GLS and LV diastolic function (4). The study design and primary results have been published previously (3). Briefly, DAPA-LVH trial was a prospective, double-blind, randomised, placebo-controlled single-centre study involving 66 normotensive individuals with T2DM with LVH, defined using echocardiography as per the American Society of Echocardiographic guidelines. Partcipants were recruited using research databases, hospital records, and local general practices and randomised to dapagliflozin 10mg or placebo for 12 months. At baseline and after 12 months of treatment, participants underwent a standard echocardiographic examination using a Phillips Epiq 7 machine performed by a British Society of Echocardiography accredited operator blinded to the study medication. LV diastolic function was assessed as per the American Society for Echocardiography guidelines. The Phillips Epiq 7 machine was installed with Automated Cardiac Motion Quantification software that allowed the measurement of GLS. GLS was then determined as the averaged peak longitudinal strain of 17 LV segments and was expressed as an absolute value in accordance with current guidelines. If image quality was not sufficient to track every myocardial segment the participant was excluded from the sub-study.

The comparison between the two groups (dapagliflozin vs placebo) was compared using an independent t-test for normally distributed continuous variables and a Mann Whitney test for non-normally distributed continuous variables. Additionally, we performed a sensitivity analysis for both the change in GLS and E:$e^{-}$ using analysis of covariance (ANCOVA) model to evaluate the robustness of treatment with GLS, E:$e^{-}$ change and treatment as fixed effects, and baseline values for GLS and E:$e^{-}$ as covariates respectively.

Four people withdrew from the main DAPA-LVH study early and on review 15 baseline echocardiograms were deemed not to have images of sufficient quality to allow accurate strain analysis and were excluded. In total 47 participants completed this sub-study, (30 men [64%], mean [SD] 65.7 [7] years, T2DM duration [IQR] 10 [7] years). There were no significant differences between the two groups in any of the baseline characteristics including baseline cardiovascular medications.

Dapagliflozin resulted in a significant improvement in GLS with a mean improvement in GLS of 1.71 ± 2.5% vs placebo 0.23 ± 1.8%; p=0.024, with a mean difference of 1.5% (95% confidence interval (CI): 2.8 to 0.2). (Table 1) Following sensitivity analysis, the improvement in GLS remained significant with an estimated marginal mean improvement with dapagliflozin of 1.63% (95% CI; 2.51 to 0.75) vs placebo 0.30% (95% CI; 1.17 to 0.56) p=0.037, suggesting that this finding was robust and not driven by baseline GLS. There was no significant difference in LV diastolic parameters between dapagliflozin and placebo. There was an observed moderate correlation between the change in GLS and the increase in haematocrit which was seen in DAPA-LVH trial with r= 0.329, n= 47, p=0.024. There were no major adverse cardiovascular events in either group during the study.

Our study has several limitations that include the small sample size due to the exclusion of participants that had poor image quality for GLS assessment. Additionally, we did not assess functional capacity that limits the clinical interpretation of our findings.

Our randomised controlled trial has shown that dapagliflozin treatment significantly improved GLS. We did not see any significant change in LV diastolic function as assessed by E/e'ratio (Table 1). Plausible mechanisms for the improvement in GLS include SGLT2i induced reduction in pre-load and afterload although this was not apparent in a recent study involving an animal model of heart failure (5). The improvement in GLS may also be due to proposed benefits of SGLT2i on myocardial energetics and fibrosis. Obviously, any evidence for these proposed mechanisms must remain speculative and cannot be inferred directly from our study. The clinical relevance of the effect size on GLS observed in our study is not known as we did not assess functional capacity and should be restricted to our study population of people with T2DM and LVH and cannot be extended to the wider stage B heart failure T2DM population. Clearly, these findings need to be confirmed by larger studies with clinical outcome measures.

**References**

1. Maack C, Lehrke M, Backs J, Heinzel FR, Hulot JS, Marx N, et al. Heart failure and diabetes: metabolic alterations and therapeutic interventions: a state-of-the-art review from the Translational Research Committee of the Heart Failure Association-European Society of Cardiology. Eur Heart J. 2018;39(48):4243-54.
2. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019;393(10166):31-9.
3. Brown AJM, Gandy S, McCrimmon R, Houston G, Struthers A, Lang C. A Randomised Controlled Trial of Dapagliflozin on Left Ventricular Hypertrophy in People with Type Two Diabetes. The DAPA-LVH Trial. Eur Heart J. In press;https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehaa419/5861974?guestAccessKey=d6d0c461-a69c-461c-8ce6-5fb783f6862e.
4. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019;380(4):347-57.

5. Connelly, K.A., Zhang, Y., Desjardins, J. *et al.* Load-independent effects of empagliflozin contribute to improved cardiac function in experimental heart failure with reduced ejection fraction. *Cardiovasc Diabetol* **19,** 13 (2020). https://doi.org/10.1186/s12933-020-0994-y