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Dapagliflozin effects on lung fluid volumes in patients with heart failure and reduced ejection fraction: results from the DEFINE-HF Trial.

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Abstract:

Sodium-glucose co-transporter-2 inhibitors (SGLT2i) have been shown to reduce the risk of CV death or worsening heart failure, improve symptom burden, physical function and quality of life in patients with heart failure and reduced ejection fraction. The mechanisms of HF benefits of SGLT-2is, however, remains unclear. In this substudy of the DEFINE-HF trial, patients randomized to dapagliflozin or placebo had lung fluid volumes measured by remote dieletric sensing at baseline and after twelve weeks of therapy. A significantly greater proportion of dapagliflozin-treated patients (as compared with placebo) experienced improvement in lung fluid volumes and fewer dapagliflozin-treated patients had no change or deterioration in lung fluid volumes after 12 weeks of treatment. To our knowledge, this is the first study to suggest a direct effect of dapagliflozin (or any SGLT2i) on more effective “decongestion”, contributing in a meaningful way to the ongoing debate regarding the mechanisms of SGLT2i HF benefits.

Background:

Sodium-glucose co-transporter-2 inhibitors (SGLT2i) are a class of medications developed for treatment of Type 2 diabetes (T2D), which lower plasma glucose concentrations via increased urinary excretion of glucose.[1] Several large cardiovascular outcome trials, and one kidney outcome trial, all conducted in patients with T2D at increased cardiovascular risk, demonstrated robust and consistent reductions in the risk of hospitalization for heart failure (HF) with three different agents in the SGLT2i class, representing primarily a HF prevention signal.[2] More recently, SGLT2i dapagliflozin was also shown to significantly reduce the risk of cardiovascular

death or worsening HF, as well as improve health status (symptoms, physical limitations and quality of life), in patients with established HF and reduced ejection fraction (HFrEF), including those with and without T2D.[3, 4] Furthermore, the health status benefit of dapagliflozin were substantial, and emerged as early as 12 weeks after randomization.[3]

The mechanisms behind the HF benefits of SGLT2i remain incompletely defined and appear to be unrelated to glucose lowering effects, with multiple theories being postulated. These include natriuresis and plasma volume reduction, improved oxygen supply via an increase in hematocrit, a metabolic shift towards the consumption of ketones, reduction of glomerular pressure and reduced oxygen consumption in the proximal tubule of the kidneys, altered Na+/H+ exchange in heart and kidney modulating adipokine production, and decreased sarcoplasmic calcium leading to increased ventricular contractility.[1, 5, 6] No previous study has directly explored the effects of SGLT2i effects on lung fluid volume (LFV) - a potential direct "decongestion" mechanism that may contribute to HF benefits. We analyzed data from the Dapagliflozin Effects on biomarkers, symptoms and functional status in patients with HF (DEFINE-HF) Trial to address this key knowledge gap.[3]

Methods:

Details of the DEFINE-HF trial were previously reported.[3] It was a multi-center, randomized, placebo-controlled trial of 263 HF patients (with or without T2D) with LVEF ≤40%, NYHA class II-III, and elevated natriuretic peptides. Patients were randomized 1:1 to dapagliflozin 10 mg daily vs placebo for 12 weeks.In this pre-specified sub-study of the DEFINE-HF trial, a subset of patients agreed to participate in an ancillary study that measured LFV with remote dielectric sensing ReDS™ (Sensivest) technology at randomization, and at 6 and 12 weeks after initiation of treatment. ReDs is an FDA-approved vest, which patients wore for 90 seconds

during study visits, to determine the absolute percentage of lung fluid. ReDS uses low-power electromagnetic signals emitted between 2 sensors (1 each on the anterior and posterior body surfaces) embedded in a wearable vest to quantify lung fluid volumes, which are expressed as a total percentage (normal range for individuals that don't have heart failure has been established as 20-35%).[7] ReDs has been validated against radiographic findings of lung fluid, and with invasive hemodynamics where thecorrelation between LFV measured by ReDs and pulmonary capillary wedge pressure was (0.49, p <0.001).[5, 7, 8]

.[5]

Data were transmitted to a secured site where the reading was interpreted by a blinded third party, reported back to the National Coordinating Center, and stored in a separate secure file (with site investigators and staff remaining blinded until the study conclusion and data lock). After unblinding, these data were matched with individual study patients for analysis. Prespecified sub-study outcomes included mean LFV at 12 weeks, which were analyzed using a mixed model adjusting for baseline LFV, age, eGFR and T2D status. A responder analysis evaluated the proportion of dapagliflozin versus placebo-treated patients with either an improvement, or no change/deterioration in LFV at 12 weeks (adjusted for baseline LFV, age, T2D and eGFR). Additional prespecified analyses included changes in NTproBNP, BNP and Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) among patients who had an improvement versus no change/deterioration in LFV at 12 weeks.

Results: Overall, of 263 patients in the trial, 85 agreed to participate in the Sensivest substudy; 41 were randomized to dapagliflozin, and 44 to placebo. Baseline characteristics were balanced between treatment groups and reflected stable, chronic HFrEF (mean age 65.1 ± 9.6 years, 29%

African American, mean LVEF 26.5 ± 8.4%, 83.5% with prior HF hospitalization). Patients received optimal guideline-directed medical and device therapy for HFrEF (97.6% on beta blockers, 90.6% on ACEI/ARB/ARNI, 69.4% on MRAs, 80% on loop diuretics, 58.8% with ICD, 46% with CRT). Baseline mean NTproBNP was 1903 ± 1775 pg/mL, mean KCCQ-CSS was 71.7 ± 20.3, and LFV was 34 percent.

There was no significant difference in mean adjusted LFV at 12 weeks with dapagliflozin vs. placebo (34% vs. 35%, p = 0.3). However, significantly fewer dapagliflozin versus placebo-treated patients experienced no change or deterioration in LFV (47% vs. 63%), and a greater proportion of dapagliflozin-treated patients had improvement in LFV (53% vs. 37%; P=0.04; Figure, panel A).

Patients who experienced improvement in LFV, as compared with those that had no change or deterioration in LFV (regardless of treatment allocation), had a numerically greater (though not statistically significant) reduction in NT-proBNP (-439 ± 1374 vs -47 ± 1273 pg/mL, p = 0.2), significantly greater decrease in BNP (-143 ± 248 vs. -18 ± 185 pg/mL, p = 0.01), and significantly greater improvement in KCCQ-CSS (+5.5 ± 9.6 vs. -2.8 ± 14.0 points, p=0.005; Figure, panels B, C).

Discussion: In this prespecified sub-study of the DEFINE-HF trial, dapagliflozin did not have a significant effect on mean LFV; however, a significantly greater proportion of dapagliflozin-treated patients experienced improvement in LFV, and fewer dapagliflozin-treated patients had no change or deterioration in LFV after 12 weeks of treatment. It has been hypothesized that SGLT-2is facilitate osmotic diuresis, and greater fluid clearance from the interstitial fluid space than from the circulating blood volume;[6] and that SGLT-2i are more effective in reducing interstitial fluid fluid than traditional loop diuretics and thus resulting in congestion relief with

minimal impact on blood volume.[9] Our data from the DEFINE-HF trial offers the first direct evidence of this concept, as there was no change in blood pressure or loop diuretic use between the dapagliflozin treated patients and placebo, but there was evidence that a greater proportion of patients treated with dapagliflozin had a decrease in their IF based on decreasing lung fluid volumes.

Notably, this was observed in patients already receiving excellent guideline-directed medical and device therapy for HFrEF. To our knowledge, this is the first data from a randomized controlled trial to demonstrate a direct effect of dapagliflozin (or any SGLT2i) on more effective "decongestion", contributing in a meaningful way to the ongoing debate regarding the mechanisms of SGLT2i HF benefits. Whether this is due to diuretic/natriuretic effects of dapagliflozin, or improvement in congestion via other mechanisms is unclear. However, as the reductions in natriuretic peptides observed with dapagliflozin in HFrEF patients to date have been relatively modest, and both DEFINE-HF and DAPA-HF saw minimal changes in diuretic dosages,[3, 10] suggesting other mechanisms may be at play in terms of the dapagliflozin effects on LFV.

Our results need to be considered in the context of potential limitations; this was a relatively small, hypothesis-generating sub-study, not sufficiently powered to detect a modest difference in LFV. Likewise, given the small number of patients, there were some baseline imbalances - notably in use of cardiac resynchronization therapy, which may have partially influenced the observed effect of dapagliflozin on lung fluid volumes. Lastly, well-defined clinically meaningful changes in LFV have not been firmly established, and thus the clinical implications of improvement vs no change/deterioration in LFV remain to be clearly determined. However, the fact that patients who had a decrease in LFV also experienced declines in natriuretic peptides,

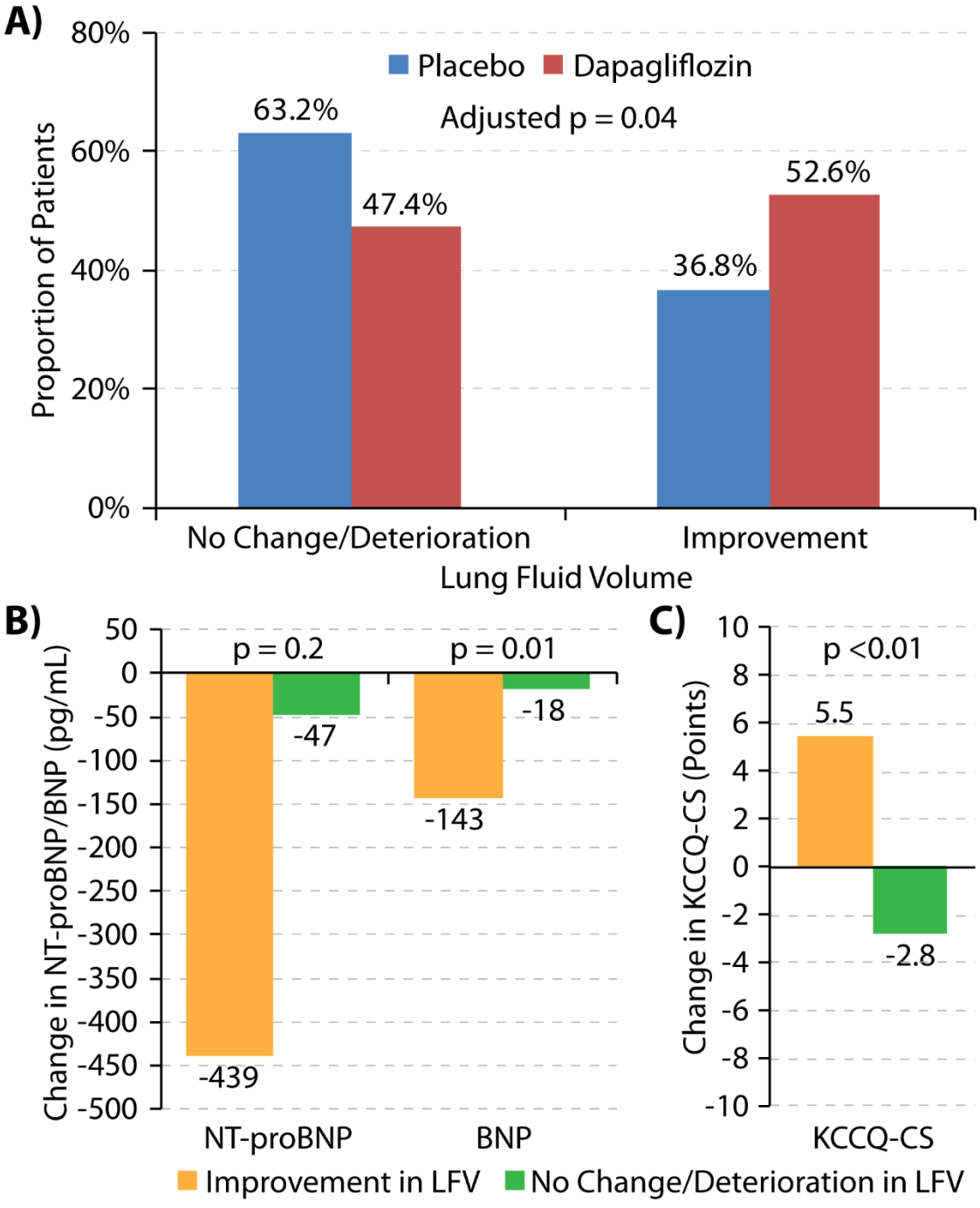
and numerically large improvements in KCCQ-CSS is reassuring. To our knowledge, this is the first effort to correlate changes in LFV with HF biomarkers and health status measures.

Table 1.

Baseline Characteristics	Dapagliflozin (n = 41)	Placebo (n = 44)	P-Value
Demographics			
Age (years)	66.0 ± 9.7	64.3 ± 9.5	0.43
Male	36 (87.8%)	39 (88.6%)	1.00
White	28 (71.8%)	29 (67.4%)	0.90
African American	11 (28.2%)	13 (30.2%)	
Medical History			
Prior hospitalization for heart failure	36 (87.8%)	35 (79.5%)	0.34
Ejection fraction (%)	27.1 ± 8.6	25.9 ± 8.2	0.53
Ischemic Heart Disease	29 (70.7%)	31 (70.5%)	0.98
Type 2 Diabetes	31 (75.6%)	32 (72.7%)	0.76
Atrial Fibrillation	18 (43.9%)	20 (45.5%)	0.29
ICD	30 (73.2%)	20 (45.5%)	0.04
CRT	18 (60.0%)	5 (25.0%)	
Baseline HF/CV Medications			
ACEI/ARB	27 (65.9%)	32 (72.7%)	0.491
ARNI	10 (24.4%)	8 (18.2%)	0.483
Beta blockers	41 (100.0%)	42 (95.5%)	0.494
MRA	30 (73.0%)	29 (65.9%)	0.467
Loop Diuretics	33 (80.5%)	35 (79.5%)	0.913
Baseline Laboratory Studies			
NT-proBNP (pg/mL) (median Q1, Q3)	1136 (887, 1879)	1419 (611, 3272)	0.153
BNP (pg/mL) (median Q1, Q3	276 (123, 544)	322 (167, 718)	0.163
eGFR (mL/min/1.73m^2)	63.34 ± 18.98	70.34 ± 20.33	0.105
Urine albumin/creatinine ratio (mg/g) (median, Q1, Q3)	30 (7, 92)	50 (15, 148)	0.929
Hemoglobin A1c (%)	7.4 ± 1.6	7.3 ± 1.7	0.78
Hematocrit (%)	42.3 ± 4.9	40.8 ± 4.6	0.14
Functional Measures			
NYHA Class II	30 (73.2%)	32 (72.7%)	0.96
NYHA Class III	11 (26.8%)	12 (27.3%)	
KCCQ-OS	70.8 ± 19.2	67.0 ± 20.5	0.38
KCCQ-CS	73.9 ± 19.6	69.6 ± 20.9	0.34
Lung Fluid Volume (%)	33.46 ± 5.5	35.34 ± 7.1	0.18

Values are shown as absolute numbers (percentages) and mean ± SD.
NYHA, New York Heart Association; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary Score; ICD, Internal Cardiac Defibrillator; HF, Heart Failure; NT-proBNP, N-Terminal Pro B-Type Natriuretic Peptide; Cr, Creatinine; eGFR, Estimated Glomerular Filtration Rate; ACE-I, Angiotensin Converting Enzyme-Inhibitor; ARB, Angiotensin II Receptor Blocker; ARNI, Angiotensin Receptor-Neprilysin Inhibitor; MRA, Mineralocorticoid Receptor Antagonist,

Figure 1. Panel A. Proportion of patients who experienced a decrease in lung fluid volume or no change/increase in lung fluid volume with placebo (blue) and dapagliflozin (red). **Panel B**. Change in NTpropBNP and BNP from baseline to 12-weeks in patients with a decrease in lung fluid volumes (yellow) and no change or increase in lung fluid volumes (green), regardless of randomized treatment allocation. **Panel C**. Change in Kansas City Cardiomyopathy Clinical Summary score (KCCQ-CSS) from baseline to 12-weeks in patients with a decrease in lung fluid volumes (yellow) and no change or increase in lung fluid volumes (green), regardless if randomized treatment allocation.



References:

1. Inzucchi SE, Zinman B, Wanner C, Ferrari R, Fitchett D, Hantel S, Espadero RM, Woerle HJ, Broedl UC and Johansen OE. SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcome trials. *Diabetes & vascular disease research*. 2015;12:90-100.
2. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH and Sabatine MS. 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;393:31-39.
3. Nassif Michael E, Windsor S, Tang F, Khariton Y, Husain M, Inzucchi Silvio E, McGuire D, Pitt B, Scirica Benjamin M, Austin B, Drazner M, Fong M, Givertz Michael M, Gordon R, Jermyn R, Katz S, Lamba S, Lanfear D, LaRue S, Lindenfeld J, Malone M, Margulies Kenneth B, Mentz R, Mutharasan RK, Pursley M, Umpierrez G and Kosiborod M. Dapagliflozin Effects on Biomarkers, Symptoms, and Functional Status in Patients With Heart Failure With Reduced Ejection Fraction: The DEFINE-HF Trial. *Circulation*. 0.
4. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Belohlavek J, Bohm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukat 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, Sjostrand M, Langkilde AM, Committees D-HT and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *The New England journal of medicine*. 2019.
5. Amir O, Ben-Gal T, Weinstein JM, Schliamser J, Burkhoff D, Abbo A and Abraham WT. Evaluation of remote dielectric sensing (ReDS) technology-guided therapy for decreasing heart failure re-hospitalizations. *Int J Cardiol*. 2017;240:279-284.
6. Griffin M, Rao VS, Ivey-Miranda J, Fleming J, Mahoney D, Maulion C, Suda N, Siwakoti K, Ahmad T, Jacoby D, Riello R, Bellumkonda L, Cox Z, Collins S, Jeon S, Turner JM, Wilson FP, Butler J, Inzucchi SE and Testani JM. Empagliflozin in Heart Failure: Diuretic and Cardio-Renal Effects. *Circulation*. 2020.
7. Amir O, Azzam ZS, Gaspar T, Faranesh-Abboud S, Andria N, Burkhoff D, Abbo A and Abraham WT. Validation of remote dielectric sensing (ReDS™) technology for quantification of lung fluid status: Comparison to high resolution chest computed tomography in patients with and without acute heart failure. *Int J Cardiol*. 2016;221:841-6.
8. Uriel N, Sayer G, Imamura T, Rodgers D, Kim G, Raikhelkar J, Sarswat N, Kalantari S, Chung B, Nguyen A, Burkhoff D and Abbo A. Relationship Between Noninvasive Assessment of Lung Fluid Volume and Invasively Measured Cardiac Hemodynamics. *J Am Heart Assoc*. 2018;7:e009175-e009175.
9. Verma S and McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. *Diabetologia*. 2018;61:2108-2117.
10. Docherty KF, Jhund PS, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, DeMets DL, Sabatine MS, Bengtsson O, Sjöstrand M, Langkilde AM, Desai AS, Diez M, Howlett JG, Katova T, Ljungman CEA, O'Meara E, Petrie MC, Schou M, Verma S, Vinh PN, Solomon SD, McMurray JJV, Investigators obotD-H and Committees. Effects of dapagliflozin in DAPA-HF according to background heart failure therapy. *European Heart Journal*. 2020;41:2379-2392.