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BRIEF REPORT

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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 cotransporter-2 (SGLT2) inhibitors have been shown to reduce the risk of cardiovascular death or worsening heart failure (HF), and improve symptom burden, physical function and quality of life in patients with HF and reduced ejection fraction. The mechanisms of the HF benefits of SGLT2 inhibitors, however, remain unclear. In this substudy of the DEFINE-HF trial, patients randomized to dapagliflozin or placebo had lung fluid volumes (LFVs) measured by remote dieletric sensing at baseline and after 12 weeks of therapy. A significantly greater proportion of dapagliflozin-treated patients (as compared with placebo) experienced improvement in LFVs and fewer dapagliflozin-treated patients had no change or deterioration in LFVs after 12 weeks of treatment. To our knowledge, this is the first study to suggest

a direct effect of dapagliflozin (or any SGLT2 inhibitor) on more effective "decongestion", contributing in a meaningful way to the ongoing debate regarding the mechanisms of SGLT2 inhibitor HF benefits.

KEYWORDS
dapagliflozin, heart failure, SGLT2 inhibitor

1 | INTRODUCTION

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are a class of medication developed for the 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 SGLT2 inhibitor class, representing primarily an HF prevention signal.[2] More recently, the SGLT2 inhibitor 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 benefits of dapagliflozin were substantial, and emerged as early as 12 weeks after randomization.[3]

The mechanisms behind the HF benefits of SGLT2 inhibitors remain incompletely defined and appear to be unrelated to the glucose-lowering effects, with multiple theories being postulated. These include natriuresis and plasma volume reduction, improved oxygen supply via an increase in haematocrit, 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 SGLT2 inhibitors on lung fluid volume (LFV), a potential direct "decongestion" mechanism that may contribute to HF benefits. We analysed 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]

2 | METHODS

Details of the DEFINE-HF trial were previously reported.[3] It was a multicentre, randomized, placebo-controlled trial in 263 HF patients (with or without T2D) with left ventricular ejection fraction ≤40%, New York Heart Association class II to III, and elevated natriuretic peptides. Patients were randomized 1:1 to dapagliflozin 10 mg daily versus placebo for 12 weeks. In this prespecified substudy 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 a US Food and Drug Administration-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 two sensors (one each on the anterior and posterior body surfaces) embedded in a wearable vest to quantify LFVs, which are expressed as a total percentage (normal range for individuals that do not have heart failure has been established as 20%-35%).[7] ReDs has been validated against radiographic findings of lung fluid, and with invasive haemodynamics where the correlation between LFV measured by ReDs and pulmonary capillary wedge pressure was 0.49 ($P < 0.001$).[5,7,8]

Data were transmitted to a secured site where the reading was interpreted by a blinded third party, reported back to the National Coordinating Centre, 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 substudy outcomes included mean LFV at 12 weeks, which was analysed using a mixed model adjusting for baseline LFV, age, estimated glomerular filtration rate (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, brain natriuretic peptide (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.

3 | 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 left ventricular ejection fraction 26.5 ± 8.4%, 83.5% with prior HF hospitalization; Table 1). Patients received optimal guideline-directed medical and device therapy for HFrEF (97.6% on beta blockers, 90.6% on angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers/angiotensin receptor neprilysin inhibitors, 69.4% on mineralocorticoid receptor antagonists, 80% on loop diuretics, 58.8% with internal cardiac defibrillators, 46% with cardiac resynchronization therapy (CRT)).

TABLE 1 Baseline characteristics

Baseline characteristics	Dapagliflozin (n = 41)	Placebo (n = 44)	*P*
Demographics			
Age, years	66.0 ± 9.7	64.3 ± 9.5	0.43
Male, n (%)	36 (87.8)	39 (88.6)	1.00
White, n (%)	28 (71.8)	29 (67.4)	0.90
African American, n (%)	11 (28.2)	13 (30.2)	
Medical history			
Prior hospitalization for heart failure, n (%)	36 (87.8)	35 (79.5)	0.34
Ejection fraction, %	27.1 ± 8.6	25.9 ± 8.2	0.53
Ischaemic heart disease, n (%)	29 (70.7)	31 (70.5)	0.98
Type 2 diabetes, n (%)	31 (75.6)	32 (72.7)	0.76
Atrial fibrillation, n (%)	18 (43.9)	20 (45.5)	0.29
Internal cardiac defibrillator, n (%)	30 (73.2)	20 (45.5)	0.04
CRT, n (%)	18 (60.0)	5 (25.0)	
Baseline HF/cardiovascular medications, n (%)			
ACE inhibitors/ARBs	27 (65.9)	32 (72.7)	0.491
ARNIs	10 (24.4)	8 (18.2)	0.483
Beta blockers	41 (100.0)	42 (95.5)	0.494
MRAs	30 (73.0)	29 (65.9)	0.467
Loop diuretics	33 (80.5)	35 (79.5)	0.913
Baseline laboratory studies			
Median (Q1, Q3) NT-proBNP, pg/mL	1136 (887, 1879)	1419 (611, 3272)	0.153
Median (Q1, Q3) BNP, pg/mL	276 (123, 544)	322 (167, 718)	0.163
eGFR, mL/min/1.73m^2	63.34 ± 18.98	70.34 ± 20.33	0.105
Median (Q1, Q3) urine albumin/creatinine ratio, mg/g	30 (7, 92)	50 (15, 148)	0.929
HbA1c, mmol/mol	165.7 ± 45.9	162.8 ± 48.8	0.78
Haematocrit, %	42.3 ± 4.9	40.8 ± 4.6	0.14
Functional measures			
NYHA class II, n (%)	30 (73.2)	32 (72.7)	0.96
NYHA class III, n (%)	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

Note: Values are shown as mean ± SD, unless otherwise indicated.
Abbreviations: ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BNP, brain natriuretic peptide; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary Score; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association.

The baseline mean NTproBNP was 1903 ± 1775 pg/mL, the mean KCCQ-CSS was 71.7 ± 20.3, and LFV was 34%.

There was no significant difference in mean adjusted LFV at 12 weeks with dapagliflozin versus 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 1A]).

Patients who experienced improvement in LFV, as compared with those who had no change or deterioration in LFV (regardless of treatment allocation), had a numerically greater (although not statistically significant) reduction in NT-proBNP (−439 ± 1374 vs. −47 ± 1273 pg/mL; *P* = 0.2), a significantly greater decrease in BNP (−143 ± 248 vs. −18 ± 185 pg/mL; *P* = 0.01), and a significantly greater improvement in KCCQ-CSS (+5.5 ± 9.6 vs. −2.8 ± 14.0 points; *P* = 0.005; [Figure 1B, C]).

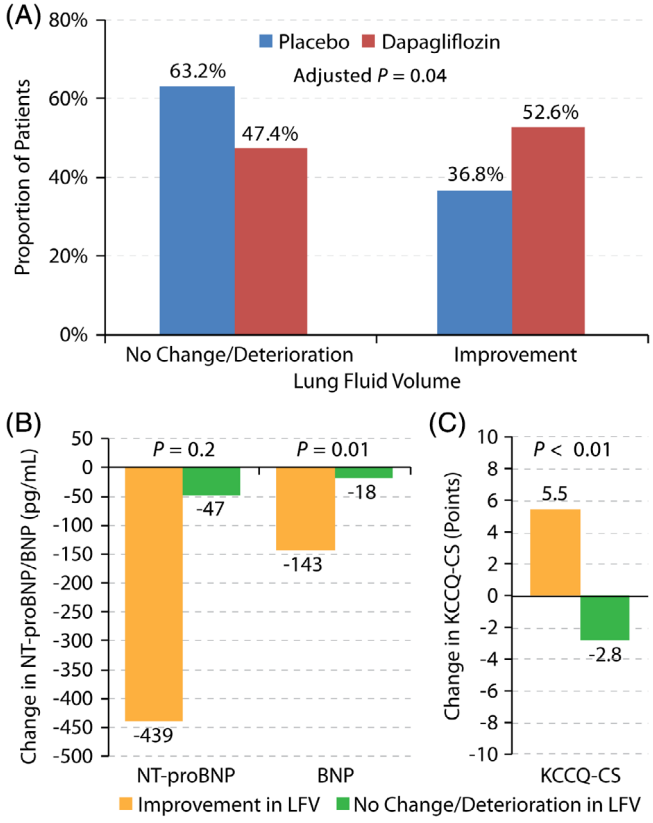

FIGURE 1 **A,** Proportion of patients who experienced a decrease in lung fluid volume (LFV) or no change/increase in LFV with placebo (blue) and dapagliflozin (red). **B,** Change in N-terminal pro B-type natriuretic peptide (NTpropBNP) and BNP from baseline to 12 weeks in patients with a decrease in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

4 | DISCUSSION

In this prespecified substudy 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 SGLT2 inhibitors facilitate osmotic diuresis, and greater fluid clearance from the interstitial fluid space than from the circulating blood volume[6]; and that SGLT2 inhibitors are more effective in reducing interstitial fluid than traditional loop diuretics, thus resulting in congestion relief with minimal impact on blood volume.[9] Our data from the DEFINE-HF trial offer 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 LFVs.

Notably, this was observed in patients already receiving excellent guideline-directed medical and device therapy for HFrEF. To our knowledge, these are the first data from a randomized controlled trial to demonstrate a direct effect of dapagliflozin (or any SGLT2 inhibitor) on more effective "decongestion", contributing in a meaningful way to the ongoing debate regarding the mechanisms of SGLT2 inhibitor HF benefits. Whether this is attributable 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] 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 substudy, not sufficiently powered to detect a modest difference in LFV. Likewise, given the small number of patients, there were some baseline imbalances, notably in the use of cardiac resynchronization therapy, which may have partially influenced the observed effect of dapagliflozin on LFVs. Lastly, well-defined clinically meaningful changes in LFV have not been firmly established, and thus the clinical implications of improvement versus 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.

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Dr Inzucchi: Grant/Research Support; Company Relationship; Dr Inzucchi has participated on clinical trial steering, executive or publications committees including related lectures for Boehringer Ingelheim, Astra-Zeneca, Novo Nordisk, Sanofi/Lexicon, Eisai. Honoraria; Company Relationship; Boehringer Ingelheim, Astra Zeneca, Novo Nordisk, Sanofi/Lexicon, Easai. Consultant; Company Relationship; Astra Zeneca, vTv Therapeutics, Merck, Zafgen, Abbott.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request

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REFERENCES

1. Inzucchi SE, Zinman B, Wanner C, et al. SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcome trials. *Diab Vasc Dis Res*. 2015;12:90-100.
2. Zelniker TA, Wiviott SD, Raz I, 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;393:31-39.
3. Nassif Michael E, Windsor S, Tang F, et al. Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction: the DEFINE-HF trial. *Circulation*. 2019;140(18):1463-1476.
4. McMurray JJV, Solomon SD, Inzucchi SE, et al; Committees D-HT and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008.
5. Amir O, Ben-Gal T, Weinstein JM, et al. 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, et al. Empagliflozin in heart failure: diuretic and cardio-renal effects. *Circulation*. 2020;142:1028-1039.
7. Amir O, Azzam ZS, Gaspar T, et al. 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;221:841-846.
8. Uriel N, Sayer G, Imamura T, et al. Relationship between noninvasive assessment of lung fluid volume and invasively measured cardiac hemodynamics. *J Am Heart Assoc*. 2018;7:e009175.
9. Verma S, 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, et al; Investigators obotD-H and CommitteesEffects of dapagliflozin in DAPA-HF according to background heart failure therapy. *Eur Heart J*. 2020;41:2379-2392.

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