Dapagliflozin initiation in chronic heart failure patients improves central sleep apnoea

Received: 24 Feb 2023
Accepted: 30 April 2023

To the Editor:

Optimising medical cardiac treatment for central sleep apnoea (CSA) in patients with chronic heart failure (CHF) remains under debate with an expert-grade C recommendation [1, 2]. Investigating the impact of established and emerging heart failure therapy on CSA is considered a research priority [3].

Dapagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor that modulates sodium-glucose transport proteins in the renal tubules. SGLT2 inhibitors were originally developed as glucose-lowering agents for the treatment of type 2 diabetes mellitus, but were also identified as potential CHF therapy. SGLT2 inhibitors have a diuretic action, but can exert antihypertrophic, antifibrotic and antiremodelling properties [4]. Thus, SGLT2 inhibitors are an emerging CHF therapy recommended by the 2021 European Society of Cardiology guidelines for patients with reduced left ventricular ejection fraction (LVEF) to reduce the risk of heart failure related hospitalisation and death (grade A) [1]. In 2022, a randomised controlled trial concluded that dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with CHF and a mildly reduced or preserved ejection fraction [5]. Whether dapagliflozin impacts CSA in CHF patients is unknown.

We present here data from a monocentric, open-label, real-life study conducted between 22 September 2020 and 18 October 2021. The design was similar to a previous study investigating the impact of sacubitril/valsartan treatment on sleep apnoea [6], except for the investigated drug (a 10 mg dose of dapagliflozin was administered once daily instead of sacubitril/valsartan).

Briefly, consecutive patients eligible for dapagliflozin (*i.e.* CHF patients who remain symptomatic (New York Heart Association (NYHA) classes II–IV) despite optimal treatment including sacubitril/valsartan when appropriate) were screened for sleep apnoea, including nocturnal ventilatory polygraphy. For patients receiving dapagliflozin after the initial ventilatory polygraphy, with an initial central apnoea–hypopnoea index (cAHI) $\geqslant$5 events·h^{-1} and/or an obstructive apnoea–hypopnoea index (oAHI) $\geqslant$15 events·h^{-1}, a polygraphy control was performed 3 months later. Based on the initial ventilatory polygraphy results, two groups were drawn; group 1: cAHI $\geqslant$5 events·h^{-1} and oAHI <15 events·h^{-1}; group 2: oAHI $\geqslant$15 events·h^{-1} regardless of the cAHI. The study complied with the Declaration of Helsinki and was reviewed and approved by the Montpellier University Hospital institutional review board (agreement number 202100950 and 202201048). Statistics presented here were performed similarly to the ENTRESTO-SAS study [6].

43 consecutive patients were screened (figure 1a) and 18 patients were analysed (group 1 n=12, group 2 n=6). 94.4% were male with a median (interquartile range (IQR)) age of 57 (48.3–65.5) years; 44.4% had ischaemic CHF, and 27.8% had atrial fibrillation. Nine patients had CHF with a reduced LVEF; seven patients had CHF with mildly reduced ejection fraction; and two patients had CHF with preserved ejection fraction. One patient presented a stroke; one patient presented nonsevere chronic kidney disease; and no patients were treated with baclofen, ticagrelor or opioids.

Patients were initially treated with angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker (5.6%), β-blockers (88.9%), spironolactone (66.7%), loop diuretics (72.2%), sacubitril/valsartan (94.4%), cardiac defibrillator (73.3%) and cardiac resynchronisation (26.7%).

Shareable abstract (@ERSpublications)
Dapagliflozin decreases central sleep apnoea in central sleep apnoea patients, thereby sparing the initiation of ventilatory therapy https://bit.ly/41e2fm0

Cite this article as: Jaffuel D, Bouchaut Y, Mallet J-P, *et al*. Dapagliflozin initiation in chronic heart failure patients improves central sleep apnoea. *ERJ Open Res* 2023; 9: 00123-2023 [DOI: 10.1183/23120541.00123-2023].

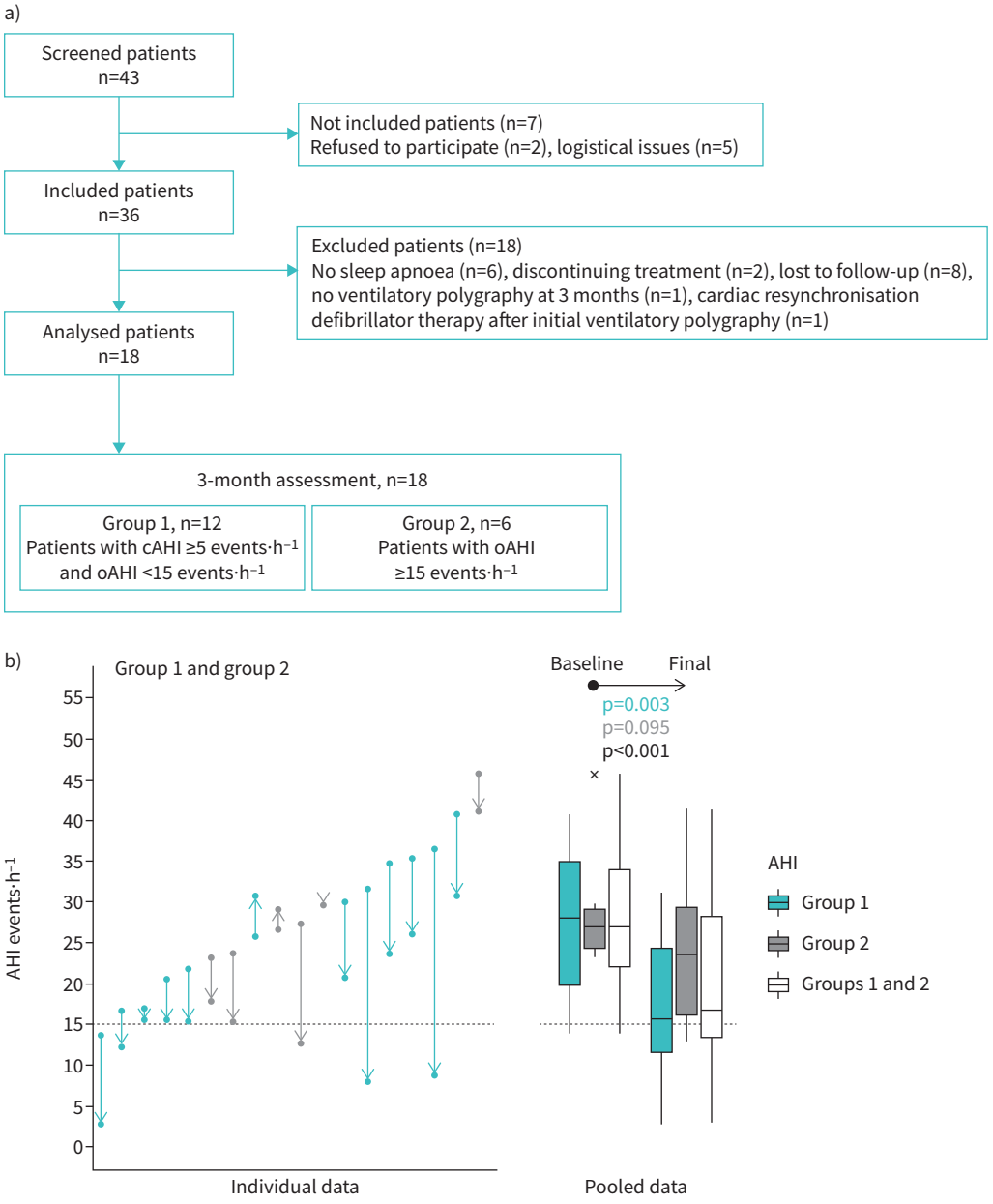

FIGURE 1 a) Study flow chart; b) apnoea–hypopnoea index (AHI) before *versus* after 3 months of dapagliflozin. cAHI: central AHI; oAHI: obstructive AHI.

At 3 months, there was no significant change in these treatments except for the dapagliflozin introduced after the initial polygraphy. No patient presented a cardiac event between the two ventilatory polygraphy assessments (except the excluded patient; figure 1a). No patient was treated with continuous positive airway pressure (CPAP).

At 3 months, in both group 1 and group 2 patients, the AHI primary outcome decreased statistically significantly by a median (IQR) −7.2 (−10.7– −4.3) events·h^{-1}, p<0.001 (figure 1b). The cAHI decreased statistically significantly by a median −4.5 (−9.9– −1.4) events·h^{-1}, p=0.012; the oAHI did not decrease statistically significantly by a median −1.1 (−3.0–1.9) events·h^{-1}, p=0.360. In group 1 patients, the cAHI decreased statistically significantly by a median –8.2 (−11.2– −4.3) events·h^{-1}, p=0.006. In group 2 patients, the oAHI decreased statistically nonsignificantly by a median −3.5 (−10.0– −1.7) events·h^{-1}, p=0.094. For three out of 11 group 1 patients with an initial AHI ⩾15 events·h^{-1}, the final AHI was <15 events·h^{-1} with dapagliflozin initiation avoiding the trial of CPAP proposed by the current guidelines in symptomatic patients [2].

In both group 1 and 2 patients, cycle length of Cheyne–Stokes respiration (CSR) showed a trend to decrease (from a median (IQR) of 47.95 (40.25–50.65) s to 35.75 (0.0–45.45) s, p=0.06), time spent with CSR decreased statistically significantly (from a median 47.99 (6.72–131.25) min to 5.90 (0.0–21.84) min, p=0.001), percentage of CSR decreased statistically significantly (from a median 9.17% (1.54–26.79%) to 1.26% (0.0–5.12%), p=0.010).

In group 1 and 2 patients, median N-terminal pro-brain natriuretic peptide (NT-proBNP) level did not decrease statistically significantly (from median (IQR) 1529 (476–2673) ng·L^{-1} to 842.5 (308–1533) ng·L^{-1}, p=0.102); the degree of dyspnoea showed a trend to decrease (NYHA functional class I/II/II from 27.8%/55.6%/16.7%, respectively, to 61.1%/33.3%/5.6%, respectively, p=0.072), LVEF increased statistically nonsignificantly (from 31.5% (27.2–40.7%) to 35.5% (30.5–41.5%), p=0.132). The Spearman coefficient r was −0.64 for the relative AHI difference and relative LVEF difference (p=0.004); 0.52 for the relative AHI difference and relative NT-proBNP difference (p=0.027) (relative variable difference defined as (initial variable minus final variable)/initial variable). The Spearman coefficient r was −0.52 for the relative AHI central difference and relative LVEF difference (p=0.028).

After 3 months, Epworth Sleepiness Scale decreased statistically nonsignificantly (median (IQR) from 10.5 (6.75–12.25) to 6.5 (3.5–8.25), p=0.140); Pichot Fatigue Questionnaire score decreased statistically nonsignificantly (from 10.5 (4.50–17.25) to 8.5 (5.5–11.75), p=0.527). Body mass index (BMI) decreased statistically nonsignificantly from a median (IQR) 26.19 (25.11–28.69) kg·m^{-2} to 26.18 (24.55–28.94) kg·m^{-2}, p=0.938.

To the best of our knowledge, we report here the first study investigating the impact of dapagliflozin on sleep apnoea in CHF patients. Interestingly, we observed a significant favourable effect of dapagliflozin on CSA, and this effect was observed in a cohort of patients treated with the 2021 recommended treatment [1].

We have recently reported sacubitril/valsartan initiation [6] as a candidate for CSA treatment in CHF patients, avoiding for 10 out of 29 patients a CPAP trial proposed by the current guidelines in symptomatic patients [2]. In this new cohort of sacubitril/valsartan-treated CSA patients, initiation of dapagliflozin avoided a CPAP trial for three out of 11 patients, and an additional three out of 11 patients having a final AHI between 15 and 16 events·h^{-1}.

In contrast to Tang *et al*. [7] (excluding CHF patients), we observed a nonsignificant effect on oAHI. We cannot rule out the possibility of a Type II error in our study because of a smaller number of patients (only six patients with obstructive sleep apnoea *versus* 18 patients in Tang *et al*. [7]). In addition, Tang *et al*. [7] reported a significant difference for BMI (mean±SD 28.17±1.21 kg·m^{-2} initially *versus* 25.92±0.92 kg·m^{-2} after 24 weeks of treatment), whereas we report no significant difference.

To explain dapagliflozin impact on CSA, we hypothesised that as the drug improves cardiac function, it might decrease central events classically considered related to the severity of heart failure. In this regard, it is important to consider the significant correlation for the relative AHI central difference and relative LVEF difference. Studies are needed to test the hypothesis that the beneficial effect of dapagliflozin on AHI is related to biomarkers such as LVEF and/or NT-ProBNP.

In conclusion, given these results and as published previously [6], we believe that optimal medical treatment of CSA CHF patients (*i.e.* including sacubitril/valsartan and dapagliflozin treatment) is a prerequisite before considering a recommended CPAP trial in symptomatic patients [2].

Dany Jaffuel [1,2], Yannick Bouchaut [2,3], Jean-Pierre Mallet [1,2], Célia Vidal [4,5], Nicolas Molinari [4,5], Arnaud Bourdin [1,2] and François Roubille [2,3]

[1]Department of Pneumology, Arnaud de Villeneuve, Regional University Hospital of Montpellier, Montpellier, France. [2]PhyMedExp, University of Montpellier, INSERM U1046, CNRS UMR 9214, Montpellier, France. [3]Department of Cardiology, Arnaud de Villeneuve, Regional University Hospital of Montpellier, Montpellier, France. [4]IDESP, INSERM, PreMEdical INRIA, Univ Montpellier, CHU Montpellier, Montpellier, France. [5]Groupe Adène, Montpellier, France.

Corresponding author: François Roubille (f-roubille@chu-montpellier.fr)

Provenance: Submitted article, peer reviewed.

Conflict of interest: D. Jaffuel reports personal fees from Philips Healthcare and Resmed, personal fees and nonfinancial support from SEFAM, personal fees from Lowenstein, grants and personal fees from Novartis, personal fees from Jazz and Bioprojet, and personal fees and non-financial support from NOMICS, outside the submitted work. J-P. Mallet reports personal fees from Novartis, GSK, Chiesi and PulmonX, outside the submitted work. N. Molinari reports personal fees from ONIRIS, outside the submitted work. A. Bourdin reports grants and personal fees from AstraZeneca, personal fees from Amgen, grants and personal fees from Boehringer Ingelheim, personal fees from Novartis, and grants and personal fees from GlaxoSmithKline, Sanofi Regeneron and Chiesi, outside the submitted work. F. Roubille reports personal fees from AstraZeneca, grants and personal fees from Novartis, personal fees from Servier, Boehringer, Vifor, Bayer, Pfizer, Novo Nordisk, Air Liquide, Abott and Lilly, outside the submitted work. The remaining authors have nothing to disclose.

References

1 McDonagh TA, Metra M, Adamo M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021; 42: 3599–3726.
2 Randerath W, Verbraecken J, Andreas S, *et al.* Definition, discrimination, diagnosis and treatment of central breathing disturbances during sleep. *Eur Respir J* 2017; 49: 1600959.
3 Orr JE, Ayappa I, Eckert DJ, *et al.* Research priorities for patients with heart failure and central sleep apnea. An official American Thoracic Society research statement. *Am J Respir Crit Care Med* 2021; 203: e11–e24.
4 Kaplinsky E. DAPA-HF trial: dapagliflozin evolves from a glucose-lowering agent to a therapy for heart failure. *Drugs Context* 2020; 9: 2019-11-13.
5 Solomon SD, McMurray JJV, Claggett B, *et al.* Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med* 2022; 387: 1089–1098.
6 Jaffuel D, Nogue E, Berdague P, *et al.* Sacubitril-valsartan initiation in chronic heart failure patients impacts sleep apnea: the ENTRESTO-SAS study. *ESC Heart Fail* 2021; 8: 2513–2526.
7 Tang Y, Sun Q, Bai X-Y, *et al.* Effect of dapagliflozin on obstructive sleep apnea in patients with type 2 diabetes: a preliminary study. *Nutr Diabetes* 2019; 9: 32.