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The effects of Dapagliflozin in a real-world population of HFrEF patients with different hemodynamic profiles: worse is better

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Abstract

Background Sodium-Glucose Cotransporter-2 inhibitors (SGLT2i) represent a deep revolution of the therapeutic approach to heart failure (HF), preventing its insurgence but also improving the management of the disease and slowing its natural progression. To date, few studies have explored the effectiveness of SGLT2i and, in particular, Dapagliflozin in a real-world population. Therefore, in this observational prospective study, we evaluated Dapagliflozin's effectiveness in a real-world HF population categorized in the different hemodynamic profiles.

Methods From January 2022 to June 2023, we enrolled 240 patients with chronic HF and reduced ejection fraction (HFrEF) on optimal medical therapy, according to 2021 ESC guidelines, that added treatment with Dapagliflozin from the HF Clinics of 6 Italian University Hospitals. Clinical, biochemical, and echocardiographic parameters were collected before and after 6 months of Dapagliflozin introduction. Moreover, the HFrEF population was classified according to hemodynamic profiles (A: SV ≥ 35 ml/m^2; E/e' < 15; B: SV ≥ 35 ml/m^2; E/e' ≥ 15; C: SV < 35 ml/m^2; E/e' < 15; D: SV < 35 ml/m^2; E/e' ≥ 15). Then, we compared the Dapagliflozin population with two retrospective HF cohorts, hereinafter referred to as Guide Line 2012 (GL 2012) group and Guide Line 2016 (GL 2016) group, in accordance with the HF ESC guidelines in force at the time of patients enrolment. Precisely, we evaluated the changes to baseline in clinical, functional, biochemical, and echocardiographic parameters and compared them to the GL 2012 and GL 2016 groups.

Results Dapagliflozin population (67.18 ± 11.11 years) showed a significant improvement in the echocardiographic and functional parameters (left ventricular ejection fraction [LVEF], LV end-diastolic volume [LVEDV], LVEDV index, stroke volume index [SVi], left atrium volume index [LAVi], filling pressure [E/e' ratio], tricuspid annular plane systolic excursion [TAPSE], tricuspid annular S' velocity [RVs'], fractional area change [FAC], inferior vena cava [IVC diameter], pulmonary artery systolic pressure [sPAP], NYHA class, and quality of life) compared to baseline. In particular, TAPSE

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and right ventricle diameter (RVD1) ameliorate in congestive profiles (B and D); accordingly, the furosemide dose significantly decreased in these profiles. Comparing the three populations, the analysis of echocardiographic parameters (baseline vs follow-up) highlighted a significant decrease of sPAP in the Dapagliflozin population ($p < 0.05$), while no changes were recorded in the GL 2012 and GL 2016 population. Moreover, at the baseline evaluation, the GL 2012 and 2016 groups needed a higher significant dose of furosemide compared to Dapagliflozin group. Finally, Dapagliflozin patients had significantly fewer rehospitalizations (1.25%) compared with the other two groups (GL 2012 18.89%, *p* 0.0097; GL 2016 15.32%, *p* 0.0497).

Conclusions We demonstrate that Dapagliflozin is rapidly effective in an HFrEF real-world population; furthermore, the more significant effect is recorded in HFrEF patients with a congestive profile (B and D), supporting the introduction of Dapagliflozin in patients with a congestive profile and a worse prognosis. In conclusion, our data suggest evaluating the patient's hemodynamic state beyond LVEF in HFrEF.

Keywords Dapagliflozin, SGLT2 inhibitors, Cardiac function, Heart failure with reduced ejection fraction, Hemodynamic profile

Introduction

Heart failure (HF) is an ever-evolving medical and economic challenge [1]. However, more and more therapeutic strategies have been implemented to prevent the onset and to improve the prognosis of this complex medical syndrome [2–4]. Current European and American guidelines for HF strongly recommend the use of a relatively new class of drug, the Sodium-Glucose Cotransporter-2 inhibitors (SGLT2i) [5–7]. This class of drugs was initially introduced as an antidiabetic medication. Since DECLARE TIMI [8] and EMPAREG-OUTCOME [9] demonstrated their potential value in diabetic patients at high cardiovascular risk, their role in the treatment of HF has been established. Subsequent large-scale randomized clinical trials, such as DAPA-HF [10], DELIVER [11], EMPEROR-Reduced [12] and EMPEROR-Preserved [13], demonstrated that Dapagliflozin and Empagliflozin, compared to placebo, reduce major adverse cardiovascular events in patients affected by HF, irrespective of left ventricular ejection fraction (LVEF) and diabetic status.

The use of SGLT2i in clinical practice has become widespread soon, as their efficacy is associated with an excellent safety profile and pleiotropic effects [14–16]. Moreover, this class of drugs has shown to be effective independently of LVEF. However, there are still few real-world studies, and the patients enrolled in trials often do not reflect those who come daily to cardiologist's observations. Consequently, in this prospective observational study, the primary aim is to evaluate how Dapagliflozin affects clinical, biochemical, echocardiographic, and functional parameters in a real-world HF with reduced ejection fraction (HFrEF) population in different hemodynamic settings, with respect to baseline. Indeed, although LVEF classification is the most used for therapeutic choices, it does not consider the hemodynamic state of the patients, and it is based on a single variable parameter that is not representative of the dynamic evolution of the disease. Clinically, patients with HF may be stratified according to the Forrester's classification, into four heamodynamic profiles depending on the peripheral perfusion (cold to warm) and the pulmonary congestion states (wet to dry) [17, 18]; however, echocardiography is an excellent noninvasive hemodynamic tool [19]. Therefore, we applied a well-specified echocardiographic defined haemodynamic classification [19–21] in a real-world HFrEF population, gaining four profiles from non-invasive data, and evaluated the benefits and efficacy of Dapagliflozin in the different groups.

Furthermore, trials on SGLT2i usually compared these drugs to placebo, and only a small percentage of patients had angiotensin receptor-neprilysin inhibitor (ARNI) on board [22]. Consequently, in the second part of our study, we compared Dapagliflozin population and two other HFrEF populations (GL 2012 and GL 2016) on optimal medical therapy (OMT) according to the guidelines in force at the time of evaluation, deriving from a previous study by our center [23], avoiding any crossover. Precisely, we decided not to compare the dapagliflozin population with the non-SGLT2i contemporary population, because the rate of administration of dapagliflozin in our clinic is high and approximately 90% of our HFrEF patients take this drug and the effects of adding dapagliflozin to therapy are already known.

Materials and methods

In this open-label, prospective, observational clinical study, we included 240 patients receiving Dapagliflozin in addition to standard OMT [6], from the HF Clinics of 6 Italian University Hospitals (University Hospital of Salerno, Riuniti Hospital of Foggia, Monaldi Hospital and Federico II University of Naples, San Carlo Hospital of Potenza, and University of Messina). All investigations were carried out according to the principles of the Helsinki Declaration, and approved by local ethics committees for human research (prot. SCCE N° 0019840), and informed consent was obtained from all participants.

To be included in the study, participants had to meet the following criteria: (i) have an age of at least 18 years; (ii) have an HFrEF diagnosis, according to 2021 European Society of Cardiology (ESC) guidelines [6]. To specifically evaluate the effects of Dapagliflozin at 6 months of follow-up and avoid potential biases from other therapy or procedure known to improve cardiac function, we excluded patients subjected to (i) CRT in the previous 6 months and/or (ii) introduction of any of the four pillars in the 2 weeks before enrolment or during the follow-up. Also, we excluded patients with (iii) history of malignancy; (iv) severe hepatic impairment; (v) estimated Glomerular Filtration Rate (eGFR) < 25 ml/min/1.73 m^2, accordingly with the possibility of prescribing this drug in Italy; (vi) echocardiographic images of low quality. On the contrary, we did not exclude patients with severe valvular disease, to reflect real world HFrEF populations. At enrolment, Dapagliflozin was introduced in therapy. The population enrolled was on OMT at the maximum tolerated dose. Parameters were collected on a predefined computerized data sheet, including demographic parameters, medical history, clinical data and pharmacological treatments, laboratory, electrocardiographic, and echocardiographic data. Clinical follow-ups were periodically performed in our HF outpatient clinics. Baseline features and clinical outcomes were reassessed in all patients at 6 months from enrolment. Moreover, the health-related quality of life (HRQoL) was evaluated at baseline and at 6 months, using the Italian adaptation of the EuroQol Group (EQ-5D). The presence of chronic kidney disease (CKD) was defined by a glomerular filtration rate of less than 60 mL/min per 1.73 m^2 (using the last serum creatinine value available at the time of enrolment and CKD-EPI equation). The ischaemic aetiology of the HF syndrome was defined as a previous history of myocardial infarction and/or prior revascularization through percutaneous and/or surgical procedures. Precisely, we have evaluated changes from baseline in clinical, biochemical and echocardiographic parameters in our real-world population, with particular attention to different hemodynamic profiles. Subsequently, to assess differences in outcome between the pre-and post-SGLT2i era, the study population was compared with two retrospective HF cohorts (GL 2016 group and GL 2012 group), on OMT in accordance with 2016 [24] and 2012 ESC HF Guidelines [25]. Precisely, the GL 2016 cohort was enrolled from June 2016 to December 2017, while the GL 2012 was enrolled between January 2014 to May 2016 (before introduction of ARNI in clinical practice). Indeed, GL 2012 patients were treated with the standard HF drugs (including ACEi or ARBs) up-titrated to the maximum tolerated dose, as recommended by 2012 HF ESC guidelines. These patients were matched with the Dapagliflozin group for age and sex. All the patients were stable, and not hospitalized.

Echocardiographic methods are reported in supplementary file.

Haemodynamic classification

By combining E/e′ ratio and SV from baseline echocardiography, patients were classified into four haemodynamic profiles [19–21]:

- Profile A: normal-flow and normal-pressure (SV ≥ 35 ml/m^2; E/e′ < 15);
- Profile B: normal-flow, high-pressure (SV ≥ 35 ml/m^2; E/e′ ≥ 15);
- Profile C: low-flow, normal-pressure (SV < 35 ml/m^2; E/e′ < 15);
- Profile D: low-flow, high-pressure (SV < 35 ml/m^2; E/e′ ≥ 15).

LV stroke volume (SV) and E/e′ were derived from echocardiographic measurement. LV stroke volume was calculated as the product of the cross-sectional area of the left ventricular outflow tract (LVOT) and time-velocity integral (VTI) at LVOT derived by pulsed-wave Doppler; precisely, this method was used to avoid overestimation of systemic output that occurs when 2D-derived stroke volume (difference between LVEDV and LVESV) is applied in patients with significant mitral regurgitation..

Statistical analysis

Continuous variables were reported as mean ± standard deviation. Numbers and percentages were used for categorical variables. The Shapiro–Wilk test was used to check for normal distribution. Student t-test was used to calculate statistical significance between means, while the chi-square and Fisher's exact tests were used to asses statistical significance between categorical parameters (baseline vs. 6 months follow-up). Repeated measures analysis of variance (ANOVA) test was performed to assess changes in clinical, biochemical, echocardiographic parameters and medications data was employed to detect differences among the three study groups (Dapagliflozin vs GL 2016 vs. GL 2012). Precisely, to assess the difference between two groups we used Sidak post-hoc analysis. For all tests, a p-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software version 23.0 (SPSS Inc., Chicago, Illinois), while the graphs were created using GraphPad Prism 6 (GraphPad Software, Boston, MA 02110).

Results

The results are structured as follows: the first section presents the total Dapagliflozin population features; the second section reports the results based on hemodynamic profiles in the Dapagliflozin population; finally, the third section concludes with the comparison of the Dapagliflozin population with GL 2012 and GL 2016 groups.

Total Dapagliflozin population features

No patients were lost at follow-up or needed to interrupt the treatment with Dapagliflozin. Demographic data, comorbidities, and medications of the study population (67.18 ± 11.11 years; 81.50% male) are reported in Tables 1 and 1S. Likewise, clinical and biochemical data of the Dapagliflozin population are reported in Table 2. Precisely, systolic and diastolic blood pressure and heart rate did not change significantly from baseline to follow-up evaluations (Table 2). Moreover, as shown in Table 2, the values of hemoglobin, creatinine, and glomerular filtrate rate did not significantly change at follow-up. As showed in Table 2 and Fig. 1, from baseline to follow-up the following echocardiographic parameters significantly improved: LVEF, LVEDV, LVEDV index (LVEDVi), SV index (SVi), LA volume index (LAVi), E/e′ ratio, TAPSE, RVs', FAC, IVC diameter and sPAP. Instead, there were no relevant modifications for SV and RVD1. Furthermore, QoL significantly improved at follow-up ($p < 0.0001$) (Table 2), while the dose of furosemide did not significantly change from basal to follow-up (Fig. 1). Finally, at 6 months follow-up, we observed no death.

Results based on hemodynamic profiles in the Dapagliflozin population

As reported in the Methods, considering E/e′ and SV, we divided patients into four hemodynamic profiles. Therefore, patients were classified as follows (Fig. 2):

Table 1 Baseline parameters of 3 groups: Dapagliflozin, GL 2016 and GL 2012 group.

Variables	Dapagliflozin (n = 240)	GL2016 (n = 111)	GL2012 n (n = 90)	Dapagliflozin vs GL2016	Dapagliflozin vs GL2012	GL2016 vs GL2012
Demographic data						
Age, years	67.18 ± 11.11	67.10 ± 11.65	67.00 ± 11.20	0.99	1	1
BSA, m^2	1.90 ± 0.19	1.92 ± 0.18	1.90 ± 0.20	1	1	1
Male, n (%)	196 (81.50)	90 (81.08)	73 (81.11)	1	1	1
Comorbidities						
Hypertension, n (%)	169 (70.42)	88 (79.28)	51 (56.70)	0.081	**0.018**	**0.0004**
Dyslipidemia, n (%)	165 (68.75)	85 (76.58)	63 (70.00)	0.132	0.829	0.295
Smoke, n (%)	55 (22.90)	31 (27.93)	33 (36.70)	0.513	**0.020**	0.149
Previous smoke, n (%)	83 (34.58)	12 (10.81)	24 (26.70)	**0.000002**	0.172	**0.003**
Obesity, n (%)	57 (23.75)	43 (38.74)	35 (38.90)	**0.003**	**0.006**	0.982
Diabetes NID, n (%)	61 (25.42)	32 (28.83)	35 (38.90)	0.501	**0.016**	0.133
Diabetes ID, n (%)	34 (14.16)	–	–	–	–	–
Chronic renal failure, n (%)	51 (21.25)	54 (48.63)	49 (54.40)	**0.0000001**	**0.016**	**0**
Atrial fibrillation, n (%)	86 (35.84)	34 (30.63)	22 (24.70)	0.340	0.333	0.051
COPD, n (%)	67 (27.91)	32 (28.83)	21 (23.30)	0.860	0.403	0.381
Anemia, n (%)	37 (15.40)	30 (27.03)	25 (27.80)	**0.010**	**0.010**	0.906
Chronic coronary syndrome, n (%)	88 (36.67)	58 (52.25)	60 (66.70)	0.050	**0.0000005**	**0.039**
Previous ICD implantation, n (%)	101 (42.00)	41 (36.94)	46 (51.10)	0.362	0.142	0.051
Previous CRT-D implantation, n (%)	48 (20.00)	37 (33.33)	12 (13.30)	**0.0066**	0.162	**0.0009**
Sinus rhythm, n (%)	180 (75.00)	89 (80.18)	82 (91.10)	0.287	**0.0012**	**0.030**
Medications						
Proton pump inhibitors, n (%)	183 (76.25)	92 (82.88)	90 (100.00)	0.161	**0.0000002**	**0.00002**
Mineralcorticoid receptor antagonists, n (%)	143 (59.58)	57 (51.35)	52 (57.80)	0.148	0.767	0.365
Furosemide, n (%)	155 (64.58)	100 (90.09)	83 (92.20)	**0.0000004**	**0.0000004**	0.600
Furosemide, mg	38.57 ± 47.45	61.18 ± 45.36	65.75 ± 82.26	**0.006**	**0.002**	0.844
Beta blockers, n (%)	201 (83.75)	91 (81.98)	85 (94.40)	0.681	**0.011**	**0.008**
ACE—inhibitors, n (%)	26 (10.83)	5 (4.50)	76 (84.40)	0.052	0	0
Angiotensin receptor antagonists, n (%)	13 (4.29)	–	14 (15.60)	–	**0.002**	–
Angiotensin receptor neprilysin inhibitors, n (%)	160 (66.67)	90 (81.08)	–	**0.005**	–	–

One-Way ANOVA except for *unpaired t test Dapagliflozin vs GL 2012 population and ** unpaired t test Dapagliflozin vs GL 2016 population. Bold values denote statistical significance at the $p < 0.05$ level

ACE, Angiotensin-Converting Enzyme; ARNI, Angiotensin Receptor-Neprilysin Inhibitor; BSA, Body Surface Area; COPD, Chronic Obstructive Pulmonary Disease; CRT-D, Cardiac Resynchronization Therapy Defibrillator; ICD, Implantable Cardioverter Defibrillator; ID, Insulin Dependent; NID, Non-insulin dependent

Table 2 Clinical, biochemical and echocardiographic parameters of Dapagliflozin population (baseline vs. 6 months follow-up)

Variables	Baseline	6 M-follow-up	*p* value
Clinical data			
Systolic blood pressure (mmHg)	118.78 ± 16.78	117.50 ± 14.08	0.3659
Diastolic blood pressure (mmHg)	70.72 ± 10.49	70.05 ± 9.40	0.4336
Heart rate (bpm)	70.48 ± 13.35	68.52 ± 10.59	0.1184
Quality of life (%)	60.82 ± 12.06	77.29 ± 12.07	**< 0.0001**
Biochemical data			
Creatinine (mg/dl)	1.19 ± 0.40	1.18 ± 0.44	0.8072
Glomerular filtrate (ml/min)	68.96 ± 28.22	75.50 ± 27.23	0.1102
Haemoglobin (g/dl)	13.28 ± 1.81	13.27 ± 2.02	0.4271
Echocardiographic data			
LVEF (%)	32.27 ± 8.34	35.92 ± 8.43	**< 0.0001**
LVEDV (ml)	184.37 ± 66.05	171.92 ± 57.26	**0.0281**
LVEDVi (ml/m^2)	96.25 ± 33.66	90.01 ± 30.05	**0.0331**
LVESV (ml)	128.62 ± 57.48	113.14 ± 47.90	**0.0015**
LVESVi (ml/m^2)	66.55 ± 1.94	58.97 ± 1.64	**0.0031**
SV (ml)	56.59 ± 17.64	59.01 ± 16.10	0.1217
SVi (ml/m^2)	29.69 ± 0.58	31.04 ± 0.53	0.1789
LAVi (ml/m^2)	47.17 ± 17.85	42.42 ± 14.89	**0.0013**
E/e' ratio	12.59 ± 5.47	10.99 ± 5.20	**0.0012**
TAPSE (mm)	18.89 ± 3.90	19.92 ± 3.78	**0.0036**
RVs' (cm/sec)	9.83 ± 2.10	10.70 ± 4.48	**0.0138**
FAC (%)	43.52 ± 9.73	46.84 ± 8.97	**0.0044**
RVD1 (mm)	36.74 ± 0.70	35.52 ± 0.60	0.1865
ICV diameter (mm)	18.19 ± 3.88	16.38 ± 4.09	**< 0.0001**
sPAP (mmHg)	37.99 ± 12.97	32.98 ± 9.72	**< 0.0001**

LVEF, Left ventricular ejection fraction; LVEDV, Left ventricle end-diastolic volume; LVEDVi, Left ventricle end-diastolic volume index; SV, Stroke volume; Svi, Stroke volume index; LAVi, Left atrium volume index; E, Early-wave transmitral diastolic velocity; e', Early-diastolic velocity at tissue Doppler imaging; TAPSE, Tricuspid annular plane systolic excursion; RVs', Tricuspid annular S' velocity; FAC, Fractional area change; RVD, Right ventricle diameter; IVC, Inferior vena cava; sPAP, Pulmonary artery systolic pressure. Bold values denote statistical significance at the p < 0.05 level

- 85 patients as profile A (normal flow, normal pressure);
- 34 patients as profile B (normal flow, high pressure);
- 76 patients as profile C (low flow, normal pressure);
- 45 patients as profile D (low flow, high pressure).

No significant changes were recorded in the clinical and biochemical parameters even after they were divided into the four hemodynamic profiles (biochemical data not shown).

The main results of the echocardiographic parameters according to the four hemodynamic profiles are reported in Fig. 3.

Specifically, LVEF and E/e' ratio significantly improved in all profiles, while LVEDV had a remarkable improvement only in profile A ($p<0.001$), and LVESV improved significantly in profile A ($p<0.001$) and B (p 0.040). Moreover, TAPSE significantly improved only for the congestive profiles B and D ($p<0.001$); accordingly, RVs' had a significant improvement in the same profiles (profile B: p 0.001; profile D $p<0.001$).

Furthermore, FAC had a remarkable reduction for profile A (p 0.005), B ($p<0.001$), and D (p 0.008), while no significant changes were recorded for profile C.

RVD1 improves only in profile B (p 0.037) and D (p 0.002). Finally, LAVi had a significant improvement only in profile A (p 0.001) and B (p 0.029).

Moreover, patients of all four hemodynamic profiles significantly improved in QoL (profile A, profile B, and D $p<0.001$ and profile C p 0.004) (Fig. 4) and in NYHA class (Fig. 5).

Contrary to the results obtained from the analysis of the total population, the dose of furosemide had no significant changes for profiles A and C but had a significant decrease in profiles B ($p<0.001$) and D (p 0.001) (Fig. 4).

Comparison of Dapagliflozin population with GL 2012 and GL 2016

As reported in Methods, our population was compared with two retrospective HF cohorts defined as GL 2012 and GL 2016 groups. The demographic and anamnestic data of GL 2012 and GL 2016 groups are reported in Table 1. All the groups were comparable for demographic parameters.

The analysis of echocardiographic parameters, from baseline to 6 months follow-up, highlighted a significant decrease of sPAP in the Dapagliflozin population ($p<0.00001$), while no changes were recorded in GL 2012 and GL 2016 groups (Fig. 6). It must be emphasized that the basal sPAP of the three groups was similar.

Moreover, at the baseline evaluation, GL 2012 group needed a significantly higher dose of loop diuretic compared to the baseline dose of furosemide of the Dapagliflozin group, while there were no differences between the basal loop diuretic dose comparing GL 2012 group and GL 2016 group.

Finally, DAPA patients had significantly fewer rehospitalizations (1.25%) compared with the other two groups (GL 2012 18.89%, p 0.0097; GL 2016 15.32%, p 0.0497) (Fig. 6).

Discussion

Our real-world, multicenter, and observational study demonstrates how Dapagliflozin can produce beneficial effects in HFrEF patients in all hemodynamic conditions from clinical, instrumental, and QoL points of view. The favorable effects are particularly evident in congestive patients, typically those with more advanced HF.

Several clinical trials on SGLT2i focused on the prognostic effects of SGLT2i in rehospitalization and mortality rates; conversely, a few real-world data provide an idea

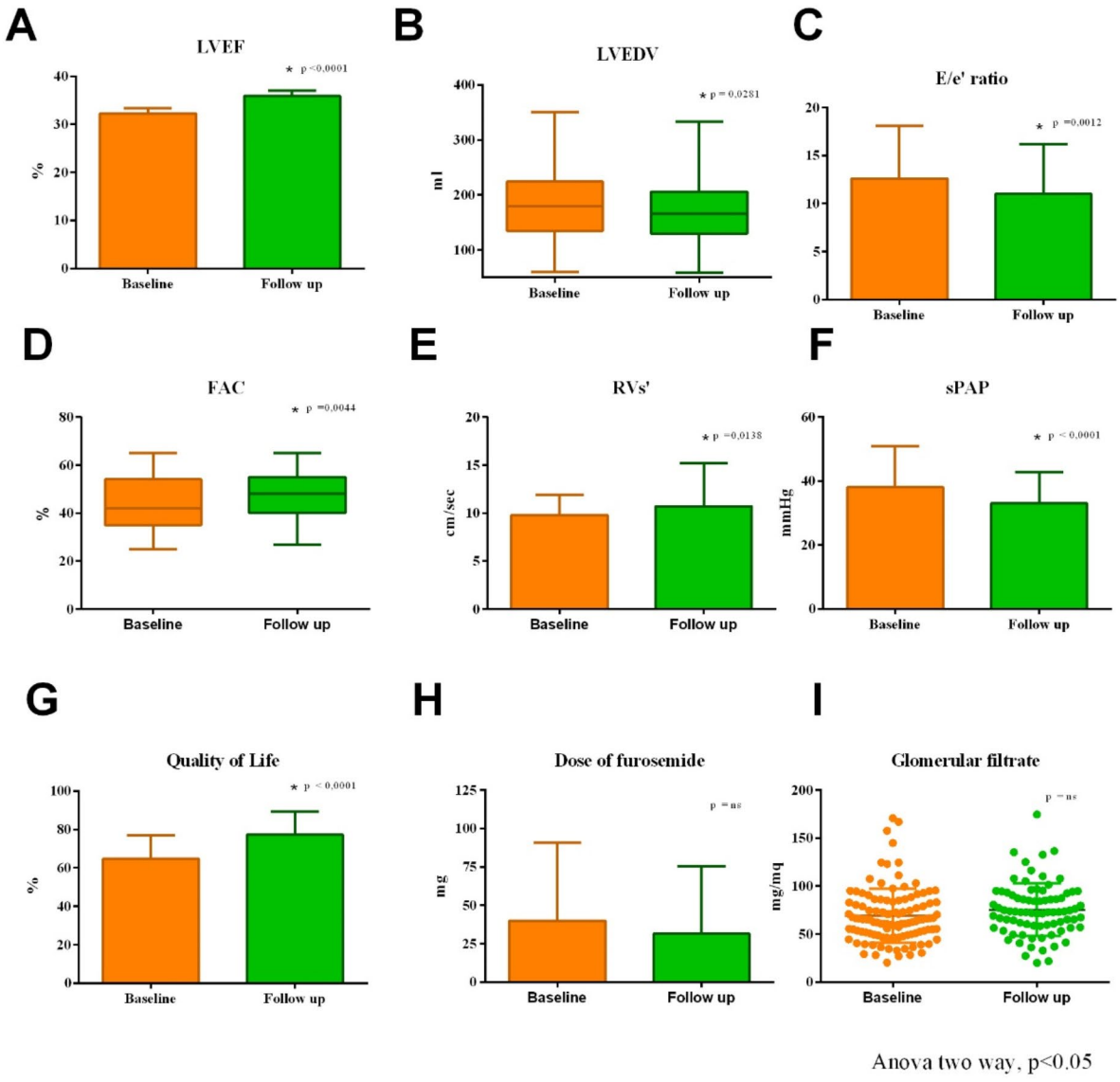

Fig. 1 Changes from baseline to 6 months follow-up of clinical, biochemical, echocardiographic and pharmacological parameters of Dapagliflozin population. The graphs show that a significant improvement was observed in LVEF (**A**), LVEDV (**B**), E/e' ratio (**C**), FAC (**D**), RVs' (**E**), sPAP (**F**), and quality of life (**G**). In contrast, there were no significant changes in dose of furosemide (**H**) and glomerular filtration (**I**). LVEF, Left ventricular ejection fraction; LVEDV, Left ventricle end-diastolic volume; E, Early-wave transmitral diastolic velocity; e', Early-diastolic velocity at tissue Doppler imaging; FAC, Fractional area change; RVs', Tricuspid annular S' velocity; sPAP, Pulmonary artery systolic pressure

of the hemodynamic and pathophysiological mechanisms involved [26, 27].

Therefore, our study aimed to highlight the huge diversity of HF patients. Per this, we introduce a hemodynamic subclassification of our population, categorized by congestion and perfusion balance. Current literature offers numerous suggestions for thought in this regard. Dini et al. [28] used a subdivision into hemodynamic profiles very similar to ours to evaluate prognostically patients affected by HFrEF who introduced ARNIs into therapy.

Firstly, we did not observe significant changes in blood pressure and heart rate values, confirming excellent hemodynamic tolerability of Dapagliflozin. Indeed, 32% of our Dapagliflozin population was not treated with ARNI, mainly due to intolerance (symptomatic hypotension and renal impairment).

On the other hand, in our clinics only approximately 10% of HFrEF patients do not take SGLT2i, mostly due to recurrent genitourinary tract infections. This data is in line with real world studies and data [29].

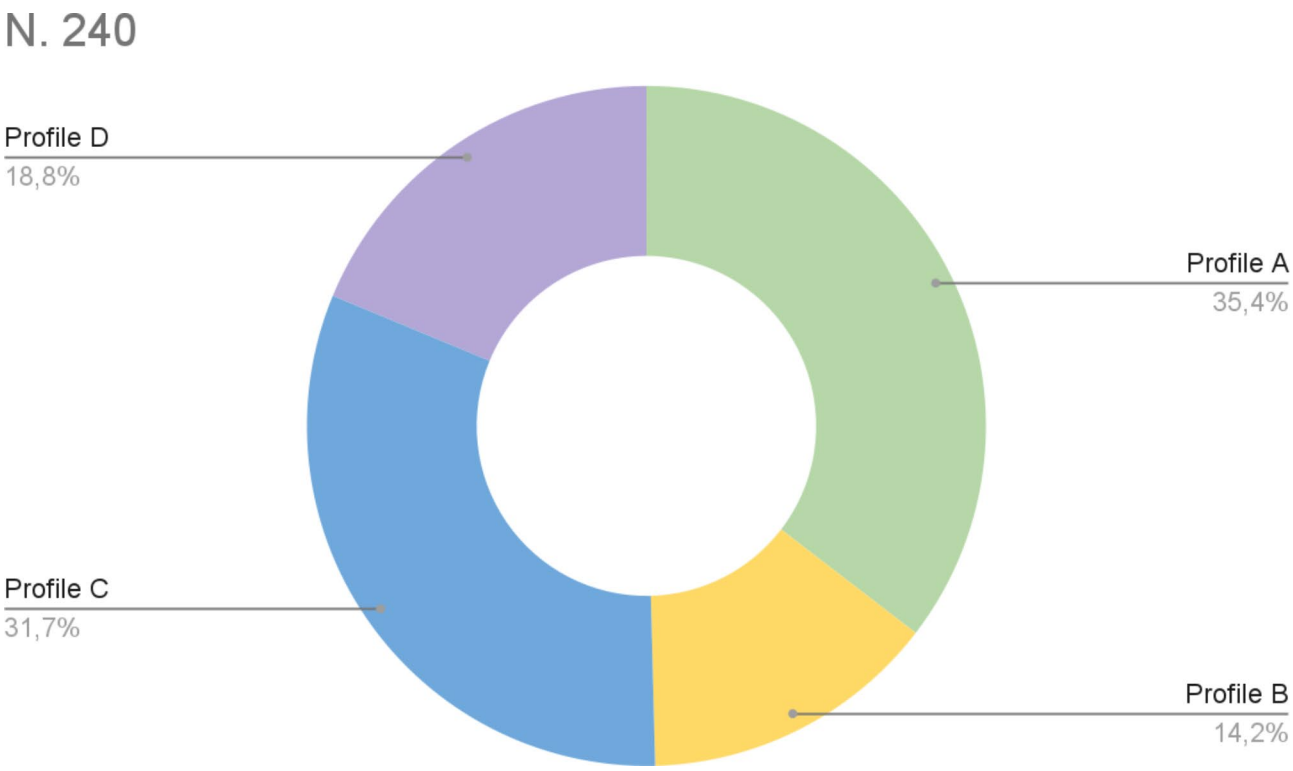

Fig. 2 Baseline hemodynamic profile of Dapagliflozin population: profile A (normal flow, normal pressure); profile B (normal flow, high pressure); profile C (low flow, normal pressure); profile D (low flow, high pressure)

Echocardiographycally, our data highlighted an increased global contractile function of the LV (LVEF and SVi), simultaneously reducing the LVEDV and LVEDVi. Regarding the changes in LV remodelling, a positive effect of SGLT2i on LV remodelling has been found in patients with type 2 diabetes and/or HFrEF [30–32]. Accordingly, DAPA-MODA study [33] recorded an improvement in left ventricular geometry. Moreover, as already shown in the literature [34, 35], SGLT2i affects body weight, and consequently body surface area (BSA); accordingly, in our patients, there was a reduction of BSA at follow-up (data not shown) with a simultaneous improvement of SVi but not of SV. Nonetheless, by dividing the population into haemodynamic profiles, LVEDV had a remarkable improvement only in profile A ($p<0.0001$), while LVEF significantly improved in all profiles. Precisely, the improvement in global cardiac contractility is not only due to a remodeling of the cardiac chambers but also to RV function because RV and LV interaction contributes to cardiac dyssynchrony [36]. RV dysfunction may impair LV function by reducing LV preload and unfavorably affecting the systolic and diastolic interaction via the intra-ventricular septum and the pericardium (ventricular interdependence) [36]. In HFrEF patients, changes in RV performance may be a sensitive indicator of variations in LV function [36, 37].

To date, the literature has little evidence of the effects of SGLT2i on RV contractility and on improving the degree of hemodynamic compensation. Only a small and monocentric study by Mustapic et al. [38] highlighted how SGLT2i substantially improved RV contractility after three months. Accordingly, our multicentric study extends this observation after six months of follow-up in a larger population, especially in the congestive profiles.

Improving the RV function opens another scenario: a reduced RV contractility negatively affects the application of OMT. In particular, some real-world studies identified how a right dysfunction was associated with a more frequent interruption of ARNI [39]. Moreover, baseline RV dysfunction hampers ARNI up-titration, as demonstrated in our recent study [39].

Consequently, the use of this class of drugs could potentially increase the patients' tolerability to ARNI due to the improvement in the RV's performance.

Likewise, we observed an improvement in the hemodynamic profile of the enrolled population, possibly due to the improved performance of the RV. Moreover, our data highlighted how Dapagliflozin is effective in all hemodynamic profiles of HFrEF without affecting renal function and hemodynamic parameters, strongly supporting the concept of SGLT2i as the first pillar in the management of HFrEF [40].

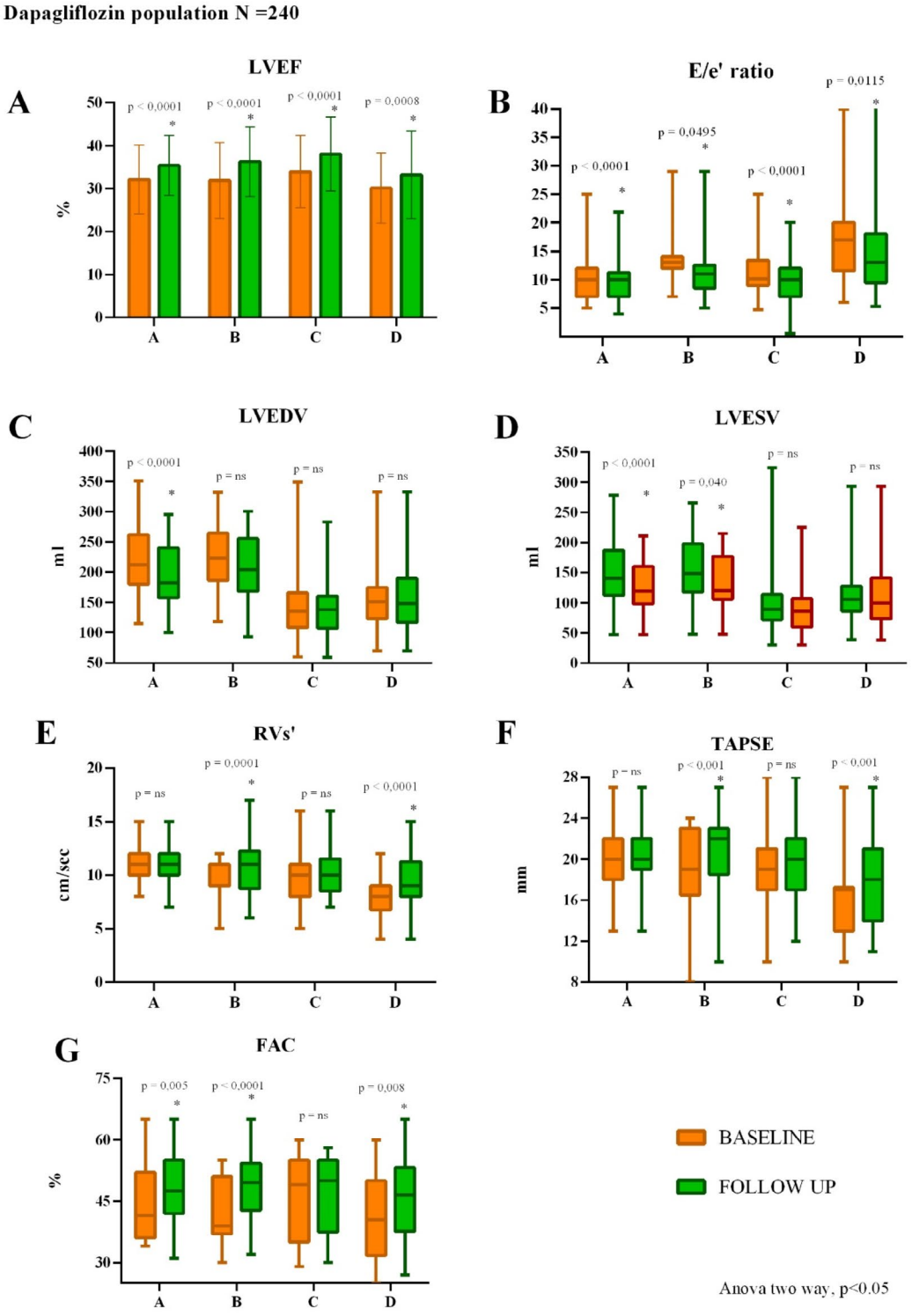

Fig. 3 Changes from baseline to 6 months follow-up of echocardiographic parameters of the four hemodynamic profiles. **A** LVEF significantly improved in all profiles. **B** E/e' significantly improved in all profile. **C** LVEDV significantly improved only in profile A. **D** LVESV significantly improved only in profile A and B. **E** RVs' significantly improved in congestive profiles (B and D). **F** TAPSE significantly improved in congestive profiles (B and D). **G** FAC significantly improved in profile A, B and D. LVEF, Left ventricular ejection fraction; E, Early-wave transmitral diastolic velocity; e', Early-diastolic velocity at tissue Doppler imaging; LVEDV, Left ventricle end-diastolic volume; LVESV, Left ventricle end-systolic volume; RVs', Tricuspid annular S' velocity; TAPSE, Tricuspid annulus plane systolic excursion; FAC, Fractional area change

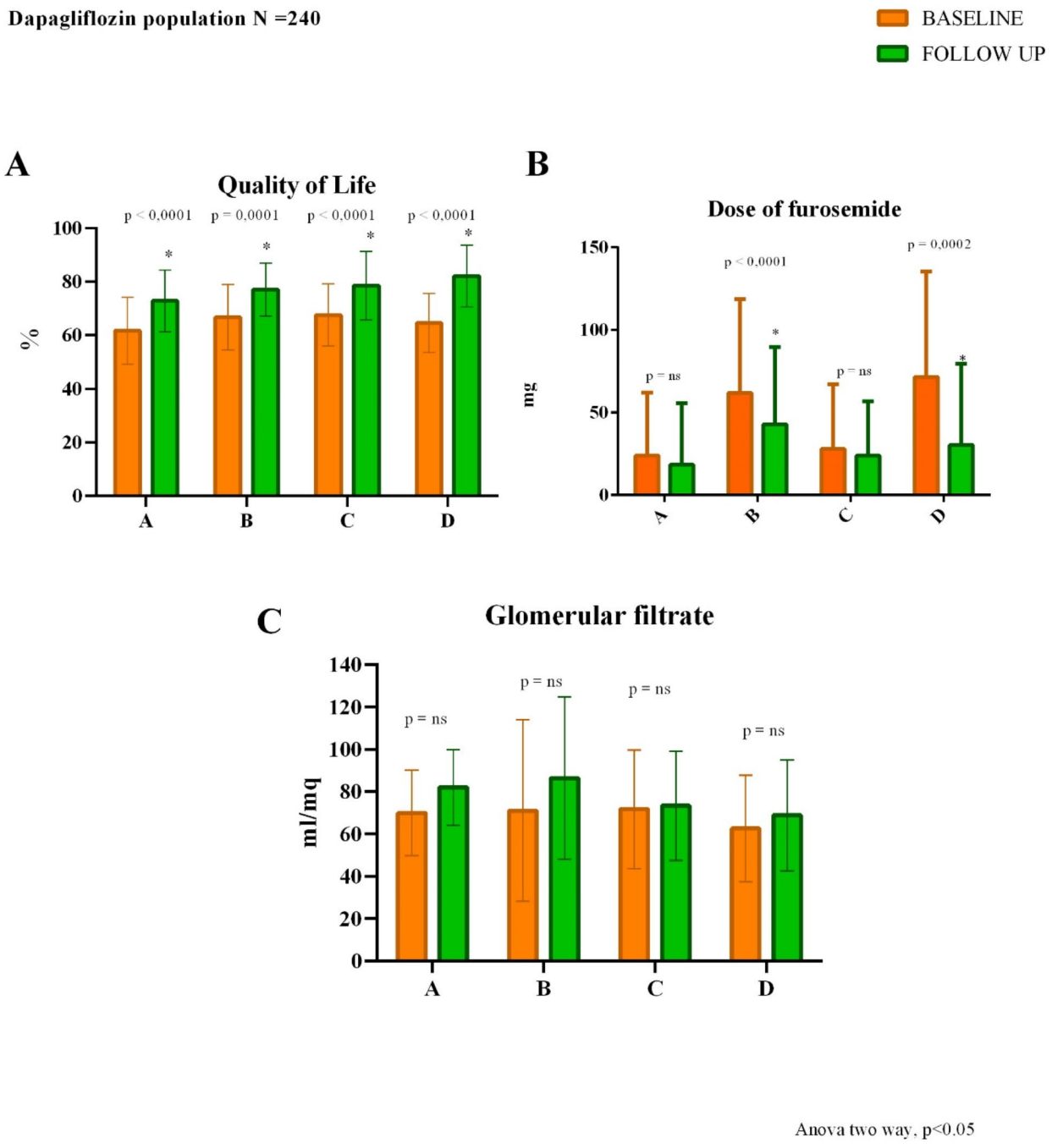

Fig. 4 Changes from baseline to 6 months follow-up of quality of life (**A**), dose of furosemide (**B**) and glomerular filtrate (**C**)

The analysis of the biochemical data highlights how, at follow-up, there were no substantial changes in the creatinine and glomerular filtration data. Indeed, DAPA-CKD [41] and DECLARE-TIMI [8] demonstrate a nephroprotective effect of Dapagliflozin. Nephroprotection is an essential element of SGLT2i effects [42]; indeed, one of the major difficulties of physicians using HF medications is reaching a compromise between the optimization of medical therapy and the protection of renal function.

It must be emphasized that HFrEF represents a therapeutic challenge with multiple objectives. Indeed, it is needed to maintain an adequate hemodynamic balance and guarantee an adequate QoL [43]. Our results show how Dapagliflozin constitutes a fair compromise in this sense, providing clinical benefit while positively affecting

Fig. 5 Changes from baseline to 6 months follow-up of NYHA class according to the four hemodynamic profiles. The Sankey diagrams show that patients of all four hemodynamic profiles significantly improved in the NYHA class. NYHA, New York Heart Association

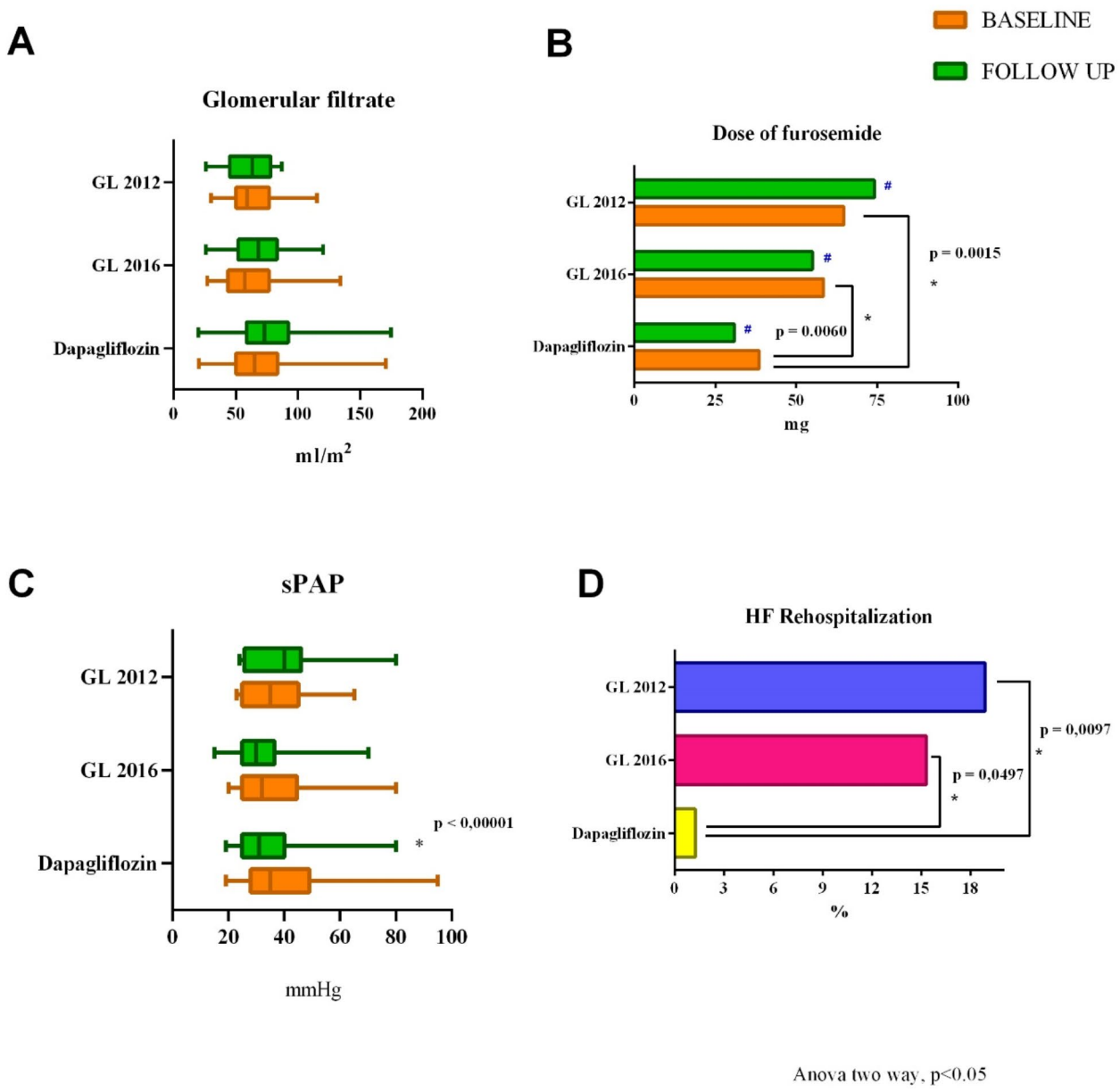

Fig. 6 Comparison of GL 2012, GL 2016 and Dapagliflozin population in terms of glomerular filtrate (**A**), dose of loop diuretic (**B**), sPAP (**C**) and HF rehospitalizations (**D**). GL, Guideline; HF, Heart Failure; sPAP, Pulmonary artery systolic pressure; #, *p* (baseline vs. follow up) > 0.05

subjectively perceived QoL. Accordingly, in DAPA-HF patients who received Dapagliflozin were more likely to have a clinically relevant improvement in their QoL after only eight months of treatment, as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) [10]. The beneficial effects of SGLT2i appeared even earlier in the DEFINE-HF, in which Dapagliflozin increased the proportion of patients achieving a combined endpoint of improved functional status (as measured by the KCCQ), or ≥20% reduction in NT-proBNP [44]. Our real-world observations perfectly fit with the results of RCT, supporting the use of Dapagliflozin as early as possible for managing HF patients.

Intriguingly, a previous investigation showed a good impact on physical function measured with a 5 m gait speed [45]. In this regard, it is essential to note that although the dose of loop diuretic remains constant in follow-up, there is a substantial difference in dosage when comparing the Dapagliflozin population to GL 2012 and GL 2016 groups. The mechanism is certainly due, at least in part, to the glycosuric effect of SGLT2i [46].

Finally, we reported fewer HF hospitalizations in Dapagliflozin population, compared to GL 2012 and GL 2016 groups. These data are in line with the literature [10], and the rate reduction of HF rehospitalization is a fundamental objective due to the evident prognostic impact.

In conclusion, the classification of HF based on LVEF gives a static image of this disease. SGLT2i and their beneficial effect independent of this echocardiographic parameter open the doors to a new definition of HF. Indeed, the HF patient is dynamic, and therapy should be personalized based on the hemodynamic characteristics. From this perspective, the LVEF, although constituting an essential cornerstone, can no longer represent the only prognostic parameter. Still, it should be accompanied by new parameters that can capture the complexity of this disease.

Study limitation

Our results cannot be extended to patients with HF with mildly reduced ejection fraction (HFmrEF) or preserved ejection fraction (HFpEF). Furthermore, our real-world patients were enrolled in the maximum OMT tolerated for several years at enrolment, and the follow-up was relatively short. The three groups are comparable in terms of age, gender and BSA, but there are differences in comorbidities. Moreover, patients with HFrEF are hemodynamically dynamic, so these data must be verified over a more extended period. Our results also require further validation on larger sample sizes.

Conclusions

HFrEF represents an ongoing therapeutic challenge, and the number of patients in this category constantly increases. To date, cardiologists are faced with increasingly complex therapeutic choices and increasingly personalized patient management. Precisely, in our real world study, we enrolled different etiologies of HFrEF patients, showing the effectiveness of this drug in different contexts, as well as in different hemodynamic profiles, and the benefits are evident already at 6 months. Furthermore, the patients who are worse off (profile D) respond best to the drug, suggesting a beneficial effect on the hemodynamic balance.

Additionally, although this data needs to be validated on a larger population, Dapagliflozin improves the performance of the RV, suggesting greater tolerance of the other therapeutic pillars for the treatment of HF. Furthermore, Dapagliflozin is well tolerated by the patient and improves the subjective perception of QoL.

Abbreviations

ARNI	Angiotensin receptor-neprilysin inhibitor
ASE	American Society of Echocardiography
CKD	Chronic kidney disease
EACVI	European Association of Cardiovascular Imaging
EAE	European Association of Echocardiography
ESC	European Society of Cardiology
FAC	Fractional area change
FU	Follow-up
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart Failure with reduced ejection fraction
HRQoL	Health-related quality of life
IVC	Inferior vena cava
KCCQ	Kansas City Cardiomyopathy Questionnaire
LA	Left atrium
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
LVESV	Left ventricular end-systolic volume
LVOT	Left ventricular outflow tract
OMT	Optimal medical therapy
RV	Right ventricle
RVD1	Basal RV diameter
RVs'	Tricuspid annular S' velocity
SGLT2i	Sodium-Glucose Cotransporter-2 inhibitors
sPAP	Pulmonary artery systolic pressure
SV	Stroke volume
TAPSE	Tricuspid annulus plane systolic excursion
VTI	Time-velocity integral

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Author contributions

Conceptualization: CV, MC, VV, Methodology: FL, PM, AR, RDF, MC, VV, Formal analysis: FL, AR, MC, VV, Data Curation: FL, PM, AR, RDF, DM, CM, MCo, AV, MG, PM, VM, FF, EDS, CI, AC, NV, ES, SB, GD, CGT, GS, MC, VV, Echocardiography: FL, AR, AV, MG, DM, FF, EDS, PM, ES, SB, GD. Investigation: FL, PM, AR, RDF, DM, CM, MCo, AV, MG, PM, VM, FF, EDS, NV, ES, SB, GD, CGT, GS, MC, VV, Writing—original draft preparation: FL, PM, AR, RDF, MC, VV, Writing—review and editing: FL, PM, AR, GS, LF, CV, MC, VV, Supervision: CV, MC, VV. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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