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Type 2 diabetes mellitus pharmacological remission with dapagliflozin plus oral semaglutide☆

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ABSTRACT

Dapagliflozin, a sodium-glucose co-transporter-2 inhibitor and semaglutide, a glucagon-like peptide 1 receptor agonist, have both demonstrated efficacy in glycemic control, reducing blood pressure, body weight, risk of renal and heart failure in type 2 diabetes mellitus. In this observational, real-world, study we aimed to investigate the efficacy of the combination therapy with those two agents over glycemic control. We thus obtained the data of 1335 patients with type 2 diabetes followed by 11 Diabetes centers in Lombardia, Italy. A group of 443 patients was treated with dapagliflozin alone, the other group of 892 patients was treated with the combination therapy of dapagliflozin plus oral semaglutide. We analyzed changes in glycated hemoglobin from baseline to 6 months of follow-up, as well as changes in fasting glycemia, body weight, body mass index, systolic and diastolic pressure, heart rate, creatinine, estimated glomerular filtration rate and albuminuria. Both groups of patients showed an improvement of glycometabolic control after 6 months of treatment; indeed, the treatment with dapagliflozin plus oral semaglutide showed a reduction of glycated hemoglobin of 1.2% as compared to the 0.5% reduction observed in the dapagliflozin alone group. Significant changes were observed in body mass index, fasting plasmatic glucose, blood pressure, total cholesterol, LDL and albumin to creatinine ratio, with a high rate (55%) of near-normalization of glycated hemoglobin. Our real world data confirmed the potential of the oral combination therapy dapagliflozin with semaglutide in inducing pharmacological remission of type 2 diabetes mellitus.

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1. Introduction

In the last 15 years or so, several novel therapeutic agents have been discovered for type 2 diabetes mellitus treatment. Particularly, the sodium-glucose contransporter-2 inhibitors (SGLT2i) and the Glucagon-like peptide-1 receptor agonists (GLP-1RA) [1] have demonstrated effectiveness. SGLT2i are a class of drugs acting on proximal convoluted tubule inhibiting the reabsorption of glucose, which is then excreted in the urine. SGLT2i were shown to reduce the progression of diabetic kidney disease, liver fibrosis, heart failure and cardiovascular in patients with type 2 diabetes [2–5]. GLP-1RA are a class of drugs which increase glucose-dependent insulin release, reduce glucagon secretion and decelerate gastric emptying, the latter inducing post-prandial fullness and weight loss [2,6–8]. Among SGLT2i, Dapagliflozin is a selective inhibitor which has a demonstrated strong efficacy in achieving optimal glycemic control, in combination with all other benefits of SGLT2i class described above [9,10]. Oral semaglutide is a GLP-1RA that has shown effectiveness in ameliorating both glycometabolic and is the first GLP-1RA developed as an oral medication, allowing an earlier initiation of GLP-1RA therapy [11,12]. Combining agents from those two classes of drugs has shown to ameliorate glycemic profile and blood pressure control [13–17]. Some studies have also shown that this combination determines a reduction in systolic blood pressure and triglycerides levels [13]. The combination therapy of dapagliflozin and oral semaglutide has not been previously investigated, on glycometabolic control in patients with type 2 diabetes mellitus. The aim of this study was to evaluate the efficacy of the combination therapy with dapagliflozin together with oral semaglutide on glycemic control in patients with type 2 diabetes and potentially in inducing the remission of type 2 diabetes in the real clinical practice.

2. Materials and methods

The PRECARE2 study is an observational, observational, real world, multicenter study, aimed at evaluating the effects of the combination therapy with dapagliflozin plus oral semaglutide on glycometabolic control and in inducing remission of type 2 diabetes. Data were collected from 11 Diabetes Centers in Lombardia, Italy. The participant centers were: Sacco and Fatebenefratelli Hospitals (Milan) (coordinating centers), Monzino Hospital (Milan), San Paolo Hospital (Milan), San Carlo Hospital (Milan), Multimedica Sesto San Giovanni Hospital, Papa Giovanni Hospital (Bergamo), San Matteo Hospital (Vigevano), San Giuliano Milanese Hospital, Ospedali Civili Hospital (Brescia). The inclusion criteria were: (a) age $>$ 18 years old; (b) diagnosis of type 2 diabetes, according to the American Diabetes Association indications for at least 3 months; (c) therapy with dapagliflozin (*dapa*) or dapagliflozin plus oral semaglutide (*dapa*+*sema*). The following data were collected at the baseline visit and after 6 months of treatment: duration of the disease, weight, height, body mass index, estimated glomerular filtration rate (according to CKD-EPI), blood pressure, glycated hemoglobin (HbA1c), fasting blood sugar, total cholesterol, HDL cholesterol, triglycerides, calculated LDL cholesterol, creatinine, urinary albumin to creatinine ratio (ACR) (mg/g), presence of diabetic retinopathy, history of ischemic heart disease, heart failure, cerebral vascular disease (transient ischemic attack or stroke), peripheral vascular disease as well as PRE-visit hypoglycemic therapy. In the follow-up visit some additional data were collected, including side effects and drug suspension. Changes in HbA1c from baseline to 6 months of follow-up, as well as in fasting glycemia, body weight, BMI, systolic and diastolic pressure, heart rate, creatinine, eGFR and albuminuria were also analyzed. Normoalbuminuria was defined as an albumin to creatinine ratio (ACR) $<$ 30 mg/g or with an albumin excretion rate (AER) $<$ 30 mg/24 h; microalbuminuria was defined in the presence of an ACR between 30 and 299 mg/g or with an AER of 30–299 mg/24 h while macroalbuminuria was defined with ACR$>$ 300 mg/g or AER$>$ 300 mg/24 h. Body Mass Index (BMI) was estimated as patient's weight (kg) divided by his/her height (meters) squared. BMI classifications was defined as underweight (under 18.5 kg/m^2), normal weight (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2), class 1 obesity (30 to 34.9 kg/m^2), class 2 obesity (35 to 39.4 kg/m^2) and class 3 obesity (40 or more). All data were analyzed by the Coordinating Center. Quantitative data are described as mean ± standard deviation and range, whereas qualitative variables have been expressed as absolute number of cases and as percentage of the cohort of evaluated patients. Normal distribution of all parameters was assessed by means of the Shapiro Wilk test. Statistical differences were determined by Mann–Whitney U and Student's t tests for nonparametric and parametric continuous variables, respectively. Discrete variables were compared by the $\chi 2$ Test or the Fisher's Exact Test. The p value for statistical significance was defined as $<$ 0.05. Differences between groups were determined by ANOVA for normally distributed variables, and by Mann-Whitney test for those not normally distributed. Levels of significance was set at $p < 0.05$. Binary logistic regression with a stepwise selection approach was employed to determine the major contributors to achieve HbA1c$<$ 6.5%. Dichotomic dependent variable was HbA1c $<$ 6.5% (1/0), while independent variables taken in account were sex, age, years of disease, BMI (Kg/m^2), FPG (mg/dl) and HbA1c (%) values at baseline, type of treatment and eGFR (mL/min/1.73 m^2) values at baseline. All statistical analyses have been performed using statistical package SPSS for Windows version 20.0 (SPPS Inc. Chicago, IL). In cases of drop-out, only the data available up to the time of drop-out have be considered for the analysis. No source data verification has been performed. Data collection and analysis were approved by the Institutional Review Board (Protocol ID 2022002; Luigi Sacco Hospital, University of Milan). The trial is registered in Trialgov.com (NCT0518946).

3. Results

3.1. Baseline data

We analyzed data from 1335 patients with type 2 diabetes, 443 of which were on dapagliflozin alone treatment and 892 were treated with dapagliflozin plus oral semaglutide combination therapy. Complete baseline characteristics, including mean age, sex, mean duration of disease and antidiabetic treatment are shown in Table 1 Suppl. online. Median HbA1c and median BMI at study entry were 7.6 ± 0.9% and 28.9 ± 4.4 kg/m^2, respectively. Obesity was present in 431 of subjects, with a prevalence of class I obesity and overweight patients (Table 1 Suppl. online). The majority of patients were affected by arterial hypertension (70%) and dyslipidemia (60%). Nearly one third of subjects had heart failure, mainly NYHA I (15.1%). A history of myocardial infarction was present in 227 of patients, 157 were affected by diabetic retinopathy and one fifth of the patients had detectable albuminuria, classified as micro-albuminuria, while only 23 had macro-albuminuria. More than half of patients had some degree of chronic kidney disease (Table 1 Suppl. online).

3.2. Follow-up

Of the 1335 baseline subjects considered at baseline, 959 were re-evaluated after 6 months of treatment, while 28% of patients were lost at follow up or suspended the treatment due to adverse events. Patients who completed the follow up were divided according to the assumption of therapy in two subgroups: group 1 ("*dapa*") on dapagliflozin (10 mg/day), group 2 ("*dapa*+*sema*") dapagliflozin (10 mg/day) plus oral semaglutide (mean dosage 12.76 mg/day) (Fig. 1 Suppl. online). *Dapa* group consisted in 415 subjects, 155 (37.3%) female, 260 (62.7%) male, mean age 67.1 ± 10.1 years. *Dapa*+*sema* group consisted in 544 patients, 260 (47.8%) female, 284 (52.2%) male, mean age 62.8 ± 7.7 years. In the group of patients treated with dapagliflozin, basal insulin was suspended in 22% of subjects, rapid insulin in 32.4% and there was a decrease in the use of sulfonylureas/glinides in the 81.6% of patients.

In the group of patients treated with dapagliflozin plus oral semaglutide, basal insulin was suspended in the 89.2% of subjects, rapid insulin in 100% and there was a decrease in the use of sulfonylureas/glinides in the 98.2% of patients. Regarding the use of antihypertensive medications, it remained stable in the 93.9% of patients treated with dapagliflozin and in the 97.4% treated with dapagliflozin plus oral semaglutide, while reduction was obtained, respectively, in the 9.9% and 4.3% of subjects.

3.3. Glycometabolic control

Glycometabolic parameters variation in the two subgroups during follow-up are reported in Table 1. As shown, in both groups there was a significant improvement in all metabolic parameters, blood pressure and lipidic profile. Fasting plasmatic glucose, glycated hemoglobin and body mass index were all improved in both treatment groups during follow-up (Figs. 1A, 1B, 1C, 1E, 1F and 1G; Figs. 2A, B, C and E). As expected, a greater a reduction of Hb1Ac was observed in the *dapa+sema* group, while being improved in the *dapa* group only. Body mass index, fasting plasmatic glucose and glycated hemoglobin all improved at a greater extent in the *dapa+sema* group (Fig. 2 A, B and C). A significant reduction in total cholesterol and LDL cholesterol, with a slight increase in HDL cholesterol, was observed in both groups, while triglycerides were significantly reduced in the *dapa* group only. The achievement of HbA1c $< 6.5\%$, suggesting a pharmacological remission of type 2 diabetes, was obtained in 22.7% (94/415) of subjects in the *dapa* group and in 51.8% (282/544) of patients in the *dapa+sema* group (Fig. 2E). We then compared the baseline characteristics of patients achieving HbA1c$< 6.5\%$ ("responders") as compared to ("non responders") in *dapa+sema* group. "Responders" were significantly younger with a shorter diabetes duration. Comparing their baselines, they were characterized by a better glycometabolic state and higher body weight values (Table 2). A logistical binary regression was performed to determine the major contributors to the obtainment of HbA1c values lower than 6.5% considering the whole population and the two different subgroups of patients. Considering the whole population, a better glycemic control and renal function at baseline and the use of dual therapy (OR 4.9, 95% CI 2.794–8.531, $p < 0.0001$) were related to HbA1c$< 6.5\%$ at follow-up (Fig. 2 Suppl. online). By contrast, age, sex and years of disease were not significantly related. Considering the two subgroups, the major determinant to HbA1c$< 6.5\%$ resulted, for both, a better glycemic control at baseline.

3.4. Renal function

Regarding renal function, at follow up serum creatinine remained stable in the *dapa* group with a slightly improvement in the *dapa+sema* group (Table 1) and albumin to creatinine ratio was improved in both treatment groups (Figs. 1D and 1H; Fig. 2D). Albumin creatinine ratio improved at a greater extent in the *dapa* group (Fig. 2D). Finally, we evaluated changes in the KDIGO risk classes, considering the whole population of patients. The statistically significant reduction in albuminuria, shown by our data together with the stability of eGFR values, permitted an improvement in the overall KDIGO class of risk at follow-up (Fig.3 Suppl. Online). Comparing KDIGO class of risk from baseline to follow-up, the group of patients at low risk increased by 5%, while the group of patients at moderate and high risk decreased by nearly 6% (Fig. 3 Suppl. online).

4. Discussion

This study investigates the effects of combination of SGLT2is and GLP-1RAs in a real-world population of patients with type 2 diabetes. Interestingly, in the dapagliflozin *plus* oral semaglutide group we observed a mean reduction of HbA1c levels, from baseline after 6 months of treatment, of -1.2%, as compared to the -0.5% reduction observed in the group treated with dapagliflozin only. This result is consistent with the very few studies employing combined SGLT2i and GLP1-RA, although using a different combination as compared to our study [18–20]. As known, the two molecules act on glucose metabolism in a very different manners; indeed, GLP-1RAs reduce glycemia by enhancing insulin secretion and decreasing glucagon release, also delaying gastric emptying, reducing hepatic glucose production and whole body insulin sensitivity, while SGLT2is provide increased glucose excretion by renal proximal tubule [18]. By contrast, they share a glucose-dependent mechanism of action, with very low hypoglycemia risk, together with a sustained weight loss through different mechanisms [21]. These combination therapy increase cardiovascular and renal benefits [22–24]. The results of this study seem to confirm that combination treatment with SGLT2i and GLP-1RA can lead to clinical benefits on glycemic control, systolic blood pressure, body weight and dyslipidemia. Moreover, a recent meta-analysis, involving 1895 patients with type 2 diabetes enrolled in 8 randomized clinical trials, confirmed that combination therapy led to a much more significant reduction in glycemic levels [25], allowing additional HbA1c reduction of -0.7%,

Table 1
Glycometabolic parameters of patients that completed the 6 months follow-up.

	Dapa (n = 415)				*Dapa+Sema* (n = 544)			
	Basal	Follow up	Mean reduction	*P value*	Basal	Follow-up	Mean reduction	*P value*
BMI (Kg/m^2)	28.4 ± 4.4	27.5 ± 4.4	-0.9	*0.001*	28.6 ± 3.3	27.1 ± 3.0	-1.5	*0.001*
Weight (Kg)	79.6 ± 14.1	77.1 ± 13.9	-2.5	*0.001*	80.4 ± 13.5	76.2 ± 12.1	-4.2	*0.001*
FPG (mg/dL)	152.7 ± 35.8	136 ± 24.6	-16.7	*0.001*	177 ± 30.8	145.1 ± 19.5	-31.9	*0.001*
HbA1c (%)	7.4 ± 0.9	6.9 ± 0.7	-0.5	*0.001*	7.6 ± 0.7	6.4 ± 0.45	-1.2	*0.001*
S-Creatinine (mg/dL)	1.0 ± 0.3	1.1 ± 0.3	+ 0.06	*Ns*	0.94 ± 0.19	0.91 ± 0.17	-0.03	*0.001*
eGFR (mL/min/1,73 m^2)	72.8 ± 23.5	72.4 ± 37.5	-0.4	*Ns*	76.2 ± 24	75.1 ± 20.1	-1.1	*ns*
ACR (mg/g)	52.7 ± 157	31.7 ± 54.9	-21.0	*0.001*	66.2 ± 160	50.9 ± 111	-15.3	*0.01*
Tot-cholesterol (mg/dL)	166.4 ± 37.4	159.7 ± 32.0	-6.7	*0.001*	188 ± 31.7	172.5 ± 19.5	-15.5	*0.001*
HDL (mg/dL)	47.5 ± 12.3	47.8 ± 11.6	+ 0.3	*ns*	42.9 ± 8.4	44.1 ± 7.1	+ 1.2	*0.01*
LDL (mg/dL)	95.0 ± 35.1	84.0 ± 23.2	-6.5	*0.001*	116.4 ± 35.3	97.8 ± 25.3	-18.6	*0.01*
Triglycerides (mg/dL)	145.3 ± 65.1	135.0 ± 53.2	-10.3	*0.000*	142.8 ± 47.3	150.7 ± 29.7	+ 7.9	*0.001*
SBP (mmHg)	134.1 ± 14.7	129.0 ± 12.0	-5.1	*0.000*	133.5 ± 13	123 ± 9,4	-10.5	*0.001*
DBP (mmHg)	80.1 ± 9.0	77.0 ± 8.4	-3.1	*ns*	80.7 ± 8.8	73.3 ± 8.3	-7.4	*0.001*
Basal Insulin treatment	68, 16.4	53, 12.7	-22	*0.001*	120, 22.1	13, 2.4	-89.2	*0.001*
Rapid Insulin treatment	37, 8.9	25, 6.0	-32.4	*0.001*	5, 0.9	0, 0.0	-100	*0.001*
Sulfonylureas/glinides treatment	38, 9.1	7, 1.6	-81.6	*0.014*	55, 1.0	1, 0.2	-98.2	*0.001*

Abbreviations: BMI, body mass index; FPG, Fasting Plasma Glucose; HbA1c, glycated hemoglobin; eGFR Estimated Glomerular Filtration Rate; ACR, albumin/creatinine ratio; HDL high density lipoprotein; LDL low density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure. T-test for repeated measures. Data are expressed as mean ± SD; n, %.

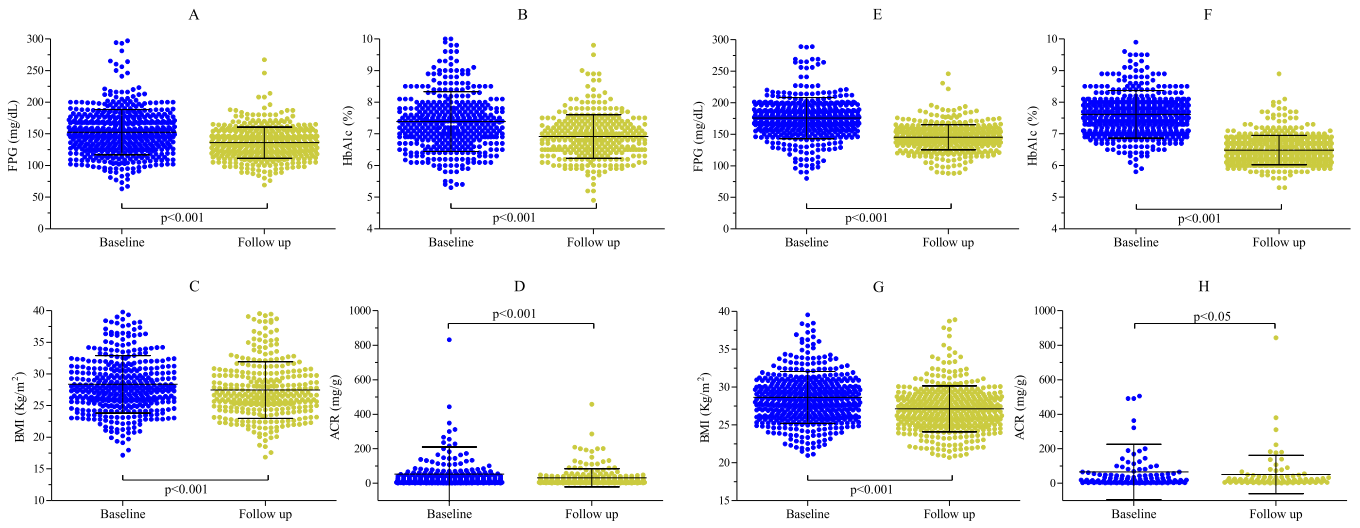

Fig. 1. Values of FPG – A, HbA1c - B, BMI - C and ACR - D at baseline and after 6 months of follow up in *Dapa* group; values of FPG - E, HbA1c - F, BMI - G and ACR - H at baseline and after 6 months of follow up in *Dapa+Sema* group. Abbreviations: FPG, Fasting Plasma Glucose; HbA1c, glycated hemoglobin; BMI, body mass index; ACR albumin/creatinine ratio. T-test for unpaired measures. Data are expressed as mean ± SD.

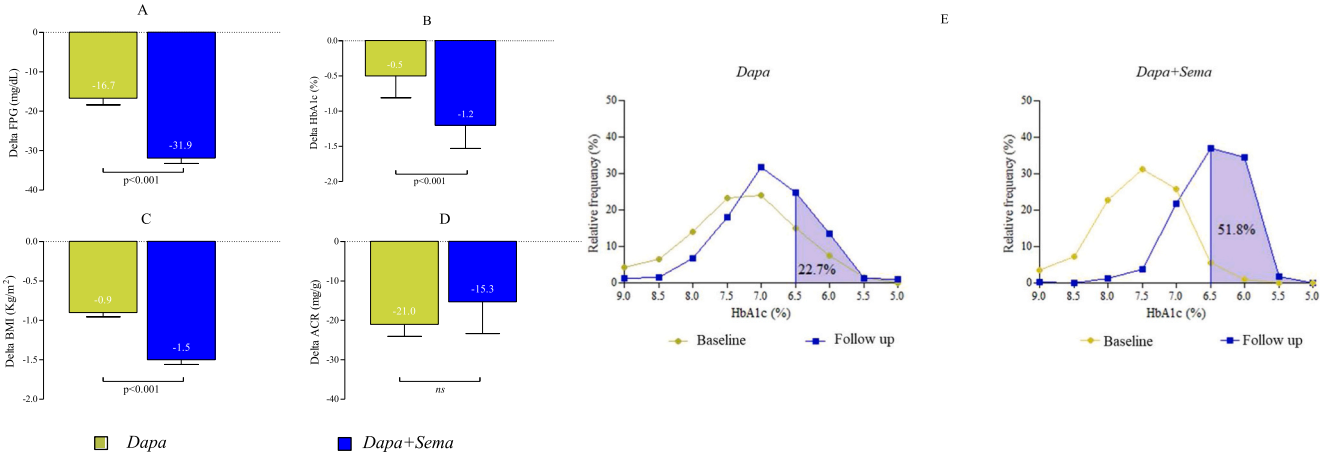

Fig. 2. Mean reduction in: A - FPG, B - HbA1c, C - BMI and D - ACR after 6 months of follow up according to the treatment groups. E - Distribution of HbA1c (%) values at baseline (green line) and after 6 months of treatment (blue line) in the 2 groups. The dark violet area represents the area under the curve of patients within the range of pharmacological remission. Abbreviations: FPG, Fasting Plasma Glucose; HbA1c, glycated hemoglobin; BMI, body mass index; ACR albumin/creatinine ratio. T-test for unpaired measures. Data are expressed as mean ± SE. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

compared to monotherapy treatment. In particular, combination therapy provides a better control in postprandial glucose levels and allows greater body weight reduction [25]. Interestingly, in our population we observed a higher mean reduction of body mass index (−0.6 kg/m2) and body weight (−1.7 kg) in the combination regimen as compared to monotherapy group. These values are slightly higher compared to the data presents in literature [26]. A partial explanation may be related to short time of follow up. In fact, both SGLT2is and GLP-1RAs can directly reduce body weight with particular effectiveness [14–16,27–30]; the first increasing energy loss and the second inhibiting energy intake and inducing thermogenesis of brown adipose tissue. These effects are synergistic although they may decrease over time. In our study we have also found a significant reduction of LDL cholesterol and total cholesterol levels and a mild increase in HDL, suggesting a potential role of this combination in type 2 diabetes patients with dyslipidemia. Indeed, these data are in line with a recent meta-analysis, that reported a significant reduction in low-density lipoprotein cholesterol (−23.4 mmol/L) among patients treated with combination regimen, even if the effect on TG, TC and HDL levels was not significant [25]. Concerning blood pressure effects, available data are not consistent; indeed, in some studies, the combination regimen seems to be effective only in reducing systolic blood pressure [31], whereas in others, a reduction in both systolic and diastolic blood pressure was observed [32,33]. When evaluating the changes in the KDIGO risk classes during follow-up, a reduction in the risk of renal function decline was observed, with an increased in the number of patients at very low risk. We observed no synergistic effect on the kidney function with the association with *dapa+sema*. This could be explained by different hypothesis: the benefit on the kidney function is mainly guaranteed by SGLT2i alone, on the other hand, with a longer period of observation, it might be demonstrated also the positive effect of the add-on semaglutide treatment. Multiple events, including hemodynamic changes, reduction of blood pressure, improvement of cardiac metabolism are responsible of the observed positive effects on renal function; furthermore, the demonstrated anti-inflammatory, anti--atherosclerotic and anti-oxidative properties, may protect the kidney [23,34–36]. Both SGLT2is and GLP1-RAs play a role in mediating anti-infiammatory and immunological effects. Both receptors are indeed expressed in different sub-types of cells involved in immune response

Table 2
Baseline characteristics of subjects achieving HbA1c values < 6.5% (Responder) or not (Non responder) after 6 months of follow up in the *Dapa+Sema* group.

	Responder (n = 282)	Non responder (n = 262)	P value
Age (years)	61.7 ± .7.2	63.7 ± 8.3	0.001
Years of disease	6.2 ± 5.4	9.3 ± 5.9	0.001
Gender M/F (%)	57.3/42.7	49.1/50.9	0.05
BMI (Kg/m^2)	28.8 ± 2.8	28.3 ± 3.8	ns
Weight (Kg)	82.3 ± 12.3	78.2 ± 14.5	0.01
FPG (mg/dL)	174.6 ± 26.4	178.8 ± 37.1	ns
HbA1c (%)	7.4 ± 0.56	7.7 ± 0.75	0.001
S-Creatinine (mg/dL)	0.93 ± 0.2	0.94 ± 0.2	ns
eGFR (mL/min/1,73 m^2)	78.5 ± 26.0	75.2 ± 23.3	ns
ACR (mg/g)	96.0 ± 310.5	65.2 ± 111.3	ns
Tot-cholesterol (mg/dL)	190.2 ± 32.1	184.0 ± 31.9	0.001
HDL (mg/dL)	42.2 ± 7.3	46.0 ± 23.9	ns
Triglycerides (mg/dL)	143.8 ± 50.5	144.5 ± 48.0	ns
Basal Insulin Treatment (%)	2.1	2.6	ns
Rapid Insulin Treatment (%)	0	1.7	0.05

Abbreviations: BMI, body mass index; FPG, Fasting Plasma Glucose; HbA1c, glycated hemoglobin; eGFR Estimated Glomerular Filtration Rate; ACR albumin/creatinine ratio; HDL high density lipoprotein; Data are expressed as mean ± SD or %.

(lymphocytes T and B, macrophages, iNTK cells, eosinophils and neutrophils for GLP1-RAs and monocytes for SGLT2is) and have demonstrated to reduce inflammatory cytokines production during clinical trials. [23,35] In our study, the use of combination therapy with dapagliflozin plus oral semaglutide lead to the suspension of basal and rapid insulin in one third of patients and a superb reduction in sulfonylureas/glinides use in almost all patients. Considering that with combination treatment the risk of hypoglycemia is very low, the use of this regimen can be useful in the more fragile classes of patients, such as elderly [37,38]. It is noteworthy that more than half of the treated patients in the *dapa+sema* group achieved a HbA1c levels < 6.5%. Even if the presence of active pharmacological treatment cannot allow a full definition of diabetes remission, which requires the absence of usual glucose-lowering pharmacotherapy for at least three months [39], the achievement of HbA1c goal of less than 6.5% in such a proportion of patients can reasonably permit us to highlight this result as a "pharmacological remission". In fact, is well known that the obtainment of a sustained glycemic control over time, without a significant increase in hypoglycemia risk, is associated with reduced odds of the diabetes-related complications of cardiovascular disease, metabolic disease, neuropathy, nephropathy, and peripheral vascular disease [40]. This was probably facilitated by few characteristics at baseline, including age and duration, suggesting that in order to maximize the clinical results, this treatment should be offered to younger patients and early in the natural history of the disease. The beneficial role of the intensive diabetes management during the earliest stages of the disease is particularly important due to the legacy effect. In fact, intensive diabetes management in the early stages of the disease translates into long-term risk reduction over all diabetes-related complication and death from any causes. [41,42] Interestingly, the binary regression analysis confirmed that the major factors contributing to achieve levels of HbA1c < 6.5% were better glycemic control and better renal function at baseline, being the use of combination therapy the most important determinant. In conclusion, our real-world study suggests that the combination of dapagliflozin plus oral semaglutide induces optimal glycemic control, weight loss, amelioration of lipid profile and kidney protection. The main limitations of the present study are the short time of follow up and absence of randomization at baseline. Even if further research is needed, we suggest that the combination regimen of dapagliflozin plus oral semaglutide may induce type 2 diabetes pharmacological remission in clinical practice in more than 50% of patients.

CRediT authorship contribution statement

Disoteo Olga Eugenia: Data curation, Supervision. **Desenzani Paolo:** Data curation. **Terranova Rosa:** Data curation. **Ghelardi Renata:** Data curation. **Girelli Angela:** Data curation. **Ben Nasr Moufida:** Methodology, Supervision. **D'addio Francesca:** Methodology, Supervision. **Folli Franco:** Conceptualization, Supervision. **Cimino Vincenzo:** Formal analysis, Writing – original draft. **Berra Cesare:** Data curation, Methodology, Supervision. **Lunati Maria Elena:** Data curation, Formal analysis, Writing – original draft. **Gandolfi Alessandra:** Data curation. **Bucciarelli Loredana:** Data curation. **Bernasconi Davide:** Investigation. **Morpurgo Paola Silvia:** Data curation, Methodology. **Fiorina Paolo:** Conceptualization, Project administration, Supervision, Writing – review & editing. **Lazzaroni Elisa:** Data curation. **Tinari Camilla:** Data curation, Methodology. **Muratori Milena:** Data curation. **Baruffaldi Laura:** Data curation. **Pastore Ida:** Data curation. **Montefusco Laura:** Data curation. **Franzetti Ivano Giuseppe:** Data curation. **Rossi Antonio:** Data curation. **Manfrini Roberto:** Data curation. **Muratori Fabrizio:** Data curation.

Declaration of Competing Interest

None.

Data availability

Data will be made available on request.

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Appendix

Other participants to the study: Andrea Laurenzi, Annalisa Creanza, Antonio Luigi Belviso, Baldassarre Grassa, Bernadetta Pasquino, Chiara Mauri, Cristiana Scaranna, Cristina Mascadri, Danila Marta Camozzi; Elena Cimino, Elena Mion, Emanuela Zarra, Enrico Pigni, Erika Pedone, Fabrizio Guerci, Francesca Pesenti, Giacomo Sturniolo, Giorgio Ragni, Giosuè Ghilardi, Giulia Massari, Laura Menicatti, Luca Zenoni, Mariaclaudia Tusi, Maria Elena Malighetti, Mario Buizza, Paolo Erpoli, Raffaella Radin, Roberto Pollastri, Roberta Serra, Rosalia Bellante, Valeria Brami.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2023.107040.

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