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Improved glycemic and weight control with Dulaglutide addition in SGLT2 inhibitor treated obese type 2 diabetic patients at high cardiovascular risk in a real-world setting. The AWARE−2 study

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ABSTRACT

We evaluated the effects on glycemic control and body weight of a GLP1-RA in obese type 2 diabetic patients treated with SGLT2-inhibitors and other hypoglycemic agents and/or insulin, in a real-world setting. A cohort of 583 type 2 diabetic outpatients treated with a SGLT2 inhibitor and/or other anti-diabetic medications were examined. Because patients had suboptimal glycemic control, the GLP1-RA Dulaglutide was added to ongoing medications. At 6 months, 334 patients had a follow-up visit. Patients were classified in terms of cardiovascular risk (CVR) employing the ESC-EASD 2019 criteria, with the AWARE app. The study's primary endpoints were changes in: 1) HbA1c level, 2) BMI, and 3) body weight after six months of treatment. Secondary endpoints were evaluation of Dulaglutide addition in type 2 diabetic patients: 1) with more or less than ten years of T2DM; 2) more or less than 75 years of age and in different subgroups of CVR. In the 334 patients which had a 6 months follow-up visit, age was 65,9$\pm$9,8; 33.5 % (112) were females and 66.5 % (222) were males. After six months of Dulaglutide treatment, we found a significant reduction in HbA1c levels (8.0$\pm$10.5 mmol/mol; $p<0.0001$) and in body mass index (1.1$\pm$1.1 kg/m^2; $p<0.0001$). Efficacy of Dulaglutide was not affected by different CVD risk categories, age and T2DM duration. This real world study provides evidence for significant reductions in HbA1c level, body mass index and body weight in obese type 2 diabetic patients who received add-on treatment with the weekly GLP-1RA, Dulaglutide.

1. Introduction

Diabetes is a leading cause of morbidity and premature mortality worldwide [1], being associated with increased risk of cardiovascular disease, heart failure and chronic kidney disease [2]. Cardiovascular complications, kidney failure and premature death seem to be decreasing recently in high-income countries [3], possibly as a consequence of pharmacological treatment with glucagon-like peptide-1 receptor agonists (GLP1-RA) and sodium-glucose co-transporter-2 inhibitors (SGLT2i).

GLP1-RA and SGLT2i have been indicated by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) as first-line antidiabetic therapies in patients with type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease

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(ASCVD) or multiple ASCVD risk factors to reduce the risk of major adverse cardiovascular events (MACE) [4].

Cardiovascular outcomes trials (CVOTs) have demonstrated that GLP1-RA reduce major adverse cardiovascular events, including non-fatal myocardial infarction, non-fatal stroke and cardiovascular death in patients with T2DM. Results from clinical trials showed a reduction of up to 27 % of 3P-MACE in patients at high CVD risk [5,6] and 12 % (HR 0.88 [95 % CI 0.79, 0.99]) in patients at lower CVD risk [7,8].

GLP1-RA modulate glucose-dependent insulin secretion by pancreatic β-cells, inhibiting glucagon secretion by pancreatic α-cells, slowing gastric emptying, and thus decreasing food intake and increasing peripheral insulin sensitivity. These combined actions improved metabolic compensation and glycaemic control [9,10].

Furthermore, by acting also on GLP1 receptors in the hypothalamus, GLP1-RA increase satiety. Increased satiety leads to weight loss [11–13], which could also be one of the essential determinants in reducing cardiovascular events [14]. In fact, a reduction of more than 10 % in body weight in one year is associated with a 21 % reduction in primary outcome and a 24 % reduction in secondary outcome in patients with T2DM [15].

The improvement in glycaemic control, resulting in a reduction in glycated haemoglobin (HbA1c) in the range of 0.8–1.5 %, is associated with a reduction in non-fatal MI, but not cardiovascular death. In addition, GLP1-RA positively affect lipid profile [16] and systolic blood pressure [17–19].

Furthermore, GLP1-RA exert anti-inflammatory and anti-atherogenic effects by modulating circulating levels of IL-6, ICAM-1, markers of oxidative stress, nitrotyrosine, 8-iso prostaglandin F2α, MCP-1, TNFα [20,21]. These anti-inflammatory/anti-atherogenic actions occur independently of the effect on glycaemic compensation and weight loss and may contribute to the cardioprotective effects of GLP1-RA [22,23].

Studies in real world have confirmed the effect of GLP1-RA in clinical practice [24–27].

On the other hand, SGLT2i improve overall patient outcomes across the different clinical conditions studied. The efficacy of sodium-glucose cotransporter inhibitors is strongly associated with slowing kidney damage and heart failure, as evidenced by the significant reduction in all-cause mortality achieved in studies of diabetic and non-diabetic patients with advanced chronic kidney disease and in real world studies [28–30].

SGLT2i acts by binding to SGLT2 in the renal proximal tubule, which is responsible for approximately 80–90 % of glucose reabsorption and thus promoting massive glycosuria.

The synergistic effects of the reduction in preload (through reduction of extracellular volume), afterload (reduction of arterial pressure) and reduction of arterial stiffness, as well as the cardio-renal and metabolic effects, lead to a significant reduction in cardiovascular risk factors associated with the use of this class of drugs [31].

Given the effects of GLP1-RA and SGLT2i, it is tempting to hypothesize that the use in combination of these two classes of drugs reduces cardiovascular risk, possibly by correcting seven of the eight elements of the Ominous Octet [32], which contribute to diabetic hyperglycaemia: excess glucagon secretion by the alpha cells, decreased pancreatic beta cells insulin secretion, decreased incretin effect, kidney increased glucose reabsorption, decreased muscle glucose uptake, brain neurotransmitter dysfunction, increased hepatic glucose production [21].

In addition, the combined use of SGLT2i and GLP1-RA results in a more significant reduction in cardiovascular risk factors than the single use of each drug class, leading to increased cardiovascular and renal benefits [33,34].

Based on the above, the use of SGLT2i + GLP1-RA combination therapy could be the key element in modifying cardiovascular risk factors in patients with T2DM and high cardiovascular risk [35]. The aim of this study was to evaluate changes in HbA1c and BMI in subjects with T2DM and inadequate metabolic control after adding a GLP1-RA to SGLT2i. Secondary endpoints were the assessment of changes in HbA1c and BMI in subjects with T2DM in different degrees of cardiovascular risk according to the AWARE App, in in patients with diabetes duration longer than 10 years as compared to those with a shorter history, in subjects older than 75 years old as compared to younger patients and the effect on HbA1c according to the advisable value of 53 mmol/mol.

2. Methods

2.1. Study design and participants

This was a retrospective, observational, multicenter real-world study conducted by a network of Diabetes Centers in Lombardy (Italy). T2DM patients treated with SGLT2-inhibitors, with inadequate metabolic control, which were subsequently treated with weekly Dulaglutide from October 2021 to March 2022, were evaluated. The inclusion criteria were: (a) age $>$ 18 years old; (b) diagnosis of T2DM, according to the American Diabetes Association criteria, for at least three months; (c) therapy with SGLT2-inhibitors (empaglifozin, dapagliflozin, canaglifozin, ertuglifozin), with or without other anti-diabetic treatments, to which Dulaglutide 1.5 mg weekly was added. The following data were collected at baseline and after six months of treatment: a) duration of T2DM, b) weight, c) height, d) body mass index, and e) glycated haemoglobin (HbA1c). Changes in HbA1c from baseline to 6 months of follow-up and in body weight and BMI were analyzed.

BMI categories were defined as follows: underweight (under 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), class 1 obesity (30–34.9 kg/m^2), class 2 obesity (35–39.9 kg/m^2) and class 3 obesity ($\geq$40 kg/m^2). Patients' data were extracted from electronic folders of the individual centers and inserted anonymously into the app AWARE for the CV risk calculation and statistical analysis. All data were collected by the Coordinating Center (IRCCS MultiMedica) and analyzed by an independent statistician. Quantitative data are described as mean ± standard deviation and range. In contrast, qualitative variables have been expressed as an absolute number of cases and a percentage of the evaluated patient cohort.

2.2. Stratification of cardiovascular risks through AWARE App

The AWARE App was used to calculate each patient's CV risk and to record their HbA1c level and pharmacological treatment. Anonymized data were stored on the App Web server and retrospectively analyzed. AWARE is a Web App that runs on a Web server and can be loaded by any Internet browser, including personal computers and mobile devices (smartphones, tablets). The AWARE App has previously been described [36]. The main function of the AWARE App is to assess CV risk based on 2019 ESC/EASD criteria [37].

The AWARE App is free and available online in English language at the following URL: https://aware.softwarevm.online/ (user ID: Aware; password: Aware).

2.3. Statistical analysis

Continuous variables are reported as mean and standard deviation (SD), while categorical variables are reported as absolute numbers and percentages representing relative prevalence.

Differences between variables in the same subject at different time points (t0 and t1) were calculated with paired Student t-test (two tails). Differences between groups were analyzed with the Chi-squared test or Fischer's exact test for categorical variables and with the Student t-test or Mann–Whitney U-test for continuous variables, as appropriate. A two-way analysis of variance (ANOVA) was performed to compare differences among continuous variables and time points. A p value $<$ 0.05 was considered statistically significant. All the analyses were performed with PRISM 10 software (GraphPad Software, 225 Franklin Street. Fl. 26, Boston, MA 02110).

3. Results

583 subjects were enrolled, and 334 patients received a 6-month follow-up visit. Table 1 shows the main characteristics of the study subjects at baseline. Age was 65.9±9.8; 33.5 % were female and 66.5 % male. At baseline, 276 patients (81.6 %) had a very high CVR (VH_{CVR}), 27 (8 %) had a high CVR (H_{CVR}), no one had a moderate CVR (M_{CVR}), and 35 (10.4 %) were moderate-to-high CVR (MH_{CVR}) (Table 1) according to the AWARE App [36].

At baseline, BMI was 30.1±4.7 kg/m^2, body weight was 84.5 ±15.9 kg, and mean HbA1c was 60.2±11.3 mmol/L. In all patients treated with SGLT2i, the addition of Dulaglutide for 6 months produced a significant improvement in HbA1c levels (7.9±10.5 mmol/L; p<0.0001), BMI (1.1±1.1; p<0.0001), and weight (3.1±3.2 kg, p<0.0001). HbA1c<53 mmol/mol and BMI<30 kg/m^2 were present on 46 subjects at baseline (13.77 %), while after 6 months treatment 130 subjects (38.92 % p<0.0001) showed the same glycometabolic and weight improvements (Table 2).

We also assessed modification of diabetes treatment after addition of dulaglutide. 237 subjects were treated with metformin, which was suspended during the study in 1 subject (p=0.93); 68 were treated with basal insulin, which was suspended in 25 subjects (38 % p<0.01); 20 were treated with rapid insulin, which was suspended in 18 subjects (90 %, p<0.001); 28 were treated with sulphonylurea or glinides, which was suspended in 27 patients (96 %, p<0.001); 16 were treated with pioglitazone, which was suspended in 9 (56 %, p=0.06) and 27 were treated with IDPPIV, which was suspended in 25 subjects (93 %, p<0.001); 3 subjects were treated with acarbose which was maintained in one (p=0.32). 3 patients were treated with another GLP1-RA which was substituted with dulaglutide (Table 3).

The modifications of HbA1c during the 6 month period are shown in Fig. 1. In Fig. 1A, HbA1c values are represented before and after dulaglutide treatment, using a HbA1c value of 53 mmol/L as the cut-off. At baseline, only 25.7 % of the patients had HbA1c values lower than 53 mmol/L while 74.3 % had higher values; after six months treatment, 58.9 % of patients had a HbA1c value lower and 41.1 % had a value higher than 53 mmol/L (p<0.0001). In Fig. 1B, the relationship between each patient's t0 and t1 HbA1c values is shown, with HbA1c 53 mmol/L as the cut-off value. The lower left quadrant of Fig. 1B represents patients with basal and follow-up HbA1c ≤53 mmol/L (23.1 %); lower right quadrant represents patients with basal HbA1c > 53 mmol/L which achieved a reduction in HbA1C value (≤53 mmol/L) following treatment (35.6 %); upper left quadrant represents the patients with basal ≤53 mmol/L that increased the HbA1c value (>53 mmol/L) following treatment (2.4 %); upper right quadrant represents patients with basal and follow up HbA1c >53 mmol/L (38.9 %); line represents the linear regression (slope 0.38±0.4, R^2=0.23). The percentage of patients responding to treatment with dulaglutide was 87.4 % (n=292) (Fig. 1C).

Changes of HbA1c levels in the different subgroups of CV risk categories are reported in Fig. 2. Dulaglutide significantly decreased HbA1c basal values (p<0.001) in every CV risk group, with no differences between different CV risk groups (Fig. 2A and 2B). No significant differences in Dulaglutide effect in reduction HbA1c were found in patients with diabetes duration longer than 10 years as compared to those with a shorter disease history (Fig. 2C). Also, there were no significant differences in HbA1c reduction in subjects older than 75 years old as compared to younger patients (Fig. 2D).

Fig. 3 shows the changes in weight (panels A, B and F) and BMI (panels C, D and E) in the whole population. The reduction in both weight and BMI was significant after 6 months of treatment: 93.7 % of patients lost weight and the percentage of patients with a BMI < 25 kg/m^2 increased from 14.2 % (baseline) to 19.5 % (at 6 months), the percentage with a BMI between 25 and 30 kg/m increased from 36.1 % to 40.2 %, and the percentage of obese patients (BMI>30) decreased from 49.7 % to 40.2 %.

Fig. 4 shows the changes in weight and BMI in the different CV risk categories. In all three groups, weight significantly decreased after treatment (all p<0.001) (panels 4 A and 4B), and a similar significant reduction was seen in BMI (all p<0.001) (panels 4 C and 4D).

The most significant reduction in HbA1c levels was observed in patients who suspended sulfonylurea treatment after dulaglutide addition (-1 %), followed by DPP4i suspension (-0.8 %), basal insulin suspension (-0.3 %), and the rapid-acting insulin suspension (-0.1 %). The greatest changes in BMI and BW were observed after sulfonylurea suspension (-1.4 kg/m^2 and −4.2 kg, respectively), followed by basal insulin suspension (-3.6 kg/m^2 and −1.3 kg), rapid-acting insulin suspension

Table 1
Characteristics of the n=334 patients.

		t0
Age (F:M)		65.9 ± 9.8 (66.9: 65.8)
Sex (F:M)		112: 222 (33.5 %: 66.5 %)
Height (m)		1.68 ± 9.5
T2DM length > 10 years		52.7 %
Risk categories	Moderate to High	35 (10.4 %)
	High	27 (8 %)
	Very High	276 (81.6 %)
Dyslipidemia		247 (73.9 %)
Hypertension		268 (80.2 %)
Proteinuria		83 (27.7 %)
Kidney failure		20 (16.7 %)

Table 2
Metabolic characteristics of the n=334 patients.

	t0	t1	t1-t0	p
Weight (Kg)	84.5 ± 15.9	81.4 ± 15.4	3.1 ± 3.2	<0,0001
BMI (Kg/m^2)	30.1 ± 4.7	29.0 ± 4.5	1.1 ± 1.1	<0,0001
HbA1c (mmol/L)	60.2 ± 11.3	52.3 ± 8.9	7.9 ± 10.5	<0,0001
HbA1c ≤ 53 (mmol/L; F:M)	85 (32: 53)	198 (67: 131)	113 (35: 78)	<0,0001
BMI ≤ 30 (kg/m^2; F:M)	174 (50: 124)	202 (58:144)	28 (8:20)	*0.019*
HbA1c ≤ 53 mmol/L **AND BMI ≤ 30** kg/m^2	46 (13: 33)	130 (40: 90)	84 (27: 57)	<0,0001

Table 3
Therapy administered before and during the study.

Therapy	Baseline	Follow-up	p
GLP−1ra	0,9 %; 3 (0; 3)	100 %; 334 (112; 222)	*n.a.*
SGLT2i	100 %; 334 (112; 222)	100 %; 334 (112; 222)	*n.a.*
Metformin	70,9 %; 237 (83; 154)	70,6 %; 236 (83; 153)	*0.93*
Long-acting Insulin	20,3 %; 68 (18; 60)	12,8 %; 43 (15; 28)	<0.01
Short-acting Insulin	5,9 %; 20 (6; 14)	0,6 %; 2 (0; 2)	<0.001
DPP4i	7,9 %; 27 (7; 20)	0,6 %; 2 (0; 2)	<0.001
Sulfonylurea	7,8 %; 26 (12; 14)	0,3 %; 1 (1; 0)	<0.001
Repaglinide	0,6 %; 2 (0; 2)	0 %; 0 (-; -)	*0.16*
Pioglitazone	4,8 %; 16 (6; 10)	2,0 %; 7 (5; 2)	*0.06*
Acarbose	0,9 %; 3 (0; 3)	0,3 %; 1 (0; 1)	*0.32*

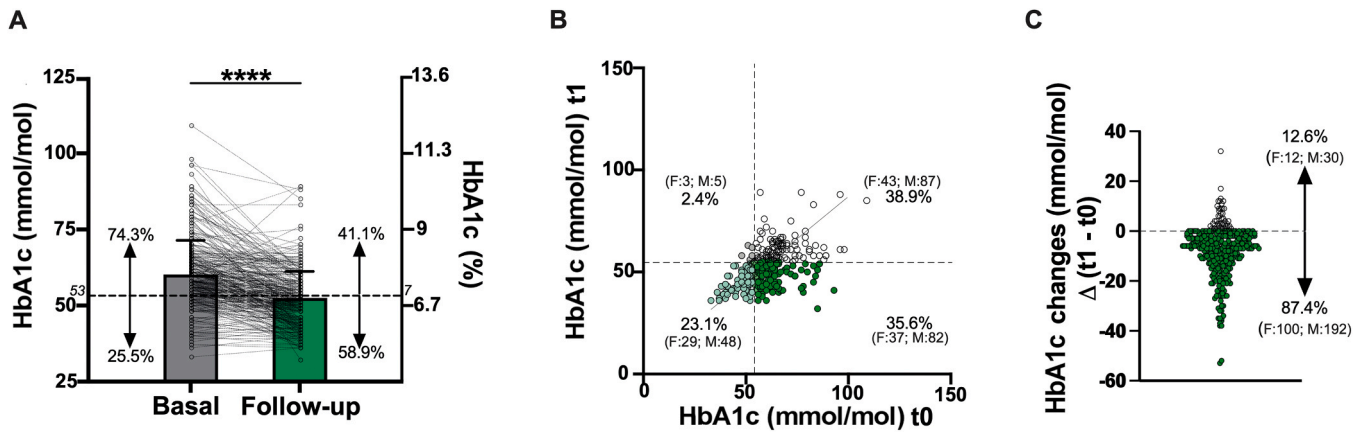

Fig. 1. (A) Before-after individual values (circle, connected with line) and mean (bars) ± standard deviation of HbA1c values (mmol/mol) at the study enrolment (t0, gray) and following 6 months of GLP-1 treatment (t1; green). Dashed line is set at the value of 53 mmol/L. (B) Graph showing the relationship between t0 and t1 HbA1c values of each patient. Lower left quadrant represents patients with basal and follow up HbA1c ≤ 53 mmol/mol (light green); lower right quadrant represents patients with basal HbA1c > 53 mmol/mol that reduced the HbA1c value (≤ 53 mmol/mol) following treatment (green); upper left quadrant represents the patients with basal ≤ 53 mmol/mol that increased the HbA1C value (> 53 mmol/mol) following treatment (gray); upper right quadrant represents patients with basal and follow up HbA1c > 53 mmol/L (white); line represent the linear regression (slope 0.38 ± 0.4, R2=0.23); (C) graphs represent the number of patients that decreased (green) or increase (white) the HbA1c value (mmol/mol) following the study. **** = p<0.001.

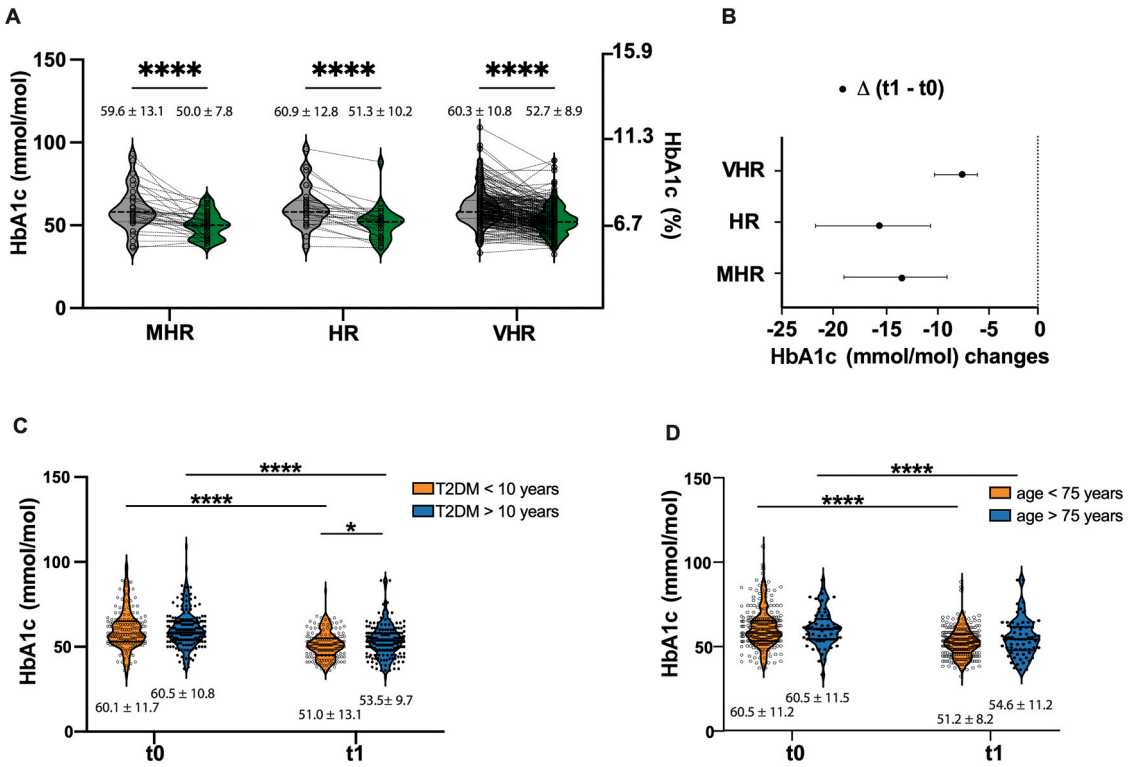

Fig. 2. (A) Before-after Individual values (circle, connected with line) and distribution (violin plot) of t0 (gray) and t1 (green) HbA1c values (mmol/mol) of patients classified in moderate to high, high and very high risk categories (see text). The treatment decreased HbA1c basal values in every risk groups. (B) Graph showing the differences of HbA1c values between t0 and t1 for each category. (C) Stratification of patients with T2DM disease duration longer (orange) or shorter (blue) than 10 years. (D) Stratification of patients older (orange) or younger (blue) than 75 years of age. HbA1c mean and SD of each category are indicated. *=p<0.05; **** = p<0.001.

(-3.4 kg/m^2 and −1.2 kg), and DPP4i suspension (-0.8 kg/m^2 and −0.8 kg) (data not shown).

4. Discussion

SGLT2i and GLP1-RA improve glucose metabolism in type 2 diabetes mellitus through different mechanisms [38,39]. SGLT2i are also endowed with hemodynamic and renal effects (reduced preload and afterload, increased osmotic diuresis, activated tubulo-glomerular feedback, and reduced glomerular pressure) and anti-fibrotic and anti-inflammatory actions [40]. GLP1-RA enhance meal-induced insulin secretion, decrease glucagon production, improve insulin sensitivity and reduces food intake though peripheral and central nervous system actions (by slowing gastric emptying and stimulating hypothalamic satiety

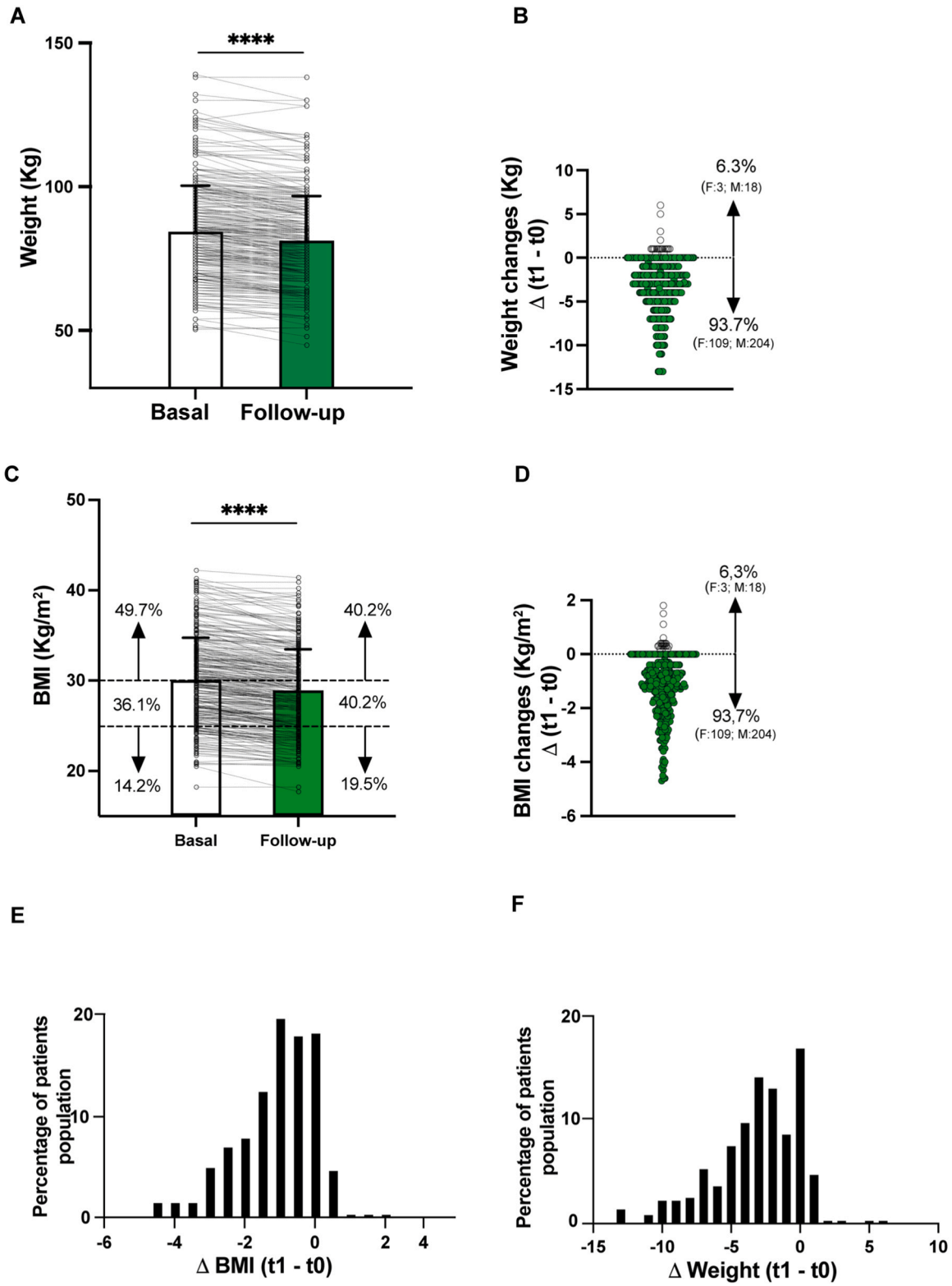

Fig. 3. (A) Before-after Individual values (circle, connected with line) and mean (bars) ± standard deviation of weight at the t0 (gray) and t1 (green). (B) Graph showing the distribution of the number of patients showing a decrease in weight during the study (t1-t0) ≤ 0. (C) Before-after Individual values (circle, connected with line) and mean (bars) ± standard deviation of BMI values (kg/m2) at the t0 (gray) and t1 (green). Dashed line is set at the value of 30 kg/m2. (D) Graph showing the distribution of the number of patients showing a decrease in BMI during the study (t1-t0) ≤ 0. (E, F) Bar graphs showing the frequency (number of patients for each BMI/weight change) of BMI (C) and Weight (D) changes.

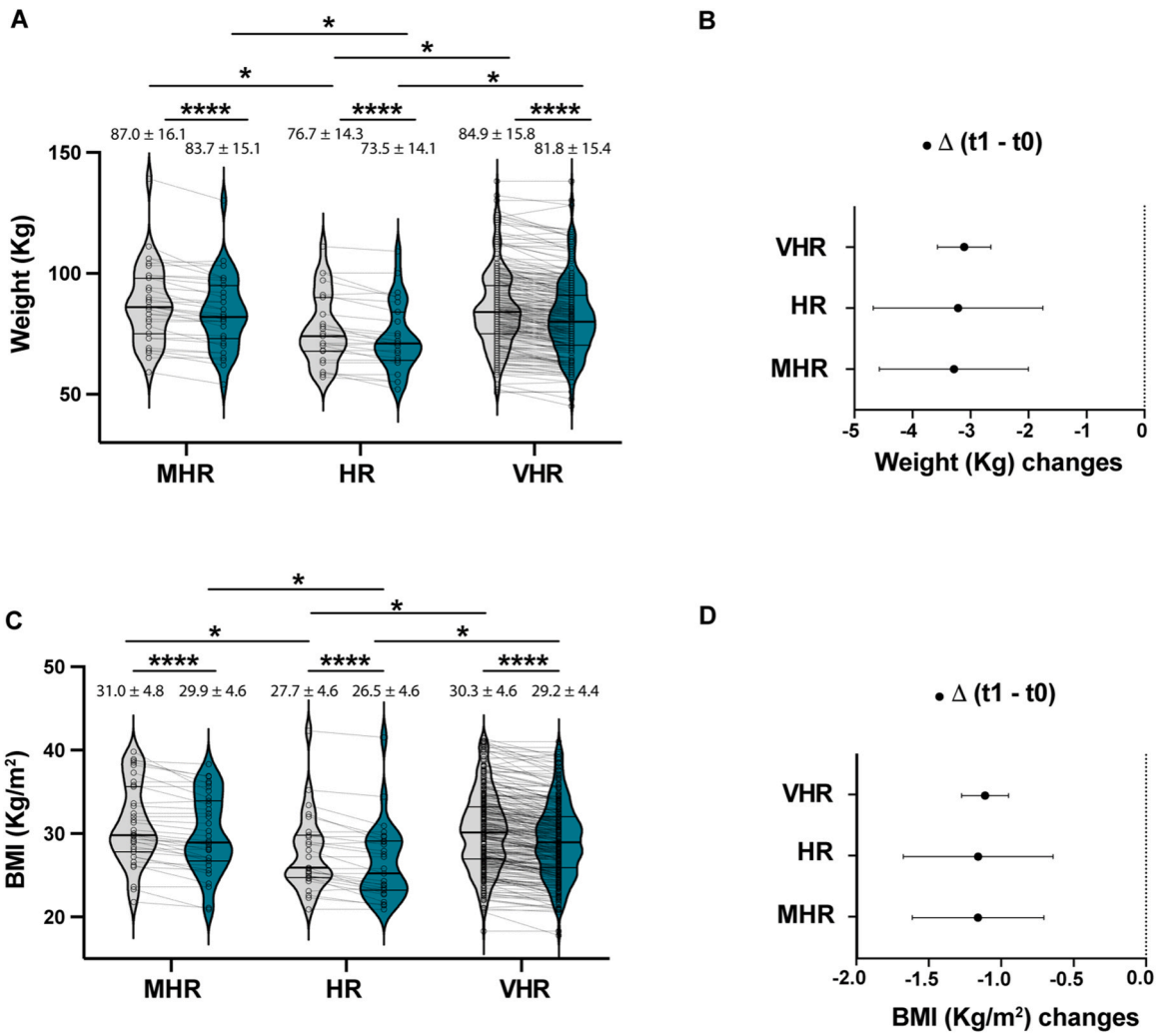

Fig. 4. (A) Before-after Individual values (circle, connected with line) Individual values (circle) and distribution (violin plot) of t0 (gray) and t1 (green) weight (Kg) of patients classified in moderate to high, high and very high risk categories (see text). The treatment decreased weight values in every risk groups. (B) Graph showing the differences of weight values between t0 and t1 for each category. (C) Before-after Individual values (circle, connected with line) Individual values (circle) and distribution (violin plot) of t0 (gray) and t1 (green) BMI values (Kg/m2) of patients classified in moderate to high, high and very high risk categories (see text). The treatment decreased Kg/m2 values in every risk groups. (B) Graph showing the differences of HbA1C values between t0 and t1 for each category. **** = $p<0.001$.

centers). In addition, GLP1-RA may have anti-atherogenic, anti--oxidative and anti-inflammatory effects [41–43]. The combined effects of these two drug classes result in cardio-renal protection also enhancing weight loss and reducing hyperglycemia [44]. Interestingly, all these actions occur with very low/null risk of hypoglycemia [45,46].

In the last decade, GLP1-RA and SGLT2i therapies have significantly improved T2DM outcomes [47,48]. Treatment with GLP1-RA and SGLT2i allows the transition from medications capable of acting mainly on reducing hyperglycemia (e.g. insulin, sulfonylureas, glinides, acarbose) without relevant benefits on the prevention of organ damage (treat-to-target concept) to medications capable of preventing the onset and reducing the progression of micro- and macrovascular complications in T2DM subjects (treat-to-benefit concept) [49,50]. In this context, the correct stratification of T2DM patients CV risk is necessary to prescribe appropriate therapies for reducing the risk of occurrence and evolution toward cardiovascular complication and renal failure [4, 51−55]. Treatment with GLP1-RA and SGLT2i alone or in combination are now recommended by all guidelines for the treatment of T2DM, especially in the presence of ischemic heart disease, heart failure, and chronic kidney disease [56–58].

To aid clinicians in assessing CV risk in T2DM, the 2019 ESC-EASD guidelines stratified the CV risk of individuals with T2DM into very high, high, and moderate risk based on the presence/absence of CV disease, target organ damage, risk factors presence/absence, and duration of the disease [37]. These guidelines are currently the gold standard for risk stratification, but their implementation is complex, especially in clinical settings characterized by high patient numbers and short visit times.

We have developed the web app (AWARE app, free and available at URL: https://aware.softwarevm.online/) for the rapid identification of the CV risk of T2DM patients based on the criteria of the 2019 Guidelines to ESC-EASD. Interestingly, the use of the AWARE app showed that about 18 % of patients did not fit into the three CV risk categories (very high, high, and moderate) of the ESC-EASD 2019 classification. These were mainly T2DM subjects with a disease duration<10 years, age 50–65 years, without a history of CV disease or target organ damage such as proteinuria, advanced renal disease, or retinopathy. However, nearly 90 % of these subjects had one or more CV risk factors, and their rates of dyslipidemia and obesity were higher than those observed in high-risk subjects. This category of patients was classified as "moderate-to-high" risk [35,36].

In this retrospective multicenter study, the AWARE App was used for

risk stratification in 548 T2DM subjects treated with SGLT2i at baseline. The effect of GLP1-RA, an add-on to SGLT2i, on metabolic and bio anthropometrics parameters was evaluated after six months of follow-up on 334 subjects in different CVR categories identified with the AWARE App [36].

The addition of a GLP1-RA to SGLT2i significantly reduced glycated haemoglobin, more than doubling T2DM patients at target (HbA1c<53 mmol/mol). Interestingly, target achievement occurred more frequently in patients with higher glycated haemoglobin at baseline, consistent with controlled trials data [59]. Glycated haemoglobin was also significantly reduced in identified risk categories with a greater reduction in the moderate-to-high and high-risk categories than in the very high risk. This finding confirms the hypoglycemic efficacy of GLP1-RA, an add-on to SGLT2i, in the majority of subjects with T2DM, while the greater reduction in glycated haemoglobin in the moderate-to-high and high-risk category than in the very high-risk could possibly be ascribed to a more severe beta cell depletion in very high cardiovascular risk patients [60]. Another hypothesis could be lower compliance and adherence to multitherapy which is often seen in very high-risk T2DM subjects, leading to sub-optimal control of metabolic and bioanthropometrics parameters (e.g. lipids, glycemia, blood pressure) [61,62]. The reduction in glycated haemoglobin in the three risk categories is independent of disease duration (>10 years or <10 years) and age (>75 years or <75 years), indicating that the add-on of GLP1-RA to SGLT2i may improve glycemic control both in the elderly population and in those with a more prolonged disease, for whom intensification of therapy is sometimes delayed or not done [63]. Also, no differences were found in glycated haemoglobin reduction at follow-up after add-on of GLP1-RA to SGLT2i, irrespective of gender (M, F), smoking habit and lipid profile.

Regarding the effect on weight, the add-on of GLP1-RA to SGLT2i significantly reduced the percentage of obese subjects (BMI>30) at follow-up, while increasing the percentage of overweight (BMI 25–30) and normal-weight subjects (BMI<25). Patients in three CV risk categories showed significant weight reduction at follow-up after intensification of GLP1-RA therapy, with no significant inter-category changes. No correlation was demonstrated between BMI at baseline and glycated haemoglobin, indicating that glycometabolic status of the three risk categories is independent of weight.

The reduction of hyperglycemia observed in our population after the add-on GLP1-RA to SGLT2i is an important effect, which implies reduced glucotoxicity and slowing the activation of pathological signalling pathways, (e.g., polyol pathway, PKC activation, upregulation hexosamine pathway, accumulation of advanced glycation end products) which are involved in the development of micro- and macrovascular complication, and thus possibly slowing or even halting progression to multiple organ failure (cardiovascular diseases including heart failure, kidney failure, retinopathy, peripheral and autonomic neuropathy) [64–71]. On the other hand, weight reduction is essential because it is also germane to reduced insulin resistance, thus reducing another key mechanism for developing, maintaining, and progressing the disease [72].

Interestingly, these bio-anthropometric and metabolic results in the real-world are consistent with previous data from a randomized controlled trial using dulaglutide in addition to SGLT2i, supporting the more widespread use of this combination therapy to minimize the burden of complications [73].

Also, in the specific moderate-to-high-risk population identified by the AWARE app, there was a reduction in glycated haemoglobin and BMI. Intensification of therapy with co-administration of GLP1-RA and SGLT2i in a population without overt macro- and microvascular disease may allow early and preventive intervention capable of slowing or even preventing the onset of complications and blocking the continuum of cardiovascular risk typical of the disease [74].

This study has some limitations because it is retrospective, does not have a control group, and has a rather short follow-up for the evaluation of the effect of dual therapy with GLP1ras and SGLT2i. However, it is representative of real-world clinical settings, characterized by a high volume and rapid turnover of patients with T2DM.

In conclusion, the addition of GLP1-RA to SGLT2i was confirmed to improve metabolic control and reduce body weight in obese T2DM patients. A more aggressive and proactive combination treatment with GLP1-RA together with SGLT2i when cardiovascular risk is present, could represent an additional important step forward in terms of organ protection.

Finally, the possibility of combining double or triple receptor agonists with SGLT2i in the various categories of cardiovascular risk in the near future opens up new and stimulating therapeutic perspectives [12]. In these scenarios, having new tools that can quickly and reliably classify the patient can give an additional advantage for more effective clinical management.

Ethics approval and consent to participate

The study was reviewed by the Ethics Committee of IRCSS MultiMedica, Sesto San Giovanni (MI), Italy (Protocol No. 498.2021, approved on 10/03/2022). The Ethics Committee waived the requirement for patients informed consents, because of the nature of the study, a non-interventional retrospective analysis of anonymized data. The study was conducted in accordance with recognized standard clinical practice principles, in compliance with the Declaration of Helsinki, and the European Medicines Agency Guidelines for Good Clinical Practice.

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CRediT authorship contribution statement

Umberto Mortola: Visualization, Formal analysis. **Elena Lunati:** Resources, Investigation, Data curation. **Renata Ghelardi:** Resources, Investigation, Data curation. **Lucia Centofanti:** Visualization, Formal analysis. **Loredana Bucciarelli:** Resources, Investigation, Data curation. **Vincenzo Cimino:** Resources, Investigation, Data curation. **Franco Folli:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Francesco Bifari:** Writing – original draft, Validation, Formal analysis. **Elisa Cipponeri:** Writing – original draft, Investigation, Formal analysis, Data curation. **Cesare Berra:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Roberto Manfrini:** Writing – original draft, Supervision, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Consent for publication

Not applicable.

Data Availability

Data will be made available upon reasonable request to the

corresponding authors.

References

[1] GBD 2021 Diabetes Collaborators, Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021, Lancet 402 (10397) (2023) 203–234, https://doi.org/10.1016/S0140-6736(23)01301-6. Epub 2023 Jun 22.

[2] A. Castro Conde, D. Marzal Martín, R. Campuzano Ruiz, Comprehensive cardiovascular and renal protection in patients with type 2 diabetes (al), J. Clin. Med 12 (12) (2023) 3925, https://doi.org/10.3390/jcm12123925.

[3] M.K. Ali, J. Pearson-Stuttard, E. Selvin, E.W. Gregg, Interpreting global trends in type 2 diabetes complications and mortality, Diabetologia 65 (1) (2022) 3–13, https://doi.org/10.1007/s00125-021-05585-2.

[4] American Diabetes Association Professional Practice Committee, 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes-2024, Diabetes Care 47 (1) (2024) S158–S178, 2024 Jan 1.

[5] S.P. Marso, G.H. Daniels, K. Brown-Frandsen, et al., Liraglutide and cardiovascular outcomes in type 2 diabetes, N. Engl. J. Med 375 (4) (2016) 311–322, https://doi.org/10.1056/NEJMoa1603827.

[6] S.P. Marso, S.C. Bain, A. Consoli, et al., Semaglutide and cardiovascular outcomes in patients with type 2 diabetes, N. Engl. J. Med 375 (19) (2016) 1834–1844, https://doi.org/10.1056/NEJMoa1607141.

[7] M. Ferdaoussi, S. Abdelli, J.Y. Yang, et al., Exendin-4 protects beta-cells from interleukin-1 beta-induced apoptosis by interfering with the c-Jun NH2-terminal kinase pathway, Diabetes 57 (5) (2008) 1205–1215, https://doi.org/10.2337/db07-1214.

[8] H.C. Gerstein, H.M. Colhoun, G.R. Dagenais, et al., Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial, Lancet 394 (10193) (2019) 121–130, https://doi.org/10.1016/S0140-6736(19)31149-3.

[9] M. Abdul-Ghani, R.A. DeFronzo, Is it time to change the type 2 diabetes treatment paradigm? Yes! GLP-1 RAs should replace metformin in the type 2 diabetes algorithm, Diabetes Care 40 (8) (2017) 1121–1127, https://doi.org/10.2337/dc16-2368.

[10] T.V. Fiorentino, F. Casiraghi, A.M. Davalli, et al., Exenatide regulates pancreatic islet integrity and insulin sensitivity in the nonhuman primate baboon Papio hamadryas, JCI Insight 4 (20) (2019) e93091, https://doi.org/10.1172/jci.insight.93091.

[11] N. Marx, M. Husain, M. Lehrke, et al., GLP-1 receptor agonists for the reduction of atherosclerotic cardiovascular risk in patients with type 2 diabetes, Circulation 146 (24) (2022) 1882–1894, https://doi.org/10.1161/CIRCULATIONAHA.122.059595.

[12] F. Folli, G. Finzi, R. Manfrini, et al., Mechanisms of action of incretin receptor based dual- and tri-agonists in pancreatic islets, Am. J. Physiol. Endocrinol. Metab. 325 (5) (2023) E595–E609, https://doi.org/10.1152/ajpendo.00236.2023.

[13] E. Lazzaroni, M. Ben Nasr, C. Loretelli, et al., Anti-diabetic drugs and weight loss in patients with type 2 diabetes, Pharm. Res (2021), https://doi.org/10.1016/j.phrs.2021.105782.

[14] A.O. Chavez, A. Gastaldelli, R. Guardado-Mendoza, et al., Predictive models of insulin resistance derived from simple morphometric and biochemical indices related to obesity and the metabolic syndrome in baboons, Cardiovasc Diabetol. 8 (2009) 22, https://doi.org/10.1186/1475-2840-8-22.

[15] Look, AHEAD Research Group, E.W. Gregg, J.M. Jakicic, et al., Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial, Lancet Diabetes Endocrinol. 4 (11) (2016) 913–921, https://doi.org/10.1016/S2213-8587(16)30162-0.

[16] D. Li, Y. Wu, C.Z. Wang, et al., Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis, BMJ 384 (2024), https://doi.org/10.1136/bmj-2023-076410.

[17] M.A. Nauck, J.J. Meier, M.A. Cavender, et al., Cardio- vascular actions and clinical outcomes with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors, Circulation 136 (2017) 849–870, https://doi.org/10.1161/CIRCULATIONAHA.117.028136.

[18] L.A. Leiter, S.C. Bain, D.L. Bhatt, et al., The effect of glucagon-like peptide-1 receptor agonists liraglutide and semaglutide on cardiovascular and renal outcomes across baseline blood pressure categories: analysis of the LEADER and SUSTAIN 6 trials, Diabetes Obes. Metab. 22 (2020) 1690–1695, https://doi.org/10.1111/dom.14079.

[19] C. Berra, R. Manfrini, D. Regazzoli, et al., Blood pressure control in type 2 diabetes mellitus with arterial hypertension. The important ancillary role of SGLT2-inhibitors and GLP1-receptor agonists, Pharm. Res 160 (2020) 105052, https://doi.org/10.1016/j.phrs.2020.105052. Epub 2020 Jul 8.

[20] G. Bendotti, L. Montefusco, M.E. Lunati, et al., The anti-inflammatory and immunological propreties of GLP-1 Receptor agonists, Pharm. Res 182 (2022) 106320, https://doi.org/10.1016/j.phrs.2022.106320. Epub 2022 Jun 20.

[21] R.A. De Fronzo, Combination therapy with GLP-1 receptor agonist and SGLT2 inhibitor, Diabetes Obes. Metab. 19 (10) (2017) 1353–1362, https://doi.org/10.1111/dom.12982.

[22] A.O. Chavez, J.C. Lopez-Alvarenga, M.E. Tejero, et al., Physiological and molecular determinants of insulin action in the baboon, Diabetes 57 (4) (2008) 899–908, https://doi.org/10.2337/db07-079.

[23] A.M. Lincoff, K. Brown-Frandsen, H.M. Colhoun, et al., SELECT Trial Investigators. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes, N. Engl. J. Med 389 (24) (2023) 2221–2232, https://doi.org/10.1056/NEJMoa2307563. Epub 2023 Nov 11.

[24] M. Mirani, G. Favacchio, E. Serone, et al., Liraglutide and cardiovascular outcomes in a real world type 2 diabetes cohort, Pharm. Res 137 (2018) 270–279, https://doi.org/10.1016/j.phrs.2018.09.003. Epub 2018 Sep 10.

[25] C.C. Berra, M.C. Rossi, M. Mirani, et al., Real word effectiveness of subcuteneous semaglutide in type 2 diabetes: a retrospective cohort study, Front Endocrinol. (Lausanne) 13 (2023) 1099451, https://doi.org/10.3389/fendo.2022.1099451. eCollection 2022.

[26] R. Napoli, C. Berra, A.M. Catarig, et al., Once-weekly semaglutide use in patients with type 2 diabetes: Real -word data from the SURE Italy observationale study, Diabetes Obes. Metab. 25 (6) (2023) 1658–1667, https://doi.org/10.1111/dom.15020. Epub 2023 Mar 12.

[27] C.C. Berra, V. Resi, M. Mirani, et al., Clinical efficacy and predictors of response to dulaglutide in type-2 diabetes, Pharm. Res 159 (2020) 104996, https://doi.org/10.1016/j.phrs.2020.104996. Epub 2020 Jun 20.

[28] E.G. Gronda, E. Vanoli, M. Iacoviello, et al., Renal effects of SGLT2 inhibitors in cardiovascular patients with and without chronic kidney disease: focus on heart failure and renal outcomes, Heart Fail Rev. 28 (3) (2023) 723–732, https://doi.org/10.1007/s10741-021-10211-9.

[29] E. Lazzaroni, M.E. Lunati, L. Montefusco, et al., Dapaglifozin acutely improves kidney function in type 2 diabetes mellitus. The PRECARE study, Pharm. Res 183 (2022) 106374, https://doi.org/10.1016/j.phrs.2022.106374. Epub 2022 Jul 28.

[30] M.E. Lunati, V. Cimino, A. Gandolfi, et al., SGLT2-inhibitors are effective and safe in the elderly: the SOLD study, Pharm. Res 183 (2022) 106396, https://doi.org/10.1016/j.phrs.2022.106396. Epub 2022 Aug 12.

[31] B. Zinman, C. Wanner, J.M. Lachin, et al., Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes, N. Engl. J. Med 373 (22) (2015) 2117–2128, https://doi.org/10.1056/NEJMoa1504720.

[32] R.A. DeFronzo, From the triumvirate to the Ominous Octet: a new paradigm for the treatment of type 2 diabetes mellitus, Diabetes 58 (2009) 773–795, https://doi.org/10.2337/db09-9028.

[33] S.A. Jabbour, J.P. Frías, C. Guja, et al., Effects of exenatide once weekly plus dapagliflozin, exenatide once weekly, or dapagliflozin, added to metformin monotherapy, on body weight, systolic blood pressure, and triglycerides in patients with type 2 diabetes in the DURATION-8 study, Obes. Metab. Jun. 20 (6) (2018) 1515–1519, https://doi.org/10.1111/dom.13206. Epub 2018 Feb 4.

[34] M.E. Lunati, V. Cimino, D. Bernasconi, et al., Type 2 diabetes mellitus pharmacological remission with dapagliflozin plus oral semaglutide, Pharm. Res 199 (2024) 107040, https://doi.org/10.1016/j.phrs.2023.107040.

[35] F. Cosentino, P.J. Grant, V. Aboyans, et al., ESC scientific document group. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD, Eur. Heart J. 41 (2020) 255–323, https://doi.org/10.1093/eurheartj/ehz486.

[36] C. Berra, R. Manfrini, M. Mirani, et al., AWARE A novel web application to rapidly assess cardiovascular risk in type 2 diabetes mellitus, Acta Diabetol. 60 (9) (2023) 1257–1266, https://doi.org/10.1007/s00592-023-02115-x.

[37] Cosentino, F. Grant, P.J. Aboyans, et al., 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD, Eur. Heart J. 41 (2) (2020) 255–323, https://doi.org/10.1093/eurheartj/ehz486.

[38] A.E. Butler, J. Janson, S. Bonner-Weir, et al., Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes, Diabetes 52 (1) (2003) 102–110, doi: 10.2337/diabetes.52.1.102.

[39] B.L. Wajchenberg, beta-cell failure in diabetes and preservation by clinical treatment, Endocr. Rev. 28 (2) (2007) 187–218, doi: 10.1210/10.1210/er.2006-0038.

[40] H.J. Heerspink, B.A. Perkins, D.H. Fitchett, et al., Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus: Cardiovascular and Kidney Effects, Potential Mechanisms, and Clinical Applications, Circulation 134 (10) (2016) 752–772, https://doi.org/10.1161/CIRCULATIONAHA.116.021887.

[41] S.R. Cechin, I. Pérez-Álvarez, E. Fenjves, et al., Anti-inflammatory properties of exenatide in human pancreatic islets, Cell Transpl. 21 (4) (2012) 633–648, https://doi.org/10.3727/096368911X576027.

[42] P. Gourdy, P. Darmon, F. Dievart, et al., Combining glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) in patients with type 2 diabetes mellitus (T2DM), Cardiovasc Diabetol. 22 (1) (2023) 79, https://doi.org/10.1186/s12933-023-01798-4.

[43] S.E. Kahn, S.M. Haffner, M.A. Heise, et al., Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy, N. Engl. J. Med 355 (23) (2006) 2427–2443, https://doi.org/10.1056/NEJMoa066224.

[44] T.A. Zelniker, S.D. Wiviott, I. Raz, et al., Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus, Circulation 139 (17) (2019) 2022–2031, https://doi.org/10.1161/CIRCULATIONAHA.118.038868.

[45] R.M. Goldenberg, V. Ahooja, K.K. Clemens, et al., Practical considerations and rationale for glucagon-like peptide-1receptor agonist plus sodium-dependent glucose cotransporter- 2 inhibitor combination therapy in type 2 diabetes, Can. J. Diabetes 45 (3) (2021) 291–302, https://doi.org/10.1016/j.jcjd.2020.09.005.

[46] E. Brown, H.J. Heerspink, D.J. Cuthbertson, et al., SGLT2 Inhibitors and GLP-1 receptor agonists: established and emerging indications, Lancet 398 (10296) (2021) 262–276, https://doi.org/10.1016/S0140-6736(21)00536-5.

[47] R. Guardado-Mendoza, A.M. Davalli, A.O. Chavez, et al., Pancreatic islet amyloidosis, beta-cell apoptosis, and alpha-cell proliferation are determinants of

islet remodeling in type-2 diabetic baboons, Proc. Natl. Acad. Sci. USA 106 (33) (2009) 13992–13997, https://doi.org/10.1073/pnas.0906471106.
[48] M.L. Morieri, E. Longato, B. Di Camillo, et al., Management of type 2 diabetes with a treat-to-benefit approach improved long-term cardiovascular outcomes under routine care, Cardiovasc Diabetol. 21 (1) (2022) 274, https://doi.org/10.1186/s12933-022-01712-4.
[49] J.M. Rodriguez-Valadez, M. Tahsin, K.E. Fleischmann, et al., Cardiovascular and renal benefits of novel diabetes drugs by baseline cardiovascular risk: a systematic review, meta-analysis, and meta-regression, Diabetes Care 46 (6) (2023) 1300–1310, https://doi.org/10.2337/dc22-0772.
[50] K. Khunti, C.L. Hertz, L.L.N. Husemoen, et al., Cardiovascular risk factors early in the course of treatment in people with type 2 diabetes without established cardiovascular disease: a population-based observational retrospective cohort study, Diabet. Med 39 (3) (2022) e14697, https://doi.org/10.1111/dme.14697.
[51] C. Damaskos, N. Garmpis, P. Kollia, et al., Assessing cardiovascular risk in patients with diabetes: an update, Curr. Cardiol. Rev. 16 (4) (2020) 266–274, https://doi.org/10.2174/1573403X15666191111123622.
[52] T.V. Fiorentino, A. Monroy, S. Kamath, et al., Pioglitazone corrects dysregulation of skeletal muscle mitochondrial proteins involved in ATP synthesis in type 2 diabetes, Metabolism 114 (2021) 154416, https://doi.org/10.1016/j.metabol.2020.154416. Epub 2020 Oct 31.
[53] T.V. Fiorentino, M. Owston, G. Abrahamian, et al., Chronic continuous exenatide infusion does not cause pancreatic inflammation and ductal hyperplasia in non-human primates, Am. J. Pathol. 185 (1) (2015) 139–150, https://doi.org/10.1016/j.ajpath.2014.09.009.
[54] Melanie J. Davies, Vanita R. Aroda, et al., Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), Diabetologia 65 (12) (2022) 1925–1966, https://doi.org/10.1007/s00125-022-05787-2.
[55] R. Paroni, I. Fermo, P. Fiorina, et al., Determination of asymmetric and symmetric dimethylarginines in plasma of hyperhomocysteinemic subjects, Amino Acids 28 (4) (2005) 389–394, https://doi.org/10.1007/s00726-005-0191-z.
[56] E. Astorri, P. Fiorina, G. Gavaruzzi, et al., Left ventricular function in insulin-dependent and in non-insulin-dependent diabetic patients: radionuclide assessment, Cardiology 88 (2) (1997) 152–155, https://doi.org/10.1159/000177322.
[57] H. Yki-Jarvinen, ADOPT: lessons from comparison of glycemic durability of rosiglitazone, metformin, or glyburide monotherapy, Curr. Diab Rep. 7 (3) (2007) 173–174, https://doi.org/10.1007/s11892-007-0028-0.
[58] UK Prospective Diabetes Study (UKPDS) Group, Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33), Lancet 352 (9131) (1998) 837–853, https://doi.org/10.1016/S0140-6736(98)07019-6.
[59] C. Li, J. Luo, M. Jiang, et al., The efficacy and safety of the combination therapy With GLP-1 receptor agonists and SGLT-2 inhibitors in type 2 diabetes mellitus: a systematic review and meta-analysis, Front Pharm. 13 (2022) 838277, https://doi.org/10.3389/fphar.2022.838277.
[60] F. Folli, S. La Rosa, G. Finzi, et al., Pancreatic islet of Langerhans' cytoarchitecture and ultrastructure in normal glucose tolerance and in type 2 diabetes mellitus, Diabetes Obes. Metab. 20 (2) (2018) 137–144, https://doi.org/10.1111/dom.13380.
[61] J.A. Schmittdiel, C.S. Uratsu, A.J. Karter, et al., Why don't diabetes patients achieve recommended risk factor targets? Poor adherence versus lack of treatment intensification, J. Gen. Intern Med 23 (5) (2008) 588–594, https://doi.org/10.1007/s11606-008-0554-8.
[62] L.E. García-Pérez, M. Alvarez, T. Dilla, et al., Adherence to therapies in patients with type 2 diabetes, Diabetes Ther. 4 (2) (2013) 175–194, https://doi.org/10.1007/s13300-013-0034-y. Epub 2013 Aug 30.
[63] F. Andreozzi, R. Candido, S. Corrao, et al., Clinical inertia is the enemy of therapeutic success in the management of diabetes and its complications: a narrative literature review, Diabetol. Metab. Syndr. 12 (2020) 52, https://doi.org/10.1186/s13098-020-00559-7.
[64] H. Zheng, J. Wu, Z. Jin, et al., Protein modifications as manifestations of hyperglycemic glucotoxicity in diabetes and its complications, Biochem Insights 9 (2016) 1–9, https://doi.org/10.4137/BCI.S36141.
[65] R.C. Turner, C.A. Cull, V. Frighi, et al., Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group, JAMA 281 (21) (1999) 2005–2012, https://doi.org/10.1001/jama.281.21.2005.
[66] S. Battault, E. Renguet, A. Van Steenbergen, et al., Myocardial glucotoxicity: mechanisms and potential therapeutic targets, Arch. Cardiovasc Dis. 113 (11) (2020) 736–748, https://doi.org/10.1016/j.acvd.2020.06.006.
[67] M. Mota, B.A. Banini, S.C. Cazanave, et al., Molecular mechanisms of lipotoxicity and glucotoxicity in nonalcoholic fatty liver disease, Metabolism 65 (8) (2016) 1049–1061, https://doi.org/10.1016/j.metabol.2016.02.014.
[68] G. Perseghin, P. Fiorina, F. De Cobelli, et al., Cross-sectional assessment of the effect of kidney and kidney-pancreas transplantation on resting left ventricular energy metabolism in type 1 diabetic-uremic patients: a phosphorous-31 magnetic resonance spectroscopy study, J. Am. Coll. Cardiol. 46 (6) (2005) 1085–1092.
[69] F. D'Addio, P. Maffi, P. Vezzulli, et al., Islet transplantation stabilizes hemostatic abnormalities and cerebral metabolism in individuals with type 1 diabetes, Diabetes Care 37 (1) (2014) 267–276.
[70] T. Eleftheriadis, G. Pissas, K. Tsogka, et al., A unifying model of glucotoxicity in human renal proximal tubular epithelial cells and the effect of the SGLT2 inhibitor dapagliflozin, Urol. Nephrol. Jun. 52 (6) (2020) 1179–1189, https://doi.org/10.1007/s11255-020-02481-3.
[71] S.K. Sinha, S.B. Nicholas, Pathomechanisms of diabetic kidney disease, J. Clin. Med. 12 (2023) 7349, https://doi.org/10.3390/jcm12237349.
[72] L.D. Clamp, D.J. Hume, E.V. Lambert, et al., Enhanced insulin sensitivity in successful, long-term weight loss maintainers compared with matched controls with no weight loss history, Nutr. Diabetes 7 (2017) e282, https://doi.org/10.1038/nutd.2017.31.
[73] B. Ludvik, J.P. Frías, F.J. Tinahones, et al., Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial, Lancet Diabetes Endocrinol. 2018 6 (2018) 370–381, https://doi.org/10.1016/S2213-8587(18)30023-8.
[74] J.J. Joseph, P. Deedwania, T. Acharya, et al., Comprehensive management of cardiovascular risk factors for adults with type 2 diabetes: a scientific statement from the american heart association, Circulation 145 (9) (2022) e722–e759, https://doi.org/10.1161/CIR.0000000000001040. Epub 2022 Jan 10.