

## Original Article

## Effectiveness of GLP-1 Receptor Agonists and SGLT-2 Inhibitors Combination Therapy in Type 2 Diabetes: A Real-World Experience

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## ABSTRACT

**Aims:** To evaluate the real-world effectiveness of combination therapy with glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose co-transporter 2 inhibitors (SGLT2-I) on glucose control in type 2 diabetes (T2D) and to identify clinical predictors of treatment response.

**Methods:** We retrospectively analyzed data from 549 subjects with T2D treated with combined GLP-1RA and SGLT2-I therapy. Clinical and biochemical parameters were collected at baseline and after 6–9 months of follow-up. Therapy response was defined according to drug-specific expected glycated hemoglobin (HbA1C) reduction thresholds, based on the known efficacy of each innovative molecule. Logistic regression and receiver operating characteristic analyses were used to identify predictors of response. Decision curve analysis was performed to assess the utility of predictive models.

**Results:** 41.9% of subjects achieved the expected HbA1C reduction. Baseline HbA1C was the strongest predictor of response (odds ratio: 6.60 per 1% [ $\approx 11$  mmol/mol] increase). Follow-up reductions in fasting plasma glucose and body mass index, and increases in high-density lipoprotein cholesterol, were also associated with response. Decision curve analysis demonstrated that both baseline and extended models provided higher net benefit than treat-all and treat-none strategies.

**Conclusions:** Combination therapy with GLP-1RA and SGLT2-I improves glucose control in a substantial proportion of subjects with T2D. Integrating baseline glycaemic burden with longitudinal metabolic changes may support individualized clinical decision-making.

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## Introduction

Type 2 diabetes (T2D) is a widespread metabolic disease whose prevalence has steadily increased in the last decades.<sup>1</sup> The cornerstone of T2D long-term management is achieving and maintaining adequate glucose control for preventing chronic complications.<sup>2–6</sup> In recent years, the therapeutic landscape of T2D

has evolved with the introduction of drug classes targeting complementary pathophysiological mechanisms. In particular, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose co-transporter 2 inhibitors (SGLT2-I) are innovative glucose-lowering agents that not only improve glucose control, but also provide cardiovascular, renal and liver protection.<sup>7–10</sup> SGLT2-I have demonstrated cardio- and nephroprotective effects in subjects with T2D and may also modulate autonomic dysfunction and vasovagal syncope risk.<sup>11–13</sup> Furthermore, recent studies suggest that combined GLP-1RA and SGLT2-I therapy may provide additive cardiometabolic benefits in subjects with ischemic heart disease, heart failure, and arrhythmia-related conditions.<sup>14,15</sup> The distinct

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and complementary mechanisms of these 2 drug classes make their combination a particularly useful therapeutic strategy.

While randomized controlled trials have explored the glucose-lowering efficacy of GLP1-RA and SGLT2-I therapies, little real-world evidence is available regarding their combined use.<sup>7,16-24</sup> Despite the known benefits of this combination, a proportion of subjects with T2D still fail to achieve their glycemic goals, highlighting an unmet clinical need to identify subject's characteristics predicting a positive therapeutic outcome.

The aim of this study was to address this knowledge gap by retrospectively evaluating the glucose-lowering effectiveness of combined GLP-1RA and SGLT2-I therapy in a cohort of subjects with T2D and to identify potential clinical factors that predict a favorable response to this combined regimen.

## Subjects, Materials, and Methods

We retrospectively analyzed data of 549 subjects with T2D receiving treatment with a combination of both GLP-1RA and SGLT2-I. All subjects referred to our diabetes and obesity tertiary care center and were identified in the electronic medical records routinely used (Smart Digital Clinic 10.12.20, Meteda s.r.l.) by using appropriate keywords for drugs and diabetes type and Boolean indicators. This survey identified 1,530 subjects with T2D, of these, 981 were excluded, after reviewing their electronic records, since they did not receive the 2 classes of innovative drugs simultaneously.

The 549 subjects with T2D considered for the analysis started the combination therapy between January 2021 and June 2023. For all subjects, data concerning demographic, anthropometric, biochemical characteristics, diabetes-related medical history were collected. Anthropometric, biochemical and diabetes therapy details were collected at baseline (time of addition of the second innovative diabetes drug) and at the routine follow-up visit (6-9 months since baseline). No missing data were present for the primary outcome or for the main demographic, clinical, anthropometric, and biochemical variables included in the analyses. Variables characterized by substantial missingness were not considered in the present study (eg blood pressure). Consequently, no imputation methods were applied.

The primary outcome of the study was the percentage of subjects who achieved the expected glycated hemoglobin (HbA1C) reduction in the 6-9 months following the addition of the second class of innovative diabetes drugs. According to published data, we defined different cut-offs of expected HbA1C reduction based on the specific innovative molecule added to background innovative drug:  $-1.3\%$  ( $-14$  mmol/mol) for injectable semaglutide;  $-1.0\%$  ( $-11$  mmol/mol) for dulaglutide and oral semaglutide;  $-0.9\%$  ( $-10$  mmol/mol) for long-acting release exenatide; and  $-0.6\%$  ( $-7$  mmol/mol) for SGLT2-I (empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin).<sup>25-27</sup> Dose-specific analyses were not performed because of the heterogeneity of treatment combinations, which would have resulted in excessive fragmentation of the study population. In routine clinical practice, drug doses were selected according to individual clinical characteristics (eg tolerability and renal function). Consequently, all subjects were categorized as either responders or nonresponders based on whether they achieved the expected HbA1C reduction. Treatment response was defined according to drug-specific expected HbA1C reduction thresholds derived from published literature and meta-analyses, in which pooled efficacy estimates and forest plots generally refer to the single molecule rather than to individual approved doses. While some dose-related differences may exist for GLP-1RA, the glucose-lowering differences between approved doses of SGLT2-I are generally minimal and likely to have a negligible impact on

## Highlights

- Glucagon-like peptide-1 receptor agonist/sodium-glucose co-transporter 2 inhibitors combination improves glucose control in real-world type 2 diabetes
- Baseline glycosylated hemoglobin was the main predictor of response to combination therapy
- Longitudinal metabolic changes improved predictive model performance
- Decision curve analysis confirmed the clinical utility of prediction models

## Clinical Relevance

In individuals with type 2 diabetes, combination therapy with glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter 2 inhibitors is increasingly used in routine clinical practice. Identifying subjects more likely to achieve a meaningful glycemic response may support treatment individualization and therapeutic intensification, while preserving the established cardio-renal benefits of these drug classes.

response classification. Accordingly, the expected glucose-lowering efficacy was considered mainly at the molecule level.

Subjects were divided into the following subgroups of baseline HbA1C tertiles: T1, T2, and T3 ( $\text{HbA1C} \leq 7.3\%$  [ $\leq 56$  mmol/mol],  $7.4\text{--}7.9\%$  [ $57\text{--}63$  mmol/mol], and  $\geq 8.0\%$  [ $\geq 64$  mmol/mol], respectively).

Secondary outcomes included: absolute changes in HbA1C, fasting plasma glucose (FPG), body weight, body mass index (BMI), renal function parameters, lipids, aspartate aminotransferase, and alanine aminotransferase (ALT), from baseline to follow-up routine visit.

BMI was calculated by dividing the weight in kilograms by height in square meters ( $\text{kg/m}^2$ ) to classify subjects as normal weight (BMI  $18.5\text{--}24.9$   $\text{kg/m}^2$ ), overweight (BMI  $25.0\text{--}29.9$   $\text{kg/m}^2$ ) or obese (BMI  $\geq 30$   $\text{kg/m}^2$ ).<sup>28,29</sup>

LDL cholesterol was calculated with the Friedewald formula (cholesterol total-high-density lipoprotein (HDL)-triglycerides/5) if triglycerides value were lower than 400 mg/dL.

The estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration formula.<sup>30</sup> Microalbuminuria and macroalbuminuria were defined as a urinary albumin-to-creatinine ratio between 30 and 299 mg/g and of 300 mg/g or higher, respectively, in a random spot urine sample. Diabetes nephropathy was defined either as the evidence of an urine albumin to creatinine ratio  $> 30$  mg/gr in random spot urine collection or the presence of an eGFR  $< 60$  mL/min according to the Chronic Kidney Disease Epidemiology Collaboration.<sup>31</sup>

Diabetes retinopathy (DR) was defined as the evidence of any form of diabetes-related retinal alteration at the eye examination (fundus oculi in mydriasis, fluorescein angiography, or optical coherence tomography).<sup>32</sup>

We also recorded the presence of documented ischemic heart disease, ischemic or hemorrhagic stroke, arterial vessel disease (ultrasound evidence of carotid/lower limbs arterial vessel plaques), and diabetes foot.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its later amendments. All subjects gave their consent for the clinical data contained in the electronic medical records to be stored and processed.

## Statistical Analysis

First, the observed differences between subgroups were analyzed. Then, the variables most related to treatment response were explored. Finally, the associations were confirmed in multivariate models that consider confounders.

Continuous variables were presented as mean  $\pm$  standard deviation (SD) and compared by using the *t* test for unpaired and paired samples. An F-test was preliminarily performed to examine the homogeneity of the variance. Dichotomous outcomes are expressed as number and percentage. Yates' $\chi^2$  test was applied to detect differences of percentage between groups. We calculated the adjusted odds ratios (ORs) related to response to combination therapy in a multivariate stepwise backward binary logistic regression models considering potential confounders identified from univariate analyses and clinical relevance. Collinearity diagnostics were assessed before model construction and no significant multicollinearity was identified (all variance inflation factor values  $< 1.2$ ). The assumption of linearity in the logit for continuous variables was evaluated during model building and no relevant deviations from linearity were observed. In addition, the number of outcome events relative to the number of predictors included in the models was adequate (approximately 29 outcome events per predictor), exceeding commonly accepted thresholds for logistic regression modelling and therefore reducing the likelihood of model overfitting.

Given the retrospective and observational design of the study, no a priori sample size or power calculation was performed. All consecutive eligible subjects treated with combined GLP-1RA and SGLT2-I therapy during the study period were included. The resulting sample size was considered adequate to ensure an adequate estimation of the primary outcome, as assessed by confidence intervals (CIs) for proportions calculated using binomial methods based on the Wilson score approach, and to support multivariate analyses, considering the number of outcome events observed and the ratio between events and covariates included in the models. Furthermore, the inclusion of consecutive real-world subjects reduced selection bias and enhanced the clinical applicability of the findings.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminatory capacity of continuous variables in distinguishing between responders and nonresponders to combination therapy. The ROC curve plots the true positive rate (sensitivity) against the false positive rate (1 - specificity) for all possible cut-off values of the test results. The overall diagnostic accuracy was assessed by calculating the area under the ROC curve (AUC), with 95% CI. The optimal cut-off value was determined using the Youden's index (sensitivity + specificity - 1).

Decision curve analysis (DCA) was performed to evaluate the clinical utility of the prediction models by quantifying net benefit across a range of threshold probabilities. Two logistic regression models were evaluated: a baseline model including baseline HbA1C, insulin use, GLP-1RA use, albuminuria, and DR, and an extended model including both baseline variables and follow-up changes in FPG, BMI, and HDL cholesterol. Net benefit was calculated for each model and compared with treat-all and treat-none strategies across clinically relevant threshold probabilities.

Statistical analyses were performed using IBM SPSS Statistics software version 20 (IBM Corp.) except for DCA computations which were performed using the R software environment for statistical computing and graphics (R Foundation for Statistical Computing).

For all the analysis, a two-sided *P* value  $< .05$  was considered statistically significant.

## Results

### Study Population Characteristics

Our analysis included 549 subjects with T2D. The main demographic, clinical, and biochemical characteristics at baseline are shown in [Table 1](#): most subjects were males (68.5%), 89.2% overweight or obese with an average BMI  $31.0 \pm 5.3$  kg/m<sup>2</sup>. Age and diabetes duration were  $65.9 \pm 9.1$  and  $18.6 \pm 8.9$  years, respectively. Baseline HbA1C was  $7.8 \pm 1.1\%$  ( $62 \pm 12$  mmol/mol), and the prevalence of subjects with HbA1C  $< 7\%$  ( $< 53$  mmol/mol) was 18.5% at baseline and 40.8% during follow-up. The distribution of GLP-1RA and SGLT2-I combinations in the study cohort is detailed in [Supplementary Table 1](#).

### Responders vs Nonresponders

#### Univariate Analysis

Overall, 41.9% (95% CI 37.8–46.1%) of subjects achieved the expected HbA1C reduction following initiation of combination therapy. The clinical and biochemical characteristics at baseline in responders vs nonresponders are described in [Table 1](#). The 2 groups were similar for age, gender, and BMI. A trend, close to reaching statistical significance ( $P = .06$ ), for a lower diabetes duration was observed in responders vs nonresponders ( $17.8 \pm 8.6$  vs  $19.2 \pm 9.1$  years,  $P = .06$ ).

At baseline, responders had a significantly higher HbA1C ( $8.4 \pm 1.1\%$  [ $68 \pm 12$  mmol/mol] vs  $7.3 \pm 0.8\%$  [ $56 \pm 9$  mmol/mol],  $P < .001$ ) and FPG ( $170.0 \pm 49.3$  vs  $139.0 \pm 38.0$  mg/dL,  $P < .001$ ) compared to nonresponders. The prevalence of subjects with baseline HbA1C  $< 7\%$  ( $< 53$  mmol/mol) was 3.9% and 29.2% in responders and nonresponders, respectively ( $P < .001$ ). Furthermore, the percentage of responders increased with increasing HbA1C tertile at baseline, with the highest prevalence observed in the tertile with the highest HbA1C levels (T1 12.0%, T2 39.7%, T3 75.6%,  $P < .001$ ). [Table 1](#) describes the diabetes therapies: no significant differences were found between responders and nonresponders, with the exception of the lower use of insulin at baseline (46.5% vs 56.4%,  $P = .02$ ), GLP-1RA (31.7% vs 58.3%,  $P < .01$ ), and SGLT2-I (28.3% vs 41.7%,  $P < .01$ ) in responders.

According to lipid profile and liver enzymes, responders, compared to nonresponders, had a lower HDL ( $42.5 \pm 11.2$  vs  $44.6 \pm 11.8$  mg/dL,  $P = .04$ ) and a higher triglycerides ( $157.3 \pm 80.9$  vs  $140.3 \pm 74.8$  mg/dL,  $P = .01$ ), aminotransferase ( $23.4 \pm 14.3$  vs  $21.0 \pm 9.3$  U/L,  $P = .03$ ), and ALT ( $27.6 \pm 21.3$  vs  $22.6 \pm 12.5$  U/L,  $P < .01$ ) ([Table 1](#)). Concerning diabetes-related complications at baseline, the prevalence of macrovascular complications did not differ between responders and nonresponders. Instead, kidney profile was more favorable in responders than in nonresponders, as demonstrated by a significantly higher eGFR ( $77.2 \pm 22.4$  vs  $73.1 \pm 23.9$  mL/min,  $P = .04$ ) and a lower prevalence of subjects with an eGFR less than 60 mL/min (22.4% vs 31.8%,  $P = .02$ ) and albuminuria (21.3% vs 31.0%,  $P = .02$ ). A trend for a lower prevalence of DR was observed in responders vs nonresponders (23.7% vs 30.4%,  $P = .09$ ) ([Table 1](#)).

During the follow-up, we observed a significantly higher decrease in body weight ( $-5.2 \pm 5.0$  vs  $-3.7 \pm 4.9$  kg,  $P < .01$ ) and BMI ( $-1.9 \pm 1.9$  vs  $-1.4 \pm 1.8$  kg/m<sup>2</sup>,  $P < .01$ ) in responders vs nonresponders.

We calculated the mean change of the main clinical and biochemical parameters during the combination therapy ([Table 2](#)). As expected, responders, compared to nonresponders, achieved a significantly greater reduction of both HbA1C ( $-1.6 \pm 0.9\%$  [ $-17 \pm 10$  mmol/mol] vs  $-0.13 \pm 0.7\%$  [ $-1 \pm 8$  mmol/mol],  $P < .001$ ) and FPG ( $-40.0 \pm 49.1$  vs  $-3.7 \pm 42.7$  mg/dL,  $P < .001$ ).

**Table 1**  
Baseline Clinical and Biochemical Characteristics of the Studied Population

| Variables                             | Overall (n = 549)   | Responders (n = 230) | Nonresponders (n = 319) | P <sup>a</sup> |
|---------------------------------------|---------------------|----------------------|-------------------------|----------------|
| <b>Clinical characteristics</b>       |                     |                      |                         |                |
| Age (y)                               | 65.9 ± 9.1          | 65.2 ± 9.0           | 66.31 ± 9.2             | .17            |
| Male Gender, n (%)                    | 376 (68.5)          | 162 (70.4)           | 214 (67.1)              | .40            |
| Diabetes duration (y)                 | 18.6 ± 8.9          | 17.8 ± 8.6           | 19.2 ± 9.1              | .06            |
| Weight (kg)                           | 85.5 ± 16.1         | 86.6 ± 16.9          | 84.6 ± 15.4             | .16            |
| BMI (kg/m <sup>2</sup> )              | 31.0 ± 5.3          | 31.3 ± 5.5           | 30.8 ± 5.1              | .33            |
| HbA1C (%) (mmol/mol)                  | 7.8 ± 1.1 (62 ± 12) | 8.4 ± 1.1 (68 ± 12)  | 7.3 ± 0.8 (56 ± 9)      | <.001          |
| HbA1C tertiles, n (%)                 |                     |                      |                         | <.001          |
| T1                                    | 184 (33.5)          | 22 (12.0)            | 162 (88.0)              |                |
| T2                                    | 189 (34.4)          | 75 (39.7)            | 114 (60.3)              |                |
| T3                                    | 176 (32.1)          | 133 (75.6)           | 43 (24.4)               |                |
| FPG (mg/dL)                           | 150.7 ± 45.2        | 170.0 ± 49.3         | 139.0 ± 38.0            | <.001          |
| Total cholesterol (mg/dL)             | 154.7 ± 36.7        | 154.4 ± 39.1         | 155.0 ± 35.0            | .84            |
| LDL (mg/dL)                           | 82.0 ± 30.7         | 80.9 ± 32.6          | 82.7 ± 29.4             | .51            |
| HDL (mg/dL)                           | 43.8 ± 11.6         | 42.5 ± 11.2          | 44.6 ± 11.8             | .04            |
| Triglycerides (mg/dL)                 | 147.3 ± 77.7        | 157.3 ± 80.9         | 140.3 ± 74.8            | .01            |
| Serum creatinine (mg/dL)              | 1.0 ± 0.4           | 0.99 ± 0.4           | 1.1 ± 0.4               | .08            |
| eGFR (mL/min)                         | 74.8 ± 23.3         | 77.2 ± 22.4          | 73.1 ± 23.9             | .04            |
| AST (U/L)                             | 22.0 ± 11.7         | 23.4 ± 14.3          | 21.0 ± 9.3              | .03            |
| ALT (U/L)                             | 24.7 ± 16.8         | 27.6 ± 21.3          | 22.6 ± 12.5             | <.01           |
| <b>Diabetes therapy</b>               |                     |                      |                         |                |
| Metformin, n (%)                      | 500 (91.1)          | 208 (90.4)           | 292 (91.5)              | .66            |
| GLP1-RA, n (%)                        | 351 (63.9)          | 165 (71.7)           | 186 (58.3)              | <.01           |
| SGLT2-I, n (%)                        | 198 (36.1)          | 65 (28.3)            | 133 (41.7)              | <.01           |
| Pioglitazone, n (%)                   | 28 (5.1)            | 14 (6.1)             | 14 (4.4)                | .37            |
| DPP-4 inhibitors, n (%)               | 10 (1.8)            | 3 (1.3)              | 7 (2.2)                 | .44            |
| Acarbose, n (%)                       | 7 (1.3)             | 5 (2.2)              | 2 (0.6)                 | .11            |
| Sulphonylurea, n (%)                  | 4 (0.7)             | 3 (1.3)              | 1 (0.3)                 | .18            |
| Repaglinide, n (%)                    | 1 (0.2)             | 0 (0.0)              | 1 (0.3)                 | .40            |
| Insulin, n (%)                        | 287 (52.3)          | 107 (46.5)           | 180 (56.4)              | .02            |
| Only basal, n (%)                     | 208 (72.5)          | 84 (78.5)            | 124 (68.9)              | .08            |
| Only bolus, n (%)                     | 2 (0.7)             | 2 (1.9)              | 0 (0.0)                 | .07            |
| Basal plus/bolus, n (%)               | 77 (26.8)           | 21 (19.6)            | 56 (31.3)               | .03            |
| <b>Diabetes complications</b>         |                     |                      |                         |                |
| <b>Macrovascular</b>                  |                     |                      |                         |                |
| Ischemic heart disease, n (%)         | 153 (28.1)          | 67 (29.4)            | 86 (27.2)               | .58            |
| Carotid artery atherosclerosis, n (%) | 260 (47.9)          | 107 (47.1)           | 153 (48.4)              | .77            |
| Lower limb atherosclerosis, n (%)     | 84 (15.6)           | 32 (14.2)            | 52 (16.5)               | .47            |
| Diabetic foot, n (%)                  | 21 (4.5)            | 6 (3.1)              | 15 (5.5)                | .22            |
| <b>Microvascular</b>                  |                     |                      |                         |                |
| Albuminuria, n (%)                    | 148 (27.0)          | 49 (21.3)            | 99 (31.0)               | .01            |
| eGFR<60 mL/min, n (%)                 | 151 (27.9)          | 50 (22.4)            | 101 (31.8)              | .02            |
| Retinopathy, n (%)                    | 148 (27.6)          | 53 (23.7)            | 95 (30.4)               | .09            |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; GLP-1RA, glucagon-like peptide-1 receptor agonists; HbA1C, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SGLT2-I, sodium-glucose co-transporter 2 inhibitors.

Continuous variables are presented as mean ± standard deviation and compared by using the *t* test for unpaired samples; dichotomous variables are presented as number and percentage of the total subjects and compared by using the Yates' $\chi^2$  test.

<sup>a</sup> Responders vs nonresponders.

We observed a major improvement of lipid profile in responders compared to nonresponders, as suggested by the higher increase of HDL ( $3.5 \pm 10.1$  vs  $0.7 \pm 7.6$  mg/dL,  $P < .01$ ) and reduction of triglycerides ( $-20.3 \pm 73.1$  vs  $1.0 \pm 66.5$  mg/dL,  $P < .01$ ). The responders also achieved a greater reduction of total cholesterol and LDL although this difference, compared to nonresponders, did not reach the statistical significance (Table 2).

During the follow-up, a significantly reduction of ALT was detected in responders vs nonresponders ( $-5.1 \pm 18.4$  vs  $-1.8 \pm 11.3$  U/L,  $P = .03$ ).

No significant differences were identified for kidney parameters, although a trend for a major improvement of eGFR was observed in responders (Table 2).

#### Multivariate Logistic Regression Analysis and ROC Analysis

Baseline HbA1C and the use of GLP1-RA are strongly related to therapeutic response. In particular, the multivariate model estimated a statistically significant 6-and-a-half-fold increase in the likelihood of response to combination therapy for each 1% ( $\approx 11$  mmol/mol) increase in baseline HbA1C (OR 6.60, 95% CI 4.43-9.67,  $P < .001$ ) (Table 3).

ROC curve analysis showed an AUC for baseline HbA1C of 0.83 (95% CI 0.79-0.89;  $P < .001$ ) suggesting a good ability to discriminate between responders and nonresponders and the HbA1C optimal cut-off threshold was 7.85% (sensitivity 0.72, specificity 0.80, Youden's index 0.52) (Fig. 1).

The use of GLP1-RA rather than SGLT2-I was associated with a two-and-a-half-fold increase of the likelihood to respond to

**Table 2**  
Changes from Baseline of the Main Study Outcomes During the Follow-Up

| Variables                 | Overall (n = 549)    | Responders (n = 230)  | Nonresponders (n = 319) | P <sup>a</sup> |
|---------------------------|----------------------|-----------------------|-------------------------|----------------|
| Weight (kg)               | -4.3 ± 5.0           | -5.2 ± 5.0            | -3.7 ± 4.9              | <.01           |
| BMI (kg/m <sup>2</sup> )  | -1.6 ± 1.9           | -1.9 ± 1.9            | -1.4 ± 1.8              | <.01           |
| HbA1C (%) (mmol/mol)      | -0.6 ± 1.1 (-7 ± 12) | -1.6 ± 0.9 (-17 ± 10) | -0.13 ± 0.7 (-1 ± 8)    | <.001          |
| FPG (mg/dl)               | -18.8 ± 48.9         | -40.0 ± 49.1          | -3.7 ± 42.7             | <.001          |
| Total cholesterol (mg/dL) | -5.5 ± 33.7          | -8.3 ± 30.7           | -3.6 ± 35.6             | .13            |
| LDL (mg/dL)               | -5.5 ± 30.0          | -7.8 ± 28.1           | -4.0 ± 31.2             | .18            |
| HDL (mg/dL)               | 1.9 ± 8.9            | 3.5 ± 10.1            | 0.7 ± 7.6               | <.01           |
| Triglycerides (mg/dL)     | -7.7 ± 69.9          | -20.3 ± 73.1          | 1.0 ± 66.5              | <.01           |
| Serum creatinine (mg/dL)  | 0.03 ± 0.2           | 0.004 ± 0.33          | -0.002 ± 0.31           | .84            |
| eGFR (mL/min)             | 16.4 ± 21.3          | 16.6 ± 31.6           | 11.8 ± 29.4             | .07            |
| AST (U/l)                 | -0.8 ± 12.3          | -0.9 ± 16.2           | -0.7 ± 8.6              | .86            |
| ALT (U/l)                 | -3.1 ± 14.7          | -5.1 ± 18.4           | -1.8 ± 11.3             | .03            |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1C, glycosylated hemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Data are presented as mean ± standard deviation and compared by using the *t* test for paired samples.

<sup>a</sup> Responders vs nonresponders.

**Table 3**  
Multivariate Logistic Regression Model Exploring the Association Among Clinical Parameters and Response to Combination Therapy

| Variables                    | B     | SE    | Wald  | OR (95% CI)      | P     |
|------------------------------|-------|-------|-------|------------------|-------|
| AT BASELINE                  |       |       |       |                  |       |
| HbA1C                        | 1.88  | 0.20  | 89.26 | 6.60 (4.43-9.67) | <.001 |
| HDL                          | -0.02 | 0.01  | 3.36  | 0.98 (0.96-1.00) | .07   |
| AST                          | 0.02  | 0.01  | 4.03  | 1.02 (1.00-1.04) | .05   |
| Insulin                      | -0.89 | 0.25  | 12.58 | 0.41 (0.25-0.67) | <.001 |
| GLP-1RA                      | 0.90  | 0.23  | 12.51 | 2.47 (1.50-4.08) | <.001 |
| Albuminuria                  | -0.64 | 0.28  | 5.26  | 0.53 (0.30-0.91) | .02   |
| Retinopathy                  | -0.59 | 0.28  | 4.44  | 0.55 (0.32-0.96) | .04   |
| CHANGES DURING THE FOLLOW-UP |       |       |       |                  |       |
| BMI                          | -0.12 | 0.06  | 4.17  | 0.89 (0.79-0.99) | .04   |
| FPG                          | -0.02 | <0.01 | 37.07 | 0.98 (0.98-0.99) | <.001 |
| HDL                          | 0.04  | 0.01  | 9.87  | 1.05 (1.02-1.07) | <.01  |

Abbreviations: AST, aspartate aminotransferase; B, regression coefficient; BMI, body mass index; CI, confidence interval; FPG, fasting plasma glucose; GLP-1RA, glucagon-like peptide-1 receptor agonists; HbA1C, glycosylated hemoglobin; HDL, high-density lipoprotein; OR, odds ratio; SE, standard error.

combination therapy (OR 2.47, 95% CI 1.50-4.08). Conversely, the use of insulin, as well as the presence of albuminuria and DR, are related to a significant 59%, 47%, and 45% decrease in the likelihood of responding to combination therapy, respectively (Table 3).

Furthermore, a greater reduction in BMI and FPG and an increase in HDL during the follow-up are significantly related to a favorable response to combination therapy: there was an 11% increase in the response rate for each one-point decrease in BMI and FPG, and a 2% increase in the response rate for each one-point increase in HDL (Table 3). The AUC derived from ROC analysis was 0.74 for FPG decrease (95% CI 0.69-0.78), 0.60 for BMI decrease (95% CI 0.55-0.64) and HDL increase (95% CI 0.54-0.65) during the follow-up. The optimal cut-off was -16.5 mg/dL for FPG (sensitivity 0.67, specificity 0.68, Youden's index 0.35), -1.3 kg/m<sup>2</sup> for BMI (sensitivity 0.61, specificity 0.57, Youden's index 0.18), and 4.5 mg/dL for HDL (sensitivity 0.46, specificity 0.72, Youden's index 0.18) (Fig. 1).

#### DCA

DCA demonstrated that both the baseline model and the baseline plus follow-up model provided a higher net benefit than treat-all and treat-none strategies across a broad range of threshold probabilities (Supplementary Table 2 and Fig. 2). The baseline plus follow-up model consistently showed greater net benefit compared with the baseline model, indicating improved clinical utility when follow-up metabolic changes were incorporated.

At lower threshold probabilities (around 0.10-0.20), the net benefit was similar to that of a treat-all strategy. However, at higher thresholds, both models maintained a positive net benefit and remained superior to a treat-none strategy (Supplementary Table 2 and Fig. 2).

#### Discussion

This study investigated the real-world efficacy on glucose control of combination therapy with GLP-1RA and SGLT2-I in T2D. We aimed to evaluate the prevalence of subjects who achieved the expected reduction in HbA1C during combination therapy and to identify clinical predictors of response.

We observed that 40.8% of the included subjects had a HbA1C lower than 7% (<53 mmol/mol) during the observation period with combination therapy and 41.9% of them reached the goal of HbA1C reduction which varies according to the type of innovative molecules administered. Our results confirm the prevalence of response to combination therapy with GLP1-RA and SGLT2-I reported in some previous observational studies.<sup>19,20</sup> Davis et al, in a retrospective cohort of 572 subjects with T2D inadequate glucose control at baseline, observed a therapeutic response in 46.0% of them. Díaz-Trastoy et al observed the achievement of HbA1C target <7% in 42.0% of the participants treated with combination therapy.<sup>20</sup> Compared to our study, these 2 ones have in common the real-world approach and the treatment with various molecules within the 2 classes of innovative diabetes drugs, although they

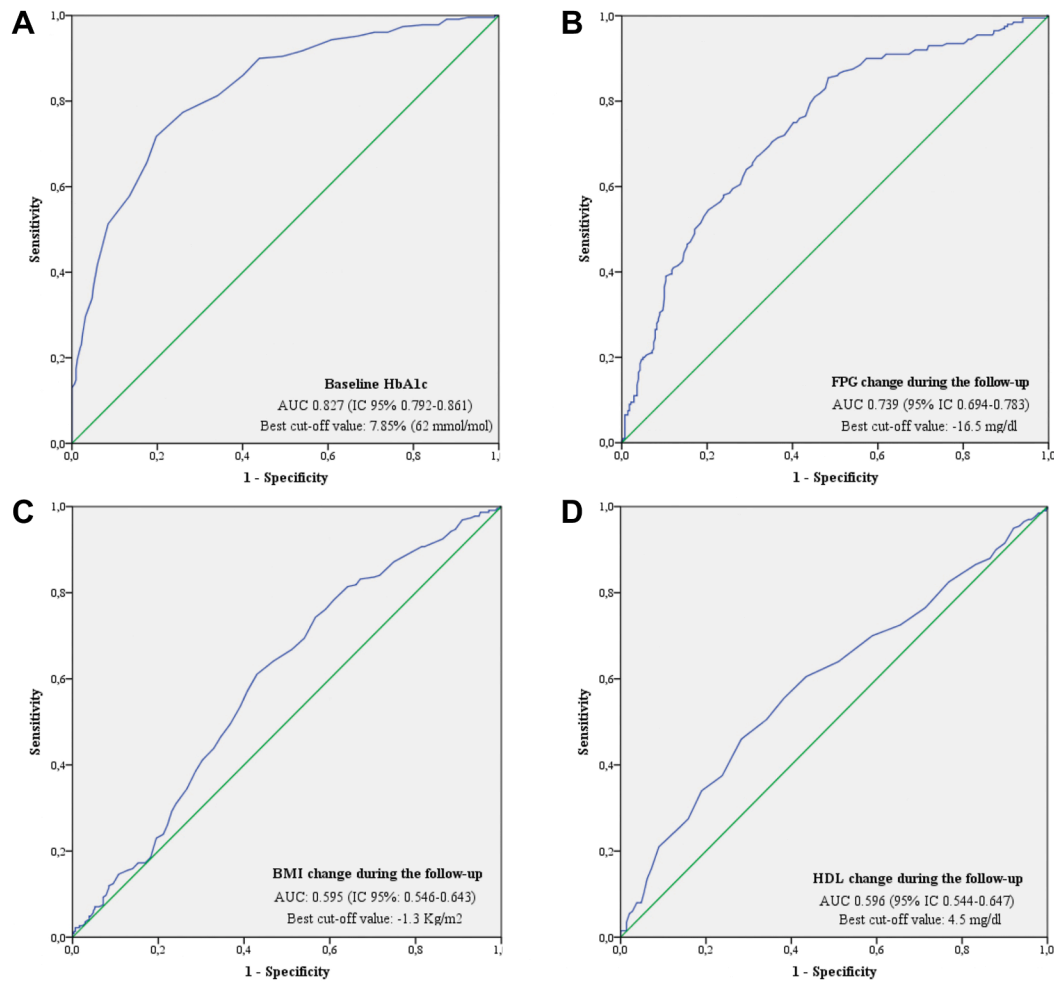


**Fig. 1.** Receiver operating characteristic (ROC) curves for predictors of response to combination therapy with glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose co-transporter 2 inhibitors (SGLT2-I). Panel A shows the ROC curve for baseline HbA1c, which demonstrated good discriminative ability for identifying responders (AUC 0.83, 95% CI 0.79–0.89), with an optimal cut-off value of 7.85% (62 mmol/mol). Panel B depicts the ROC curve for fasting plasma glucose (FPG) reduction during follow-up (AUC 0.74, 95% CI 0.69–0.78), with an optimal cut-off of –16.5 mg/dL. Panel C shows the ROC curve for body mass index (BMI) reduction during follow-up (AUC 0.60, 95% CI 0.56–0.64), with an optimal cut-off of –1.3 kg/m<sup>2</sup>. Panel D illustrates the ROC curve for HDL cholesterol increase during follow-up (AUC 0.59, 95% CI 0.54–0.65), with an optimal cut-off of 4.5 mg/dL. The diagonal line represents the reference line corresponding to no discrimination. AUC, area under the ROC curve; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein.

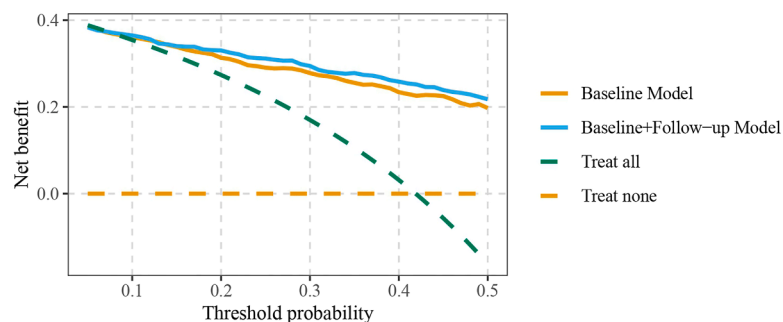


**Fig. 2.** Decision curve analysis for prediction of response to combination therapy with GLP-1 receptor agonists (GLP-1RA) and SGLT2 inhibitors (SGLT2-I). The figure shows net benefit across a range of threshold probabilities for 2 prediction models: a baseline model including baseline HbA1c, insulin use, GLP-1RA use, albuminuria, and diabetic retinopathy, and an extended model including baseline variables plus follow-up changes in fasting plasma glucose, body mass index, and HDL cholesterol. Model performance is compared with default treat-all and treat-none strategies. Across clinically relevant threshold probabilities, both models provided higher net benefit than the default strategies, with the baseline plus follow-up model consistently showing greater net benefit. GLP-1, glucagon-like peptide 1; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein.

differ in the definition of response to combination therapy, which in our study was personalized based on the expected efficacy of each molecule, providing a more accurate definition of response.

Other studies focused on specific molecules belonging to GLP1-RA and SGLT2-I classes.<sup>23,33,34</sup> Similarly to our study, Ghosal et al observed a 46.7% prevalence of responders during treatment with

liraglutide or dulaglutide added to SGLT2-I. However, the baseline HbA1C of the 60 subjects recruited was higher (8.4%) than that described in our study.<sup>33</sup> Berra et al, in the AWARE-2 study, reported that 58.9% of subjects with T2D and baseline HbA1C of 7.7% achieved the HbA1C target of <7% (<53 mmol/mol) during the treatment with dulaglutide added to the background SGLT2-I.<sup>34</sup>

Our findings are consistent with previous studies suggesting that, despite combination therapy with GLP-1RA and SGLT2-I, some subjects did not achieve the expected reduction in HbA1C. The existing evidence indicates that the reduction in HbA1C achieved through combination therapy is lower than the effect of each molecule alone. Therefore, when 2 diabetes drugs are administered in combination, the reduction in HbA1C is not necessarily additive.<sup>35,36</sup> DeFronzo et al demonstrated that changes in HbA1C are highly dependent on baseline HbA1C, with greater glycosuria and compensatory hepatic glucose uptake observed at higher baseline HbA1C levels.<sup>35,37</sup>

Few data are available on predictors of response to combination therapy with GLP-1RA and SGLT2-I. Our analysis identified baseline HbA1C as the strongest predictor of response to combination therapy, with a six-and-a-half-fold increase in the likelihood of response for each 1% increase in HbA1C. ROC curve analysis further confirmed the good discriminative performance of baseline HbA1C in identifying responders to combination therapy with GLP-1RA and SGLT2-I, as reflected by an AUC of 0.83 (Fig. 1). It should be acknowledged that greater HbA1C reductions are inherently more likely in subjects with poorer baseline glycemic control. However, unlike previous real-world studies, which generally evaluated treatment response according to absolute HbA1C changes, our study adopted molecule-specific HbA1C reduction thresholds derived from published literature to provide a more clinically meaningful definition of response. In addition, the possibility of regression to the mean should also be considered when interpreting the greater HbA1C reductions observed in subjects with higher baseline HbA1C levels. Because treatment response was partly defined according to HbA1C reduction, some degree of mathematical coupling between baseline HbA1C and response cannot be excluded. Furthermore, the association between baseline HbA1C and treatment response was evaluated within multivariate models adjusted for potential confounding variables. The identified optimal cut-off value of 7.85% (62 mmol/mol) provided a balanced trade-off between sensitivity and specificity, suggesting potential usefulness for guiding clinical decision-making. These findings are consistent with those of Davis and Deol, who also reported a positive association between higher baseline HbA1C and response to combination therapy.<sup>19</sup>

We explored the correlation between baseline diabetes therapies and response to combination therapy. The multivariate analysis showed that baseline use of GLP-1RA was significantly associated with an increased likelihood of responding to combination therapy (OR 2.47,  $P < .001$ ), whereas insulin use was negatively associated with therapeutic response to combination therapy (OR 0.41,  $P < .001$ ) (Table 3). Previous studies of small cohorts did not find a clear association between the index drugs and response to combination therapy.

GLP-1RA are well recognized for their higher impact on weight loss compared to SGLT2-I. We could hypothesize that using GLP-1RA before SGLT2-I, leading to a better weight reduction, increases the likelihood of responding to combination therapy. To support these findings, our data show that BMI reduction during the follow-up was a significant predictor of response to combination therapy (OR 0.89,  $P < .05$ ). The inverse correlation between insulin use and the response rate to combination therapy, as observed in our results at both univariate and multivariate analysis, would be expected. Indeed, the need for insulin therapy in T2D could

indicate a reduced residual  $\beta$ -cell reserve, longer diabetes duration, and a history of chronic metabolic decompensation and diabetes-related complications.<sup>38</sup> In this phenotype, the benefits of innovative diabetes therapy in terms of glucose control could be smaller due to their mechanism of action. Our study did not evaluate the residual  $\beta$ -cell secretion but we observed a shorter, although not statistically significant, diabetes duration in responders vs nonresponders ( $17.8 \pm 8.6$  vs  $19.2 \pm 9.1$ ,  $P = .06$ ) (Table 1). Notably, the presence of albuminuria and DR at baseline, are related to a significant 47% and 45% decrease of the likelihood of responding to combination therapy. Furthermore, the nonresponder group had a significantly lower eGFR than the responder group in the univariate analysis, although the multivariate logistic regression model did not confirm this finding.

Out of all the parameters observed during the follow-up, a reduction in FPG (OR 0.98,  $P < .001$ ) and an increase in HDL (OR 1.05,  $P < .01$ ) were found to be related to the response to combination therapy.<sup>19,21</sup> ROC curve analysis revealed that the discriminative ability of follow-up metabolic changes was modest and inferior to that observed for baseline HbA1C. Although reductions in FPG and BMI, as well as increases in HDL cholesterol, were significantly associated with treatment response, their individual AUC values indicated a modest discriminatory power. Differently from our study, previous reports that focused on identifying predictors of response to combination therapy did not identify a role of FPG. A retrospective study by Imai et al found that an early reduction in FPG after the start of GLP-1RA predicted a positive long-term response to treatment.<sup>39</sup> The increase of HDL observed in our cohort was in accordance with the studies by Díaz-Trastoy et al and Saroka et al.<sup>20,23</sup>

While multivariate regression analysis and ROC curve analysis provided relevant insights into the strength and discriminative ability of individual predictors of treatment response, these approaches do not fully capture the clinical consequences of applying such information to real-world decision-making. In this context, DCA was performed to evaluate the net clinical benefit of using prediction models to guide therapeutic choices. In our study, DCA showed that both predictive models provided a net clinical benefit compared with default treat-all and treat-none strategies (Fig. 2). Notably, the model incorporating follow-up metabolic changes demonstrated a consistently higher net benefit than the baseline model across a wide range of threshold probabilities. While the magnitude of the net benefit was moderate, this pattern is consistent with what is typically observed in chronic metabolic conditions, where treatment decisions are multifactorial and the incremental benefit of predictive models is expected to be modest but clinically significant. The extended model's consistent superiority suggests that longitudinal metabolic information meaningfully contributes to individualized treatment decisions, even when improvements in net benefit are incremental.

The main strength of this study lies in its real-world design and its large, unselected cohort of subjects with T2D who were treated in routine clinical practice. This enhances the clinical relevance of the findings, as they reflect the heterogeneity and complexity of subjects encountered outside randomized controlled trials. By integrating baseline characteristics with longitudinal metabolic changes, this study provides a pragmatic framework for understanding responses to combination therapy involving GLP-1RA and SGLT2-I in settings beyond those of RCTs.

This study has some limitations that should be acknowledged. First, its retrospective single-center design may limit the generalizability of the findings and does not allow the establishment of causal relationships. Furthermore, the predictive models were not externally validated and should therefore be interpreted with caution until confirmed in independent cohorts. We also did not

systematically assess treatment adherence, which may have influenced the observed therapeutic response. Although drug doses were available, dose-specific analyses were not performed because of the heterogeneity of treatment combinations. Finally, markers of residual  $\beta$ -cell function, such as C-peptide levels, were not available. Future prospective studies and independent validation cohorts are therefore required to confirm the robustness of these findings and assess their applicability in different clinical settings.

From a clinical perspective, the results suggest that baseline glycemic burden is the main factor in determining response to combination therapy, while follow-up metabolic changes provide additional information. Importantly, decision curve analysis indicates that integrating baseline and longitudinal data could support therapeutic choices across clinically relevant decision thresholds.

The identified HbA1C threshold should not be interpreted as an absolute criterion for treatment initiation, but rather as a potential marker of higher probability of glycaemic response to combined GLP-1RA/SGLT2-I therapy. Therefore, the model may help support individualized therapeutic intensification and follow-up strategies in routine clinical practice. However, the choice of these drug classes should not rely exclusively on the expected HbA1C reduction, since the cardio-renal benefits of GLP-1RA and SGLT2-I are at least partially independent from their glucose-lowering effects and represent a major component of current therapeutic decision-making in T2D.

Rather than identifying rigid cut-off values, this approach enables more tailored treatment decisions and could assist clinicians in better balancing potential benefits when considering combination therapy with GLP-1RA and SGLT2-I in clinical practice.

## Disclosure

The authors have no conflicts of interest to disclose.

## Author Contributions

Conceptualization: A.M., L.F.; Data curation: A.M., G.Q., F.D.G.B., V.O.; Methodology and formal analysis: A.M.; Supervision: A.M., G.Q., F.D.G.B., M.D.M., N.C., V.O., L.S., L.F.; Visualization: A.M., G.Q., F.D.G.B., M.D.M., N.C., V.O., L.S., L.F.; Writing (original draft): A.M., G.Q., L.F.; Writing (review and editing): A.M., G.Q., F.D.G.B., M.D.M., N.C., V.O., L.S., L.F.

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