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Original Research

# Achieving Good Metabolic Control Without Weight Gain with the Systematic Use of GLP-1-RAs and SGLT-2 Inhibitors in Type 2 Diabetes: A Machine-learning Projection Using Data from Clinical Practice

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ABSTRACT

*Purpose:* Recently, the 2022 American Diabetes Association and European Association for the Study of Diabetes (ADA-EASD) consensus report stressed the importance of weight control in the management of patients with type 2 diabetes; weight control should be a primary target of therapy. This retrospective analysis evaluated, through an artificial-intelligence (AI) projection of data from the AMD Annals database—a huge collection of most Italian diabetology medical records covering 15 years (2005–2019)—the potential effects of the extended use of sodium–glucose co-transporter 2 inhibitors (SGLT-2is) and of glucose-like peptide 1 receptor antagonists (GLP-1-RAs) on $HbA_{1c}$ and weight.

*Methods:* Data from 4,927,548 visits in 558,097 patients were retrospectively extracted using these exclusion criteria: type 1 diabetes, pregnancy, age >75 years, dialysis, and lack of data on $HbA_{1c}$ or weight. The analysis revealed late prescribing of SGLT-2is and GLP-1-RAs (innovative drugs), and considering a time frame of 4 years (2014–2017), a paradoxic greater percentage of combined-goal ($HbA_{1c}$ <7% and weight gain <2%) achievement was found with older drugs than with innovative drugs, demonstrating aspects of therapeutic inertia. Through a machine-learning AI technique, a "what-if" analysis was performed, using query models of two outcomes: (1) achievement of the combined goal at the visit subsequent to a hypothetical initial prescribing of an SGLT-2i or a GLP-1-RA, with and without insulin, selected according to the 2018 ADA-EASD diabetes recommendations; and (2) persistence of the combined goal for 18 months. The precision values of the two models were, respectively, sensitivity, 71.1 % and 69.8%, and specificity, 67% and 76%.

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*Findings:* The first query of the AI analysis showed a great improvement in achievement of the combined goal: 38.8% with prescribing in clinical practice versus 66.5% with prescribing in the "what-if" simulation. Addressing persistence at 18 months after the initial achievement of the combined goal, the simulation showed a potential better performance of SGLT-2is and GLP-1-RAs with respect to each antidiabetic pharmacologic class or combination considered.

*Implications:* AI appears potentially useful in the analysis of a great amount of data, such as that derived from the AMD Annals. In the present study, an LLM analysis revealed a great potential improvement in achieving metabolic targets with SGLT-2i and GLP-1-RA utilization. These results underscore the importance of early, timely, and extended use of these new drugs.

## Introduction

The achievement of the combined goal of $HbA_{1c}$ within the target value and without weight gain is the primary (but not the only) objective of the daily activity of physicians, especially diabetologists.[1] A large amount of literature indicates that this is not an easy business, as many series around the world report that only 40% to 50% of the population with diabetes achieves the $HbA_{1c}$ target.[2,3] The 2022 American Diabetes Association and European Association for the Study of Diabetes (ADA-EASD) consensus report stressed the importance of weight control in the treatment of patients with type 2 diabetes mellitus. Weight loss of 5% to 15% should be a primary goal of the management of patients living with type 2 diabetes, as weight loss confers better results and can have a disease-modifying effect.[4]

Although many studies have examined the effects of drugs on the reduction of blood glucose and $HbA_{1c}$ in patients with diabetes mellitus, to our knowledge, only one article[5] has examined, using data from clinical practice, the factors associated with a combined goal ($HbA_{1c\ at}$ target, weight). In that article, several factors (clinical, organizational, and physician-related) were reported; in particular, the use of an innovative drug, such as a sodium–glucose co-transporter 2 inhibitor (SGLT-2i) or a glucose-like peptide 1 receptor antagonist (GLP-1-RA), was associated with better weight control.

In Italy, a continuous improvement effort has been implemented by a network of diabetes clinics, termed the AMD (*Associazione Medici Diabetologi*) Annals, since 2006.[6,7] After 12 years from the launch of the initiative, half of the diabetes clinics in Italy have participated, treating more than one sixth of all diagnosed patients. In recent years, the process and intermediate-outcomes measures have improved consistently in parallel with a more intensive and appropriate use of pharmacologic treatments.[8]

Considering the unique knowledge contained in >12 years of experience in the AMD Annals database, AMD decided to exploit the potential offered by artificial intelligence (AI) and machine learning. The benefits of these methods are reported in many published articles on the topic,[9] including some with a specific focus on diabetes.[10] A proprietary "clear box explainable" AI algorithm, namely Logic Learning Machine (LLM; Italian National Research Council CNR-IEIIT, Genoa, Italy), was chosen for this analysis, as it produces sets of intelligible rules with the capacity to achieve an accuracy comparable to or superior to that of the best machine-learning algorithms.[11]

By exploring data from the AMD Annals database with LLM, the present study aimed to verify the potential effects of different antidiabetic therapies on $HbA_{1c}$ and weight control in clinical practice.

## Characteristics of LLM

Machine learning has the capacity to both perform an analysis without making any *a priori* assumptions, and reveal unknown aspects of the situation analyzed. A specific type of machine-learning technique, the rule-generation method, builds models described by a set of intelligible rules, thus allowing for the extraction of important data on the variables included in the analysis and their relationships with the target attribute. In the literature, two paradigms for rule generation have been proposed: (1) decision trees,[12] which adopt a divide-and-conquer approach to generate the final model; and (2) Boolean function reconstruction,[13,14] which follows an aggregative procedure to build the set of rules.

LLM is a proprietary algorithm with the capacity for an efficient implementation of the *switching neural network model,*[15] which allows one to solve classification problems by producing sets of intelligible rules expressed in the "*if* [premise] . . ., *then* [consequence]" format, where *premise* refers to a combination of conditions (*conditional clauses*) using input variables, and *consequence* contains information about the target function (*yes* or *no*).

The LLM rule-generation technique not only produces a subset of relevant variables associated with a specific outcome, but also informs of explicit intelligible conditions related to a particular outcome. Relevant thresholds of each input variable are identified and represent valuable information to better understand the phenomenon under study.

LLM has the capacity to achieve accurate results comparable to or superior to those of the best machine-learning methods.[11] More specifically, the application of LLM to the analysis of biomedical datasets included in the Statlog benchmark[11] permits one to appreciate the optimal results obtained by this innovative analytic method.[16]

## Participants and Methods

This observational, longitudinal, retrospective study considered data from 9,970,124 diabetes consultations in 1,194,005 patients from the AMD Annals database (2005–2019). Data from 4,927,548 visits in 558,097 patients were retrospectively extrapolated according to five exclusion criteria: type 1 diabetes or pregnancy diagnosis, age >75 years, dialysis, and the absence of combined $HbA_{1c}$ or weight data.

The definition of the *combined goal*, described previously,[5] was $HbA_{1c}$ <7% and weight increase of <2%. The frequency and associated factors of the combined goal were the primary outcomes of interest. The secondary outcome was *persistence,* defined as sustaining of the combined goal at 18 months after initial prescribing.

Cohorts were selected considering a sequence of visits that met the following criteria: a visit at which an antidiabetic drug was first prescribed, with no treatment change from the immediately-preceding consultation, followed by at least one visit from which data were available. Based on these criteria, data from 69,429 sequences corresponding to 62,742 patients were analyzed.

The analysis was divided into two data types: (1) historical data, from clinical practice, on innovative-drug (SLGT-2i or GLP-1-RA) prescribing considering the time frame of 2014–2017; and (2) LLM-derived data. More information on the AI model is available in the Supplemental Material accompanying this article.

Data are presented as mean values of $HbA_{1c}$, body mass index (BMI), and estimated glomerular filtration rate (eGFR; calculated using the CKD-EPI formula [Collaboration on Chronic Kidney Disease Epidemiology]) and percentage of drug use, by HbA1c or background-treatment subgroup and time point.

Seventeen treatment strategies were considered: a GLP-1-RA, a SGLT-2i, a GLP-1-RA + a SGLT-2i, diet only, metformin, a secretagogue, acarbose, insulin, insulin + metformin,

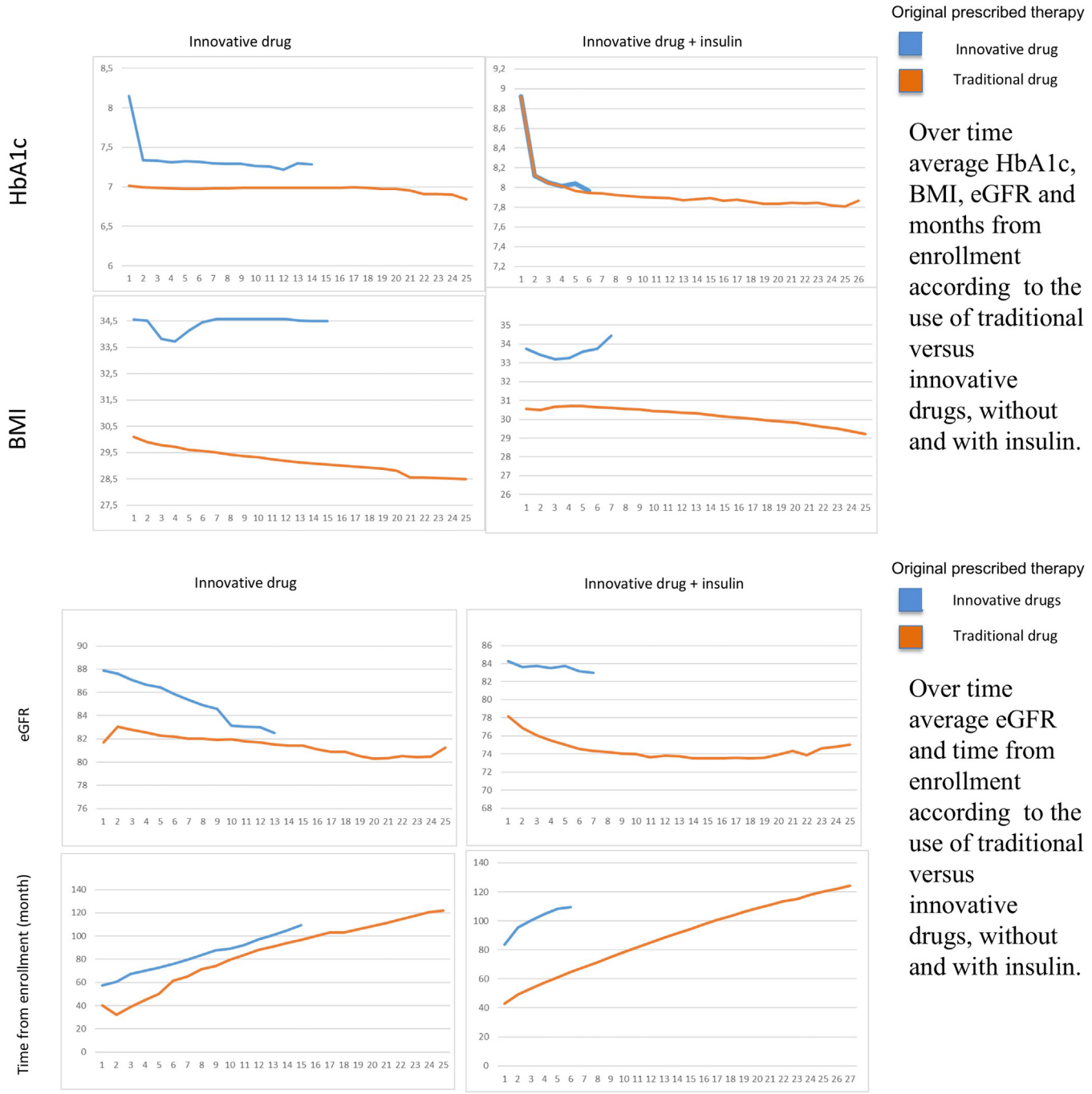


**Fig. 1.** Mean $HbA_{1c}$ (A), BMI (B), eGFR (C), and time (months) from enrollment in the center (D), with innovative drug versus traditional drug, with and without insulin.

metformin + a secretagogue, a dipeptidyl peptidase 4 inhibitor (DPP-4i), a thiazolidinedione, insulin + metformin + a secretagogue, insulin + a DPP-4i, and "other" combinations.

The accuracy, sensitivity, and specificity of both models were calculated.

The "what-if" method was the simulation carried out using the LLM on data from clinical practice. The simulation investigated: (1) the percentage of visits in which the combined target would be achieved with the a SGLT-2i or a GLP-1-RA (*innovative drugs*); and (2) the persistence of the combined goal for 18 months after the prescribing of the innovative drug. In both cases, the prescribing of the innovative drug was simulated by systematic application of the criteria suggested by existing recommendations[17] and the 2018 consensus report from the ADA-EASD.[18]

In the simulation process, data from patients who presented criteria for inclusion in the innovative-drugs group (see the preceding paragraphs) were selected from the database, and then prescribing was forced. The uniqueness of Rulex machine learning lies in the fact that these effects were based on rules calculated within the database itself and not from other sources, such as articles in the literature.[18–21]

Four simulation scenarios were created to investigate the percentages of situations in which the combined goal was achieved at the visit subsequent to the prescribing of systematic therapy with (1) an innovative drug or (2) an innovative drug + insulin; and in which the combined


**Fig. 2.** Historical data on the achievement of the combined goal ($HbA_{1c}$ <7% and weight gain <2%) at the visit subsequent to the prescribing of antidiabetic treatment with innovative drug versus traditional drug, with and without insulin. Note the disappointing percentage of patients who achieved the combined goal in the historical data.

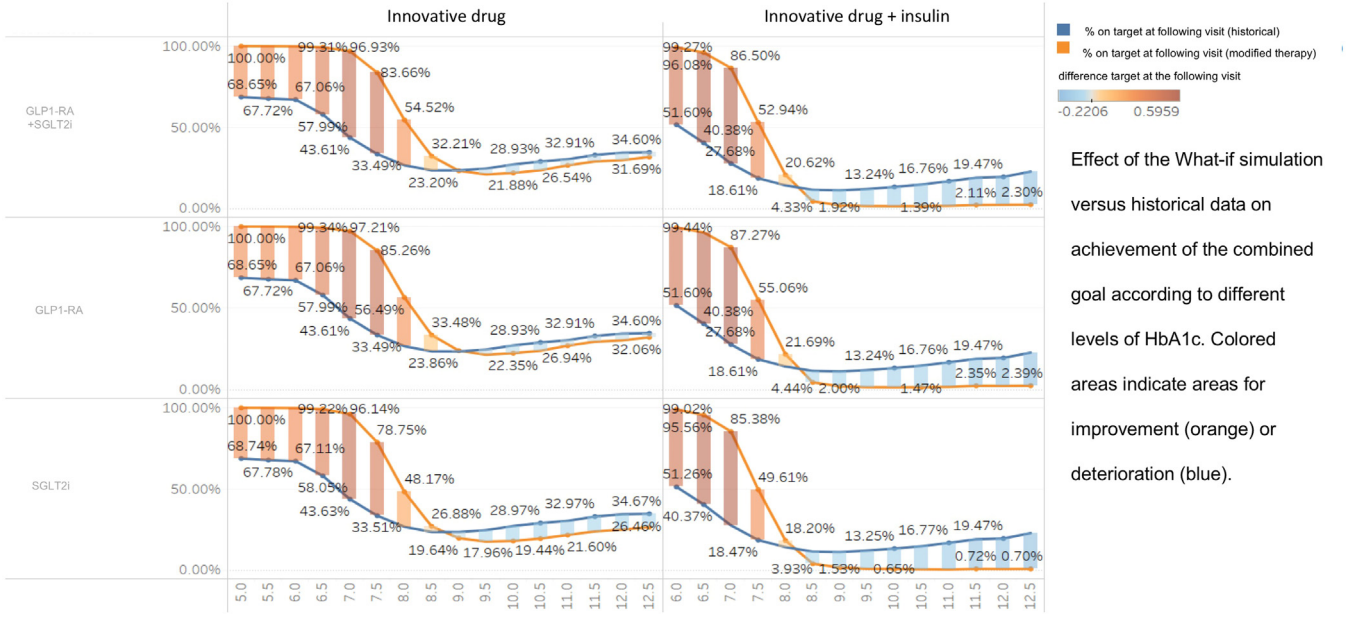


**Fig. 3.** What-if simulation of the achievement of the combined goal ($HbA_{1c}$ <7% and weight gain <2%) at the visit subsequent to the prescribing of antidiabetic therapy, by $HbA_{1c}$ level.

goal persisted at 18 months after the initiation of systematic therapy with (3) an innovative drug or (4) an innovative drug + insulin.

Each of the four models was used for identifying a pattern (combination of variables) correlated with achieving the combined goal, as well as a pattern correlated with situations in which the outcome was not achieved. The four models were applied separately to the elaborated data, and the results are presented as percentages of situations in which the outcome would have been achieved if the innovative drug had been prescribed according to current recommendations and guidelines. As mentioned, the criteria for the virtual prescribing of a GLP-1-RA or a SGLT-2i were derived from the recommendations and guidelines used in 2018.

The prescribing of a GLP-1-RA, regardless of the $HbA_{1c}$ value, was forced if a patient was at high cardiovascular risk (history of cardiac or cerebral event, coronary artery bypass graft, percutaneous coronary intervention, or hospitalization for angina; history of stenosis >50% in the carotid, coronary, or peripheral arteries; history of left ventricular hypertrophy; or age >55 years); had chronic kidney disease and an eGFR >15 mL/min and treatment with a SGLT-2i was contraindicated (micro- or macroalbuminuria); or had a $HbA_{1c}$ >7% and a high risk for hypoglycemia or was obese (BMI >30 kg/$m^2$).

The prescribing of a SGLT-2i, regardless of $HbA_{1c}$ value, was forced if a patient was at high cardiovascular risk (history of cardiac or cerebral event, coronary artery bypass graft, percutaneous coronary intervention, hospitalization for angina; history of stenosis >50% in the carotid, coronary, or peripheral arteries; history of left ventricular hypertrophy; or age >55 years) and a contraindication to treatment with a GLP-1-RA; a history of heart failure or ejection fraction <45%; had a $HbA_{1c}$ >7% and a high risk for hypoglycemia or was obese (BMI >30 kg/$m^2$) and a contraindication for treatment with a GLP-1-RA; or had chronic kidney disease and an eGFR >45 mL/min.

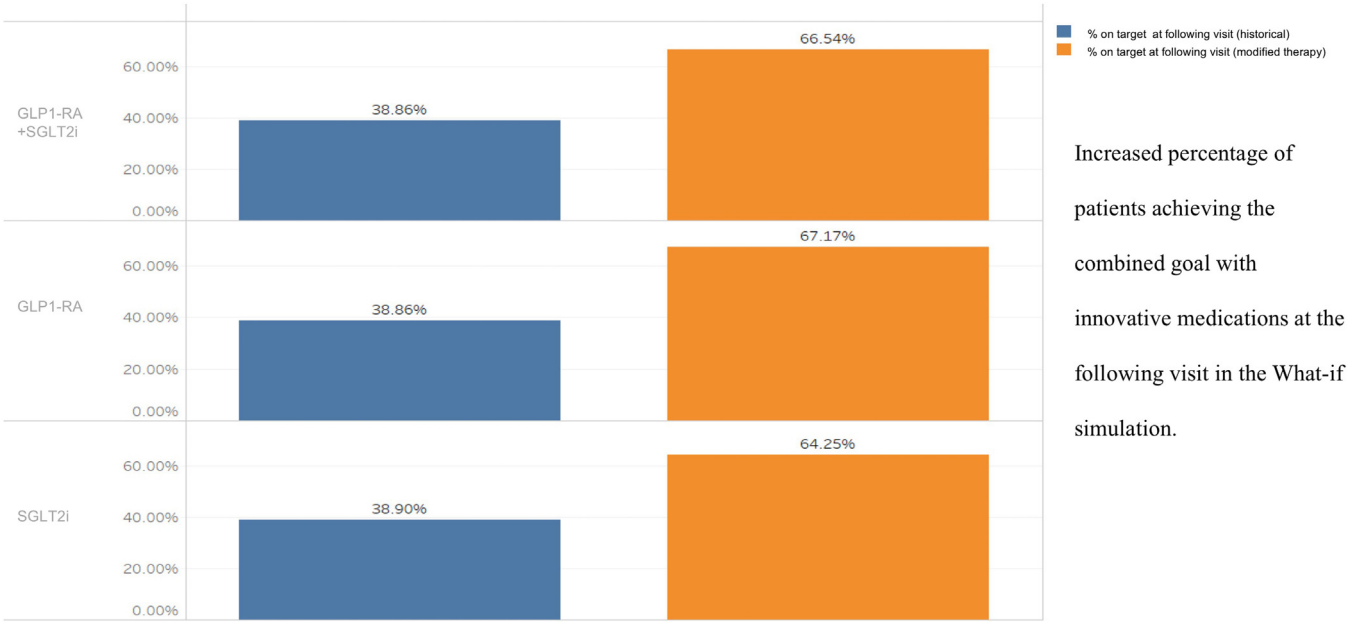


**Fig. 4.** In the what-if projection, the achievement of the combined goal ($HbA_{1c}$ <7% and weight gain <2%) at the visit subsequent to the prescribing of antidiabetic treatment is increased with innovative drug.

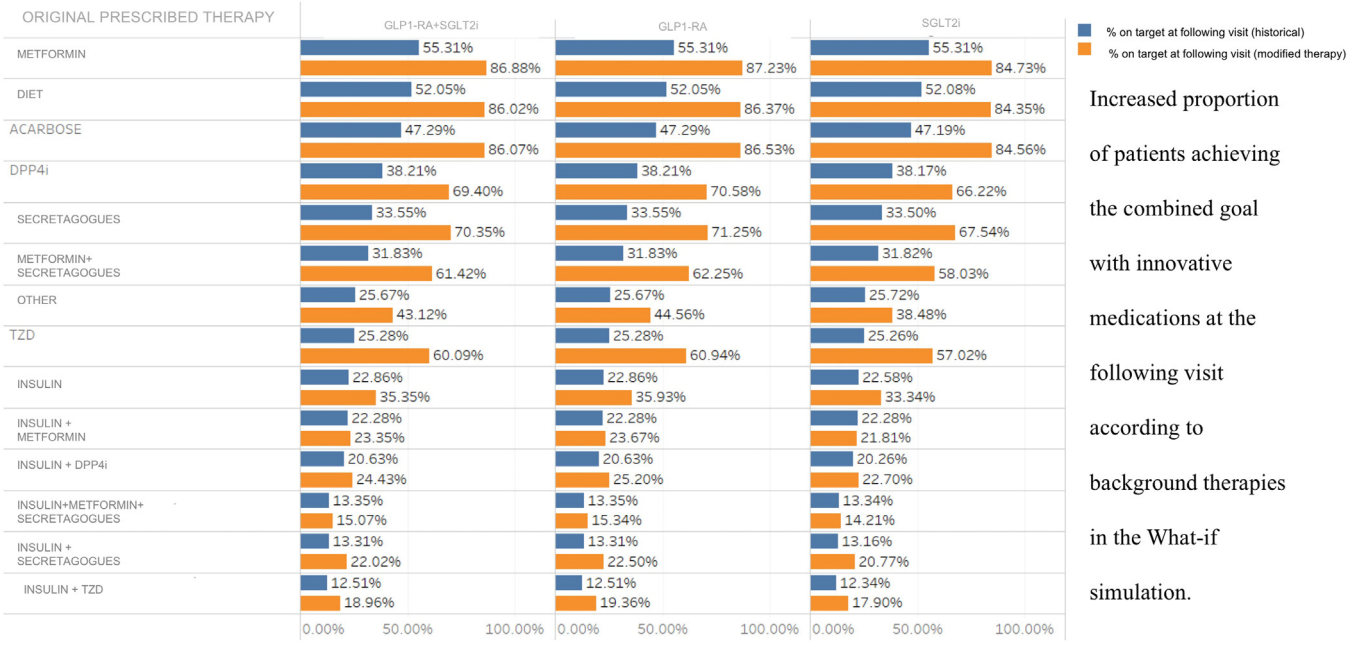


**Fig. 5.** In the what-if simulation, the achievement of the combined goal ($HbA_{1c}$ <7% and weight gain <2%) at the visit subsequent to the prescribing of antidiabetic treatment, by background therapy, is increased with innovative drug.

## Results

Data from patients aged >75 years, receiving hemodialysis, or without available data on baseline $HbA_{1c}$ or weight were removed from the analysis. The final analysis consisted of data from 266,370 women, 291,727 men, and 4,927,548 visits.

Both adopted models were of good accuracy, around 70%. In the first, the sensitivity and specificity were, respectively, 71.1% and 69.8%, and in the second (on the persistence of the combined goal [$HbA_{1c}$ <7% and weight gain <2%]), these values were 67% and 76%.

Results are presented in graphic format as products of AI-based analysis.

### *Retrospective Historical Data Analysis Considering Prescribing Patterns in Clinical Practice*

Fig. 1 reports background information on the use of conventional versus innovative drugs in relation to the mean $HbA_{1c}$, BMI, eGFR, and time from enrollment in the center. Fig. 2 shows the disappointing percentage of patients in whom the combined goal was achieved at the subsequent visit, using historical data.

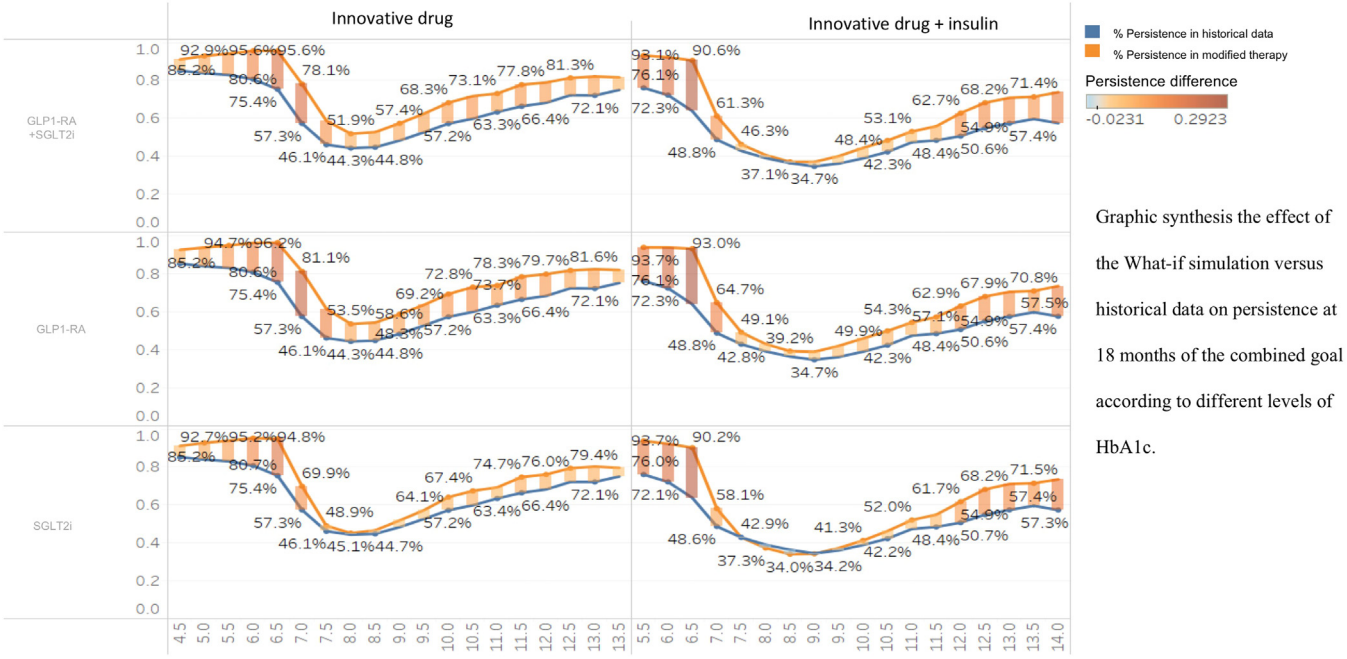


**Fig. 6.** What-if persistence projection, by $HbA_{1c}$ level. Effect at 18 months of the what-if simulation on the combined goal ($HbA_{1c}$ <7% and no weight gain).

*LLM (What-If) Analysis on Achievement of the Combined-Goal Outcome*

Fig. 3 shows simulation-derived versus historical data on the achievement of the combined goal, according to different levels of $HbA_{1c}$. Fig. 4 reports the projections (significant increase) of the what-if simulation with regard to the achievement of the combined goal with innovative medications at the subsequent visit. Fig. 5 reports the what-if projections (notable increase) in patients who achieved the combined goal with innovative medications at the subsequent visit, according to background therapies.

*LLM (What-If) Analysis of Achievement of the Persistence Outcome*

Fig. 6 shows simulation-derived versus historical data on persistence of the combined goal at 18 months, according to $HbA_{1c}$ level, and Fig. 7, by background therapy. The main characteristics associated with the achievement of the combined goal at the first visit were $HbA_{1c}$ <7.8%, BMI >38 kg/$m^2$, prescribing of a GLP-1-RA, and age <47 years, while those associated with the persistence outcome were $HbA_{1c}$ <7.7%; absence of albuminuria, hypertension, and liver disease; and prescribing of a GLP-1-RA.

## Discussion

The aim of this work was to provide a snapshot of the typology of pharmacologic treatment by analyzing a nationally based sample of specialist visits and, thanks to AI, to assess the achievement of goals by hypothesizing the appropriate use of GLP-1-RAs and SGLT-2is.

The context is that many series around the world report that only around 40% to 50% of the population with diabetes achieves the $HbA_{1c}$ goal. Previously, it was found that, in part due to the biological or phenotypic characteristics of the patients and the degree of metabolic decompensation, an important factor involved in weight control was the use of innovative medications such as injectable incretins and SGLT-2is.[16] Considering historical data, the predominant pattern is a tardive prescribing in deteriorated patients, especially obese, decompensated patients. Fig. 3 represents the consequence of this therapeutic inertia, that is, that more patients receiving conventional antidiabetic medications reached the target at the subsequent visit than did those receiving incretins and SGLT-2is. In other words, there is an apparent indication bias in which innovative medications are prescribed to decompensated, overweight patients in an ultimate attempt to regain good metabolic control.

As reported in the Results section, the first what-if model had good accuracy, sensitivity, and specificity. Its key message is condensed in Fig. 4, where an average 75% increase in combined-goal achievement could be obtained if a SGLT-2i or GLP-1-RA were used systematically in all patients who have the characteristics outlined in the 2018 guidelines. Interestingly, the effect was maximal in patients with moderately poor $HbA_{1c}$ levels and disappears in those with an $Hba_{1c}$ value >9.5%, and it becomes reduced in patients receiving insulin as background therapy. Again, in general, these findings highlight that a late intervention might be fruitless for the quick achievement of good metabolic control.[22]

All of the therapies analyzed in this study were consistent with goal achievement, and the favorable effect of adding innovative medications is roughly the same regardless of the background medication, as evidenced in the analysis in Fig. 5. The only difference that is most relevant is the unfavorable role that insulin treatment appears to play when used in combination therapies. Arguably, in this case, insulin is a marker of tardive intervention in more deteriorated patients, and no direct effect of insulin itself can be hypothesized.

The second what-if model, assessing the outcome of persistence of the combined goal over time, also had good accuracy, sensitivity, and specificity. Its key message is reported in Fig. 6. Similarly to model 1, but less pronounced, persistence was improved by an average of 10% when the systematic use of a SGLT-2i or a GLP-1-RA were simulated. Fig. 7 also supports that the favorable effect is obtained regardless of the background drug considered. Again, with insulin, efficacy was reduced for reasons similar to those proposed for target achievement.

The greatest strength of this work is that the what-if simulation by LLM was calculated on internal database–derived data; in other words, the rules of the simulation were deduced from associations already present in the data itself. With regard to the possible perplexity of an LLM analysis, another strongpoint was that the results regarding the

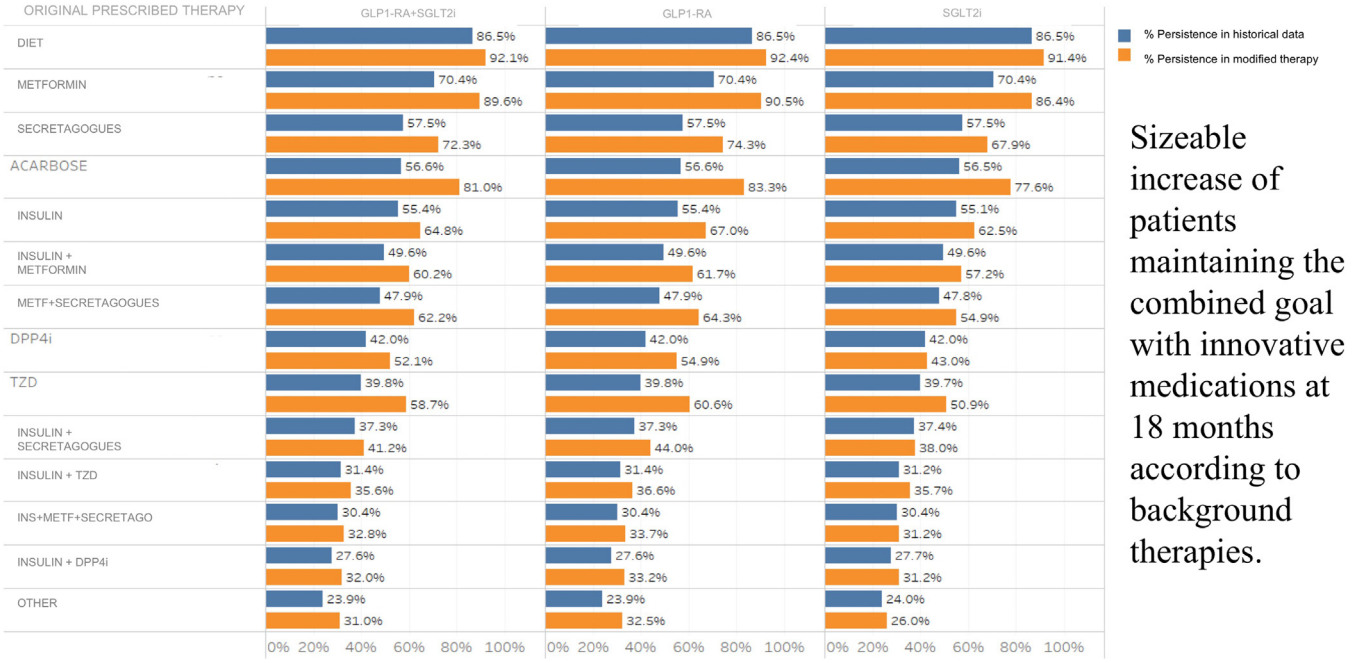


**Fig. 7.** What-if persistence projection, by background therapy. Effect at 18 months of the what-if simulation on the combined goal (HbA1c <7% and no weight gain).

relevance and appropriateness of the rules created by the LLM were likely to be highly statistically significant also with classic statistics, due to the data available from high numbers of visits and measurements.

A limitation of this work was that the guidelines and recommendations considered were from 2018. Current (2022) ADA-EASD recommendations stress a more widespread use of innovative drugs so that the result could be even more relevant.

## Conclusions

The greatest value of the present results lies in the message that emerges, that is, in clinical practice, the prescribing of effective drugs is delayed and reserved for already compromised patients. AI shows that more timely and widespread prescribing would have important repercussions on metabolic control and cardiovascular risk factors, also resulting from better prescribing of drugs such as GLP-1-RAs and SGLT-2is. A reasonable conclusion is that to achieve the best results, an effort should be made to treat patients with diabetes using innovative drugs as early as possible, likely before the appearance of $\beta$-cell deterioration and harmful hyperglycemic exposures.

## Author Contributions

All of the authors contributed equally to the literature search, extraction, and analysis of the information, and writing and critical review of the article. All of the authors acted, free of charge, as members of the AMD (Associazione Medici Diabetologi).

## Declaration of Competing Interest

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2023.06.006.

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