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# Real-world prescriptions of GLP-1RAs and SGLT2is in type 2 diabetes prioritise BMI and age over cardiorenal risk: a machine learning-based large cohort analysis

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## Abstract

**Background** Understanding how SGLT2 inhibitors (SGLT2is) and GLP-1 receptor agonists (GLP-1RAs) are prescribed in relation to cardiorenal risk is crucial for assessing adherence to guidelines and optimize outcomes in type 2 diabetes (T2D). This study aimed to determine whether prescription patterns across different cardiorenal phenotypic subgroups reflect clinical risk or are affected by demographic factors. Explainable artificial intelligence (XAI) was used to identify the key factors influencing therapeutic decisions.

**Methods** We analyzed 139,202 adults with T2D from the Italian AMD Annals registry (2023), stratified into four cardiorenal phenotypic subgroups based on ADA criteria: low risk, chronic kidney disease (CKD) without cardiovascular disease (CVD), atherosclerotic CVD without heart failure, and heart failure. Predictive models were developed using a Logic Learning Machine (XAI algorithm), with variable importance ranked by normalized relevance scores. Business intelligence tools and statistical analysis were used for validation.

**Results** SGLT2i prescriptions were strongly associated with cardiorenal markers, including reduced eGFR (31–59 mL/min), intermediate HbA1c (5.5–8.1%), and lower BMI, with model accuracies ranging from 63.7% to 83.1%. Women were consistently less likely to receive SGLT2is across subgroups. GLP-1RA prescriptions were predominantly driven by higher BMI (> 30 kg/m$^2$), younger age, and glycemic extremes (< 5.5% or > 8.1%), with lower model performance (31.6%–54.1%). Individuals with lower BMI were less frequently prescribed GLP-1RAs, even in the presence of renal or cardiovascular risk.

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**Conclusions** While SGLT2i prescribing generally aligned with cardiorenal risk, sex-based disparities persist. GLP-1RA use was less consistently linked to clinical indications and more heavily influenced by BMI. These findings highlight missed opportunities to deliver proven cardiorenal protective therapies to high-risk individuals, emphasising the need for more equitable, phenotype-driven prescribing strategies in T2D.

**Research insights**

**What is currently known?**

SGLT2is and GLP-1RAs reduce cardiovascular and renal risk in people with T2D.

**What is the key research question?**

Do cardiorenal phenotypes influence real-world use of SGLT2is and GLP-1RAs in T2D?

**What is new here?**

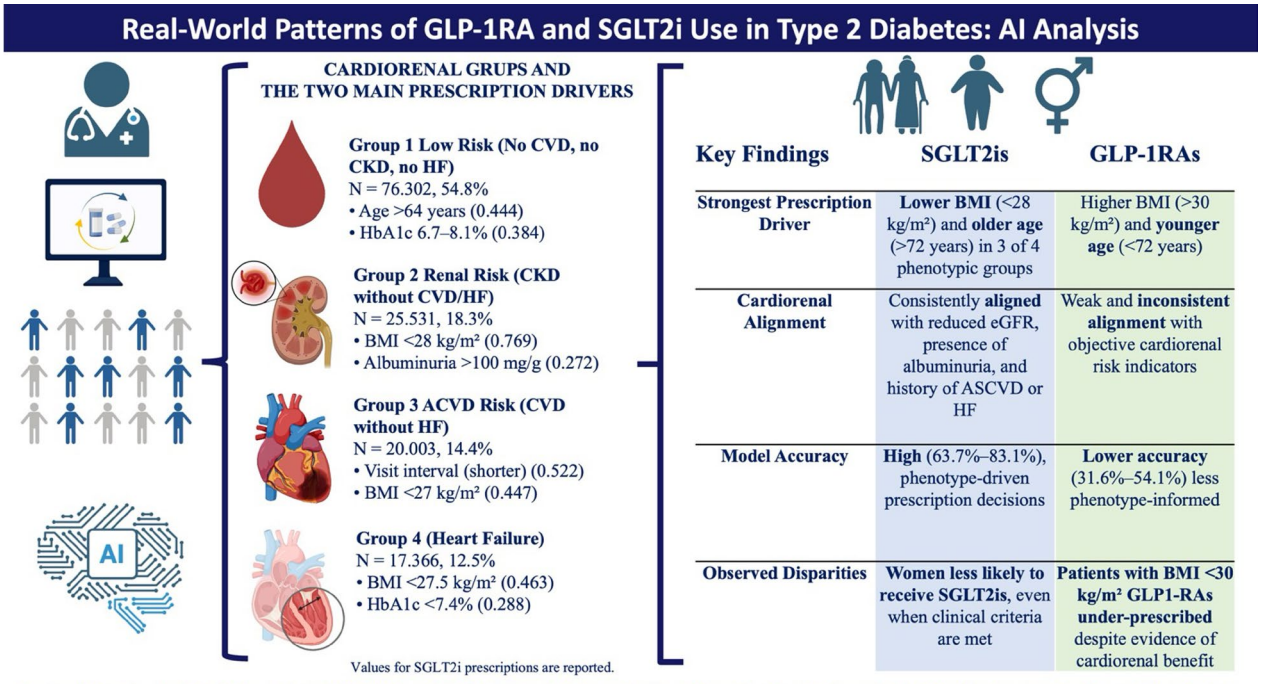
- Lower BMI is the strongest driver of SGLT2i use in CKD, ASCVD, and HF groups.
- GLP-1RA use is guided more by younger age and higher BMI than by cardiorenal risk.
- Women and lower-BMI individuals are less likely to receive SGLT2is and GLP-1RAs, respectively, independently from cardiorenal risk.

**How might this study influence clinical practice?**

XAI-driven insights may support more equitable, risk-based prescribing of cardiorenal therapies.

**Keywords** Type 2 diabetes mellitus (T2D); Sodium-glucose co-transporter-2 inhibitors (SGLT2is), Glucagon-like peptide-1 receptor agonists (GLP-1RA), Machine learning analysis, Cardiorenal risk stratification, Prescription patterns and patient-centered outcomes

**Graphical Abstract**




## Introduction

The advent of sodium–glucose co-transporter-2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) has transformed the management of type 2 diabetes (T2D), particularly in individuals with high cardiovascular (CV) and renal diseases [1–5]. Beyond their weight and glucose-lowering properties, both drug classes have demonstrated robust, independent efficacy in reducing major adverse cardiovascular events (MACE), slowing the progression of chronic kidney disease (CKD), and preventing hospitalisation for heart failure (HF) in large-scale randomised controlled

trials [2–6]. As a result, international guidelines now recommend prioritising these agents in patients with established atherosclerotic cardiovascular disease (ASCVD), CKD, or HF [7]. Yet, in clinical practice, decisions to prescribe these medications are shaped by eligibility and demographic and organizational factors. Studies show lower use in women, older or frail patients, and socioeconomically disadvantaged groups, while BMI and prescriber specialty influence class selection [8–14]. In fact, while the effectiveness of GLP-1RAs in reducing weight is well established and frequently drives their preferred use in clinical practice, emerging evidence also supports their direct renal and cardiovascular protective effects independent of weight loss [15–17].

However, given the high prevalence of obesity among individuals with T2D [18], body mass index (BMI) may disproportionately influence treatment decisions. This can bias prescribing patterns towards GLP-1RAs in individuals with higher BMI, even when SGLT2is may provide adequate cardiorenal protection in that clinical setting. Conversely, individuals with lower BMI might be less likely to receive GLP-1RAs, despite strong evidence that their cardiorenal benefits go beyond weight reduction [15–17]. These patterns raise concerns that treatment decisions could be influenced more by demographic factors, particularly BMI, age and sex, than by objective clinical need. When these factors are given undue weight, they may lead to suboptimal, non-cardiorenal evidence-based prescribing and may perpetuate disparities in access to disease-modifying, guideline-recommended therapies [8–14]. Prior studies have underscored persistent inequities and deviations from guideline-based recommendations, but they have not leveraged Explainable artificial intelligence (XAI) approaches to disentangle the relative impact of cardiorenal risk versus demographic factors.

XAI, particularly transparent machine learning (ML), offers a novel way to address this gap by helping to identify the individual clinical and demographic features correlated with prescribing choices in real-world practice [19]. Similarly, our study advances the field by applying the XAI to a nationwide Italian cohort of adults with T2D, divided into four cardiorenal phenotypic subgroups. Our goal was to identify the key clinical and demographic factors that influence the use of SGLT2is and GLP-1RAs, and to evaluate whether these reflect cardiorenal risk as recommended in current guidelines. This approach may offer new insights into how risk-based, phenotype-driven strategies can improve therapeutic equity and clinical precision [20, 21].

## Research design and methods

### Study population and data source

This cross-sectional study is based on the AMD Annals 2023 dataset, a large Italian EHR initiative. Data included clinical, demographic, and therapeutic information for adults (≥ 18 years) with T2D seen in 2022–2023. Subjects ($n$ = 139,202) were stratified into four clinical cohorts based on American Diabetes Association (ADA) guidelines, considering CV and renal risk factors [7]. Group 1 had eGFR ≥ 60 mL/min, no established coronary artery disease (CAD), no previous cardiovascular events (stroke/myocardial infarction), and no heart failure (HF), ($n$ = 76,302); Group 2 had eGFR < 60 mL/min, no established CAD, no previous cardiovascular events (stroke/myocardial infarction), and no heart failure (HF), ($n$ = 25,531); Group 3 had established CAD and/or previous cardiovascular events (stroke/myocardial infarction), but no heart failure (HF), ($n$ = 20,003), and Group 4 was composed of subjects with heart failure (HF), regardless of eGFR or cardiovascular disease status, ($n$ = 17,366). For Group 3, only the ADA secondary prevention phenotype + ASCVD (Atherosclerotic Cardiovascular Disease) was included, excluding the ADA primary prevention phenotype + Indicators of High CVD Risk due to the low availability of albuminuria data across the cohort (less than 50% in all groups; see Supplementary Table W - Table 1 and Supplementary Methods for complete definitions). Baseline eligibility for SGLT2i/GLP-1RA therapy was defined according to the SID/AMD Italian guidelines [22], which closely mirror the ADA recommendations. Nevertheless, in routine practice diabetologists may prescribe these agents even at diagnosis or in well-controlled patients on metformin alone; therefore, our analyses reflect actual EHR-recorded prescriptions rather than restricting the cohort to strictly guideline-eligible cases. Given the heterogeneity of centers, prescriber specialties, and patient profiles, these diverse real-world data support good external validity and generalizability across routine clinical settings. Patients were classified according to their first recorded new prescription; subsequent switching or concomitant use of SGLT2is and GLP-1RAs could not be fully captured. Supplementary Table W shows that albuminuria data were available in less than 40% of patients across all subgroups (37.6% in Group 2, 38.0% in Group 1, 39.4% in Group 3, and 40.0% in Group 4). A preliminary analysis restricted to individuals with available albuminuria values did not reveal a significant association with prescription patterns, and in multivariable models albuminuria was not an independent determinant once age, BMI, HbA1c, and renal function were accounted for. Given the high degree of missingness and the absence of a robust independent effect, albuminuria was excluded from subgroup definitions to ensure methodological robustness and comparability across groups

(see supplementary materials). Therefore, eGFR, cardiovascular history, and heart failure status were prioritized for subgroup stratification (supplementary Table W). Ethical approval and patient consent were waived under national guidelines for retrospective studies utilizing anonymized data. This study followed the STROBE reporting guideline for cross-sectional studies.

#### Machine learning analysis

This algorithm (Rulex, version 1.2.x) generates threshold-based classification rules for each variable, enabling a clear interpretation of their contribution to the model's predictive decision-making process. We implemented a natively transparent, rule-based classifier that outputs human-readable thresholds and rules. Relevance scores, normalized between 0 and 1, quantified each variable's impact, with higher scores indicating stronger predictive power (feature relevance computed as normalized importance from the explainable model as detailed in the Supplementary Materials). Input variables included anthropometric, biochemical, and clinical parameters, such as BMI, age, HbA1c, LDL cholesterol, renal function (eGFR), and therapy history together with derived features (per-patient mean, trend, and SD; HbA1c drop speed; HbA1c gap; number of out-of-range HbA1c values), and indicators of complications/comorbidities and ongoing treatments (see Supplemental Table X for a complete list). We also included non–anti-diabetic medications (NADMs) and a composite clinical quality indicator (ScoreQ, reflecting risk score). Binary class labels were assigned a priori as GLP1-RA = "positive (P)" and SGLT2i = "negative (N)".

Thresholds were identified for variables where the probability of prescribing one drug class over the other shifted, reflecting clinical tipping points. Models were fit separately within the four predefined clinical subgroups (Groups 1–4) to mirror the clinical strata used throughout the study; missing data were handled by complete-case analysis (no imputation). When no clear thresholds were found, the model still included variables to capture potential underlying subpopulation differences or additional explanatory noise.

#### Software and parameterization

Excel 2407 (Build 17830.20238) and Rulex 1.2.x were used for all statistical and machine learning analyses, with only Rulex 1.2.x applied for machine learning analyses. This natively transparent, rule-based classifier provides several configurable hyperparameters—such as the maximum number of variables per rule, minimum rule distance, and maximum permissible error—which can be tuned to optimize model complexity and performance (see Supplementary Methods, which includes the table with the detailed configuration of the hyperparameters used for modeling). In addition, the rule learning procedure includes internal pruning and regularization to limit overfitting and produces normalized relevance scores in the [0–1] range. Given the threshold-based approach, no feature scaling was required.

#### Validation strategy

The Rulex model evaluation was performed with repeated 70/30 train-test split using Monte Carlo cross-validation with 3 iterations. For statistical validation, machine learning findings were further assessed using distribution charts, Welch's t-test (for continuous variables), the Mann-Whitney U test (as a nonparametric alternative), and the chi-square test (for categorical variables).This combination ensured robust validation across variable types, accounting for potential asymmetry or outliers. A p-value $< 0.05$ was considered statistically significant. Missing data were excluded from the analysis. Model discrimination and error profiles were summarized by ROC-AUC, accuracy, sensitivity, specificity, PPV, and NPV, computed separately in each subgroup (see Supplementary Tables Y and Z). In addition, we applied "probability profiles" from business-intelligence dashboards to verify the clinical plausibility of thresholds (i.e., points where class probabilities invert), providing a qualitative cross-check of the rule set against observed prescribing patterns. (See supplementary methods and supplementary Table T and W).

#### Classification rules and discriminatory power

Classification rules were developed for each subgroup of patients to highlight the thresholds most relevant for distinguishing between SGLT2is and GLP1-RA prescriptions. Variables with the highest relevance scores (BMI, HbA1c, eGFR, age and sex) provided clear decision boundaries consistent with the explainable model's rule set and validated through comparison with averages calculated by traditional statistical methods, ensuring consistency and discriminatory power at key clinical tipping points. Feature relevance is reported on a normalized 0–1 scale to enable direct comparison across predictors (see Supplementary Materials).

#### Bias detection and validation

Post hoc analyses used descriptive and inferential statistics to assess potential biases in prescribing patterns, particularly overreliance on specific variables (e.g., LDL cholesterol or age) and inconsistencies in threshold applications. Where the explainable model suggested potential demographic or organizational drivers (e.g., age, sex, BMI, Q-score, years of observation), we compared their distributions between predicted and observed classes to detect systematic skew.

**Table 1** Baseline clinical and treatment characteristics of patients with type 2 diabetestreated with GLP-1 receptor agonists (GLP-1RA) or SGLT2 inhibitors (SGLT2i), stratified bycardio-renal phenotype

| | Group 1 | | p | Group 2 | | p | Group 3 | | p | Group 4 | | p |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Patients with eGFR ≥ 60, no CAD, no previous events (stroke/myocardial infarction), and no heart failure | | | Patients with eGFR < 60, no CAD, no previous events (stroke/myocardial infarction), and no heart failure | | | Patients with confirmed CAD and/or previous events (stroke/myocardial infarction), but no heart failure | | | Patients with heart failure | | |
| **n (total patients in the group; total cohort*n* = 139,202)** | | | | | | | | | | | | |
| | **76,302** | | | **25,531** | | | **20,003** | | | **17,366** | | |
| **Males, n (% in the group)** | | | | | | | | | | | | |
| | **46,229 (61%)** | | | **13,970 (55%)** | | | **14,722 (74%)** | | | **11,338 (65%)** | | |
| **Treatment, n (% of total group)** | | | | | | | | | | | | |
| | **GLP1-ra** | **SGLT2is** | | **GLP1-ra** | **SGLT2is** | | **GLP1-ra** | **SGLT2is** | | **GLP1-ra** | **SGLT2is** | |
| | 35.510 (47%) | 40.792 (53%) | | 9.080 (36%) | 16.451 (64%) | | 7.155 (36%) | 12.848 (64%) | | 5.277 (30%) | 12.089 (70%) | |
| **Males. n (% by treatment)** | | | | | | | | | | | | |
| | 20.210 (57%) | 26.019 (64%) | < 0.01 | 4.526 (49%6) | 9.767 (58%) | < 0.01 | 4.975 (70%) | 9.747 (76%) | < 0.01 | 3.241 (61%) | 8.097 (67%) | < 0.01 |
| **Age (Years)** | | | | | | | | | | | | |
| Mean ± SD | 63.2 (10.54) | 66.01 (10.04) | < 0.01 | 71.6 (9.3) | 73.1 (9.6) | < 0.01 | 71.6(9.3) | 72.5(8.7) | < 0.01 | 73.1(9.6) | 74.7(8.6) | < 0.01 |
| Median (IQR) | 64.0 (56.0–71.0) | 67.0 (59.0–73.0) | | 76.0 (70.0–81.0) | 76.0 (71.0–81.0) | | 73.00 (66.0–78.0) | 73.0 (67.0–79.0) | | 74.0 (67.0–80.0) | 76.0 (70.0–81.0) | |
| **Duration of disease** | | | | | | | | | | | | |
| Mean ± SD | 118(104) | 132(106) | < 0.01 | 186(120) | 175(117) | < 0.01 | 189(116) | 183(116) | < 0.01 | 209(118) | 203(116) | > 0.05 |
| Median (IQR) | 96 (30–180) | 120 (42–202) | | 179 (96–264) | 169 (85–251) | | 180 (103–264) | 175 (96–259) | | 196 (127–277) | 196 (121–273) | |
| **HbA1c, mmol/mol (%)** | | | | | | | | | | | | |
| Mean ± SD | 64(19) (7.99–1.71) | 62(16) (7.77–1.47) | < 0.01 | 62(17) (7.79–1.49) | 57(14) (7.39–1.26) | < 0.01 | 60(15) (7.60–1.37) | 57(13) (7.37–1.20) | < 0.01 | 60(15) (7.65–1.34) | 57(13) (7.36–1.15) | < 0.01 |
| mmol/mol Median (IQR) | 60 (51–73) | 58 (51–67) | | 59 (51–69) | 55 (49–63) | | 57 (50–67) | 55 (49–63) | | 57 (50–67) | 55 (49–63) | |
| % Median (IQR) | 7.60 (6.80–8.80) | 7.46 (6.82–8.30) | | 7.55 (6.80–8.50) | 7.18 (6.60–7.91) | | 7.37 (6.63–8.23) | 7.18 (6.60–7.90) | | 7.40 (6.72–8.30) | 7.20 (6.60–7.90) | |
| **Fasting blood glucose. mg/dl** | | | | | | | | | | | | |
| Mean ± SD | 165(60) | 157(51) | < 0.01 | 155(56) | 145(46) | < 0.01 | 152(50) | 145(44) | < 0.01 | 151(50) | 144(43) | < 0.01 |
| Median (IQR) | 150 (124–190) | 146 (123–176) | | 143 (118–176) | 137 (116–162) | | 142 (119–173) | 136 (117–163) | | 142 (119–171) | 137 (116–162) | |
| **Albuminuria** | | | | | | | | | | | | |
| Mean ± SD | 36.43(125.20) | 56.09(168.09) | < 0.01 | 96.69(261.51) | 113.32(286.38) | > 0.05 | 73.22(226.00) | 84.52(244.02) | > 0.05 | 71.75(214.68) | 83.77(238.25) | > 0.05 |
| Median (IQR) | 9.00 (4.30–21.70) | 10.10 (4.75–34.30) | | 15.40 (5.48–60.93) | 17.00 (5.30–73.00) | | 12.40 (5.57–39.70) | 13.00 (5.00–50.00) | | 12.00 (5.00-41.15) | 13.00 (5.00–51.00) | |

**Table 1** (continued)

| | Group 1 | | p | Group 2 | | p | Group 3 | | p | Group 4 | | p |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Patients with eGFR ≥ 60, no CAD, no previous events (stroke/myocardial infarction), and no heart failure | | | Patients with eGFR < 60, no CAD, no previous events (stroke/myocardial infarction), and no heart failure | | | Patients with confirmed CAD and/or previous events (stroke/myocardial infarction), but no heart failure | | | Patients with heart failure | | |
| **Serum Creatinine** | | | | | | | | | | | | |
| Mean ± SD | 0.82(0.17) | 0.84(0.17) | < 0.01 | 1.44(0.47) | 1.42(0.39) | < 0.05 | 1.10(0.47) | 1.11(0.38) | < 0.01 | 1.13(0.46) | 1.17(0.41) | < 0.01 |
| Median (IQR) | 0.80 (0.70–0.92) | 0.83 (0.71–0.96) | | 1.33 (1.15–1.59) | 1.34 (1.20–1.56) | | 0.99 (0.81–1.25) | 1.02 (0.84–1.30) | | 1.01 (0.82–1.32) | 1.09 (0.87–1.39) | |
| **eGFR** | | | | | | | | | | | | |
| Mean ± SD | 88(14) | 85(14) | < 0.01 | 44(11) | 45(10) | < 0.01 | 69(22) | 67(21) | < 0.01 | 65(23) | 62(21) | < 0.01 |
| Median (IQR) | 89 (77–98) | 86 (74–95) | | 46 (37–54) | 47 (39–54) | | 71 (52–87) | 68 (50–85) | | 66 (46–85) | 61 (44–80) | |
| **Sistolic BP** | | | | | | | | | | | | |
| Mean ± SD | 137(18) | 137(19) | > 0.05 | 137(19) | 137(20) | > 0.05 | 136(19) | 135(19) | < 0.01 | 136(19) | 134(19) | < 0.01 |
| Median (IQR) | 136 (121–150) | 135 (120–150) | | 140 (120–150) | 137 (120–150) | | 135 (120–150) | 133 (120–147) | | 135 (120–150) | 130 (120–145) | |
| **Diastolic BP** | | | | | | | | | | | | |
| Mean ± SD | 80(10) | 79(10) | < 0.01 | 77(10) | 76(10) | < 0.01 | 77(10) | 75(10) | < 0.01 | 77(10) | 75(10) | < 0.01 |
| Median (IQR) | 80 (70–85) | 80 (70–85) | | 80 (70–80) | 78 (70–80) | | 80 (70–80) | 75 (70–80) | | 80 (70–80) | 75 (70–80) | |
| **LDL** | | | | | | | | | | | | |
| Mean ± SD | 99(37) | 94(36) | < 0.01 | 89(34) | 87(33) | < 0.01 | 77(32) | 74(31) | < 0.01 | 81(31) | 79(30) | < 0.01 |
| Median (IQR) | 94 (70–122) | 90 (67–117) | | 83 (63–109) | 82 (62–106) | | 70 (54–94) | 68 (52–89) | | 76 (58–98) | 73 (57–96) | |
| **HDL** | | | | | | | | | | | | |
| Mean ± SD | 48(12) | 49(13) | < 0.01 | 47(13) | 48(13) | < 0.01 | 45(12) | 46(12) | < 0.01 | 47(12) | 47(13) | < 0.05 |
| Median (IQR) | 46 (39–55) | 48 (40–56) | | 45 (38–54) | 46 (39–55) | | 44 (37–52) | 45 (38–53) | | 45 (38–53) | 46 (39–54) | |
| **Triglycerides** | | | | | | | | | | | | |
| Mean ± SD | 157(106) | 144(100) | < 0.01 | 160(86) | 148(84) | < 0.01 | 141(78) | 132(76) | < 0.01 | 140(80) | 131(71) | < 0.01 |
| Median (IQR) | 132 (96–185) | 120 (88–168) | | 140 (105–190) | 130 (96–177) | | 123 (92–168) | 115 (87–158) | | 122 (91–165) | 114 (85–157) | |
| **BMI. kg/m2** | | | | | | | | | | | | |
| Mean ± SD | 32.00(6.27) | 28.69(5.10) | < 0.01 | 31.16(5.89) | 28.65(4.98) | < 0.01 | 29.79(5.23) | 27.94(4.50) | < 0.01 | 30.91(5.70) | 28.63(5.07) | < 0.01 |
| Median (IQR) | 31.15 (27.62–35.49) | 28.03 (25.21–31.44) | | 30.36 (27.01–34.34) | 28.03 (25.22–31.25) | | 29.05 (26.14–32.75) | 27.46 (24.82–30.47) | | 30.30 (26.99–34.05) | 28.02 (25.11–31.29) | |
| **Weight. kg** | | | | | | | | | | | | |
| Mean ± SD | 89.47(19.70) | 80.18(16.43) | < 0.01 | 83.99(17.57) | 78.21(15.26) | < 0.01 | 82.83(16.36) | 78.27(14.49) | < 0.01 | 85.38(18.08) | 79.13(15.74) | < 0.01 |
| Median (IQR) | 87.0 (76.0-100.0) | 79.0 (69.0–90.0) | | 82.0 (72.0–94.0) | 77.0 (68.0–87.0) | | 81.0 (71.5–92.0) | 77.0 (68.5–87.0) | | 83.0 (73.0-95.5) | 78.0 (68.0–88.0) | |

**Table 1** (continued)

| | Group 1 | | p | Group 2 | | p | Group 3 | | p | Group 4 | | p |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Patients with eGFR ≥ 60, no CAD, no previous events (stroke/myocardial infarction), and no heart failure | | | Patients with eGFR < 60, no CAD, no previous events (stroke/myocardial infarction), and no heart failure | | | Patients with confirmed CAD and/or previous events (stroke/myocardial infarction), but no heart failure | | | Patients with heart failure | | |
| **Comorbidities. n (%*)** | | | | | | | | | | | | |
| Dyslipidemia. n (%) | 32.506 (92%) | 37.246 (91%) | > 0.05 | 8.367 (92%) | 15.099 (92%) | > 0.05 | 6.918 (97%) | 12.374 (96%) | > 0.05 | 5.074 (96%) | 11.540 (95%) | < 0.05 |
| Hypertension. n (%) | 23.506 (66%) | 28.114 (69%) | < 0.01 | 7.596 (84%) | 14.046 (85%) | < 0.01 | 7.497 (91%) | 11.786 (92%) | < 0.05 | 4.961 (94%) | 11.436 (95%) | > 0.05 |
| Liver disease† | 7.633 (22%) | 7.812 (19%) | < 0.01 | 1.401 (15.4%) | 2.495 (15.2%) | > 0.05 | 1.584 (22%) | 2.616 (20%) | < 0.01 | 1.206 (23%) | 2.701 (22%) | > 0.05 |
| **Diabetes related complications. n (%1)** | | | | | | | | | | | | |
| Neuropathy‡ | 1.186 (3.3%) | 1.622 (4.0%) | < 0.01 | 574 (6.3%) | 1.028 (6.2%) | > 0.05 | 689 (9.6%) | 1.253 (9.8%) | > 0.05 | 772 (15%) | 1.704 (14%) | > 0.05 |
| Kidney Disease§ | 5.853 (17%) | 8.605 (21%) | < 0.01 | 5.458 (60.1%) | 10.339 (62.8%) | < 0.01 | 3.445 (48%) | 6.491 (51%) | < 0.01 | 2.868 (54%) | 7.282 (60%) | < 0.01 |
| Eye Disease‖ | 2.378 (7%) | 3.605 (9%) | < 0.01 | 1.116 (12.3%) | 2.057 (12.5%) | > 0.05 | 1.341 (19%) | 2.231 (17%) | > 0.05 | 1.251 (24%) | 2.717 (22%) | > 0.05 |
| PAD¶ | 1.465 (4%) | 2.121 (5%) | < 0.01 | 706 (7.8%) | 1.411 (8.6%) | < 0.05 | 1.055 (15%) | 2.003 (16%) | **> 0.05** | 927 (18%) | 2.272 (19%) | **> 0.05** |
| CVD (Cerebrovascular Diseases) /stroke#, | 0 | 0 | | 0 | 0 | | 2.403 (34%) | 3.150 (25%) | < 0.01 | 604 (11%) | 1.215 (10%) | < 0.05 |
| CAD/MI††,‡‡ | 0 | 0 | | 0 | 0 | | 5.357 (75%) | 10.632 (83%) | < 0.01 | 1.779 (34%) | 5.060 (42%) | < 0.01 |
| **Statins. n (%*)** | | | | | | | | | | | | |
| | 19.890 (56%) | 24.701 (61%) | < 0.01 | 5.514 (60.7%) | 10.466 (63.6%) | < 0.01 | 5.876 (82%) | 10.736 (84%) | < 0.01 | 3.913 (74%) | 9.148 (76%) | < 0.05 |
| **ARBs/ACE-I. n (%*)** | | | | | | | | | | | | |
| | 17.270 (49%) | 20.260 (50%) | < 0.01 | 5.630 (62.0%) | 10.425 (63.4%) | < 0.05 | 4.749 (66%) | 8.551 (67%) | **> 0.05** | 3.540 (67%) | 7.899 (65%) | < 0.05 |

**Table 1** (continued)

| | Group 1 | | p | Group 2 | | p | Group 3 | | p | Group 4 | | p |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Patients with eGFR ≥ 60, no CAD, no previous events (stroke/myocardial infarction), and no heart failure | | | Patients with eGFR < 60, no CAD, no previous events (stroke/myocardial infarction), and no heart failure | | | Patients with confirmed CAD and/or previous events (stroke/myocardial infarction), but no heart failure | | | Patients with heart failure | | |
| **Other therapies (100%)** | | | | | | | | | | | | |
| Metformin | 85.14% | 56.40% | < 0.01 | 49.94% | 39.63% | < 0.01 | 67.65% | 45.59% | < 0.01 | 63.22% | 42.06% | < 0.01 |
| Secretagogues | 7.16% | 7.38% | | 10.43% | 8.33% | | 7.90% | 6.85% | | 9.32% | 7.23% | |
| TZD | 1.79% | 1.63% | | 3.28 | 2.26% | | 1.54% | 0.83% | | 2.08% | 1.13% | |
| DPP4i | 1.25% | 23.34% | | 3.34% | 36.45% | | 2.28% | 24.32% | | 3.30% | 30.25% | |
| Acarbose | 0.01% | 0.00% | | 0.24% | 0.00% | | 0.08% | 0.00% | | 0.15% | 0.00% | |
| Premix insulin | 0.01% | 0.09% | | 0.03% | 0.16% | | 0.06% | 0.10% | | 0.09% | 0.27% | |
| BI | 10.32% | 9.36% | | 14.87% | 10.63% | | 12.70% | 9.36% | | 12.83% | 10.65% | |
| BB | 2.21% | 6.34% | | 5.59% | 10.74% | | 6.32% | 13.79% | | 6.35% | 14.80% | |
| RAI | 0.07% | 0.20% | | 0.34% | 0.39% | | 0.25% | 0.45% | | 0.17% | 0.43% | |
| FRC | 9.95% | 0 | | 21.34% | 0 | | 14.69% | 0 | | 19.12 | 0 | |

Clinical and demographic characteristics of patients treated with GLP-1 receptor agonists or SGLT2 inhibitors, stratified by clinical phenotype in a real-world cohort. Patients were classified into four mutually exclusive groups: Group 1 (patients with eGFR ≥ 60 mL/min/1.73 $m^2$, no coronary artery disease [CAD], no history of stroke/myocardial infarction, and no heart failure); Group 2 (patients with eGFR < 60 mL/min/1.73 $m^2$, no CAD, no previous stroke/myocardial infarction, and no heart failure); Group 3 (patients with confirmed CAD and/or previous stroke/myocardial infarction, without heart failure); Group 4 (patients with heart failure, regardless of other comorbidities). Continuous variables are reported as mean ± standard deviation (SD) and median (interquartile range, IQR). Categorical variables are presented as number and percentage. Comparisons between patients treated with GLP-1 receptor agonists and SGLT2 inhibitors within each group were performed using appropriate statistical tests, and p-values are reported

Abbreviations: BI (Basal Insulin). BB (Basal Bolus), RAI (Rapid Acting Insulin), FRC (Fixed Ratio Combination Insulin + GLP1-RA)

* Percentage calculated relative to the total patients treated with GLP1-RA and SGLT2is

† Liver disease includes: elevated liver enzymes, metabolic associated fatty liver disease, metabolic associated steatohepatitis

‡ Neuropathy includes: polyneuropathy, mononeuropathy, autonomic neuropathy

§ Kidney Disease includes: micro-macro albuminuria and/or eGFR < 60 ml/min/m2, dialysis, kidney transplantation

‖ Eye Disease includes: any degree of diabetic retinopathy, macular edema, and other diabetes-related eye conditions

¶ PAD (Peripheral Arterial Disease) includes: lower limb artery disease, peripheral angioplasty/bypass

# Cerebrovascular disease includes: TIA, revascularization of intracranial and neck vessels, pathology of the epiaortic vessels, ischemic/hemorrhagic stroke

Cerebrovascular diseases for group 4: since heart failure is always present, the indicated values refer to 'heart failure' combined with other cerebrovascular disease comorbidities

†† CAD/MI includes: arterial hypertension, coronary disease, acute myocardial infarction, angina pectoris, coronary revascularization procedure. ‡‡ CAD/MI for group 4: since heart failure is always present, the indicated values refer to 'heart failure' combined with other CAD/MI comorbidities

### Performance metrics

Model performance was evaluated using standard binary classification metrics (ROC-AUC, sensitivity, specificity, PPV, NPV). Performance by subgroup is reported in Supplementary Table Z: ROC-AUC ranged from 0.594 (Group 1) to 0.719 (Group 4); accuracy from 0.572 to 0.704. Specificity exceeded sensitivity in all groups (e.g., 0.832 vs. 0.316 in Group 4), indicating better identification of SGLT2i prescriptions than GLP1-RA. PPV and NPV are provided for transparency on class-specific errors (Supplementary Table Z). In the main text, values ranging from 63.7% to 83.1% for SGLT2is and from 31.6% to 54.1% for GLP-1RAs refer to class-specific prediction accuracies, i.e. the ability of the model to identify each drug class correctly. By contrast, overall model accuracy ranged from 57.2% to 70.4% across subgroups, with class-specific PPV and NPV also reported in Supplementary Table Z. Specificity consistently outperformed sensitivity, indicating better performance in identifying SGLT2is prescriptions. Supplemental Tables Y and Z. While overall model discrimination was moderate (ROC-AUC 0.594–0.719; accuracy 0.572–0.704), this level of performance is consistent with the complexity of real-world prescribing, which is influenced by clinical and non-clinical factors not fully captured in EHRs. The primary goal of this XAI approach was interpretability and the identification of prescribing drivers, rather than maximizing predictive accuracy.

### Integration of business intelligence

Explicit Machine learning outputs were further validated using business intelligence analysis. Probability profiles illustrated trends in SGLT2is and GLP-1RA prescriptions, identifying thresholds where probabilities inverted between drug classes, confirming findings with descriptive analyses, and supporting the face validity of the learned rules in routine practice.

## Results

A total of 139,202 subjects with T2D were categorized into four groups according to ADA criteria for renal function, CVD history, and HF status. Overall, 62% were male, with treatment distributed between GLP-1RAs and SGLT2is (Table 1). Across the cohort, SGLT2i users were typically older, more often male, with lower BMI, reduced eGFR, and HbA1c values in the moderate range, whereas GLP-1RA users were generally younger, more often female, with higher BMI and HbA1c values < 5.5% or > 8.1%. In Group 1 ($n = 76,302$), GLP-1RA users had slightly better renal function, higher LDL cholesterol, and lower prevalence of hypertension, neuropathy, and kidney disease (all $p < 0.01$). In Group 2 ($n = 25,531$), GLP-1RA users had lower albuminuria and reduced prevalence of kidney disease and hypertension (all $p < 0.01$). In Group 3 ($n = 20,003$), albuminuria was higher in SGLT2i users, triglycerides higher in GLP-1RA users (both $p < 0.01$), and cerebrovascular disease more common with GLP-1RAs while coronary disease and prior MI predominated with SGLT2is. In Group 4 ($n = 17,366$), GLP-1RA users had higher BMI and HbA1c ($p < 0.01$) and slightly better renal function ($p < 0.01$), while kidney disease was more common with SGLT2is ($p < 0.01$). Across groups, metformin use was consistently higher with GLP-1RAs, while statins and ACE-I/ARBs were more common with SGLT2is (Table 1).

Prescription patterns were further characterized using explainable ML. Key common predictors for SGLT2i prescriptions included older age, lower BMI, reduced eGFR, and male sex, while GLP-1RA prescriptions were consistently associated with younger age, higher BMI, and broader HbA1c ranges. In Group 1 (54.8% of the cohort), SGLT2i predictors were age > 64 years (score 0.444), HbA1c 6.7–8.1% (0.384), eGFR < 88 mL/min/1.73 $m^2$ (0.262), LDL < 84 mg/dL (0.163), triglycerides < 100 mg/dL (0.138); GLP-1RAs were linked to younger age, BMI > 30 kg/$m^2$, HbA1c < 6.7% or > 8.1. In Group 2 (18.3%), primary SGLT2i predictor was BMI < 28 kg/$m^2$ (0.769), followed by age 72–82 years (0.245), HbA1c 5.5–7.5% (0.250), albuminuria (0.272), and eGFR 38–48 mL/min/1.73 $m^2$ (0.050). In Group 3 (14.4%), SGLT2i use was associated with shorter visit intervals (0.522), BMI < 27 kg/$m^2$ (0.447), HbA1c 5.8–7.3% (0.240), eGFR 33–63 mL/min/1.73 $m^2$ (0.214), triglycerides < 105 mg/dL (0.136), older age (0.152). In Group 4 (12.5%), SGLT2i predictors included BMI < 27.5 kg/$m^2$ (0.463), HbA1c < 7.4% (0.288), eGFR 31–59 mL/min/1.73 $m^2$ (0.207), CKD with macroalbuminuria (0.142), and age > 75 years (0.112) (Table 2; Fig. 1, Supplementary Figure S1).

Model reliability showed consistently higher predictive accuracy for SGLT2is compared with GLP-1RAs across all subgroups: Group 1: 63.7% vs. 47.5%; Group 2: 69.5% vs. 54.1%; Group 3: 79.8% vs. 34.8%; Group 4: 83.1% vs. 31.6%. This pattern was observed in both ROC-AUC and classification performance metrics (Table 2; Fig. 1, Supplementary Figure S1). Overall, SGLT2is were preferentially prescribed to older males with lower BMI, impaired renal function, and higher albuminuria, often with coexisting cardiovascular disease, whereas GLP-1RAs were more common in younger, obese individuals, predominantly females, with extreme HbA1c values. Subgroup-specific nuances included higher cerebrovascular disease among GLP-1RA users in ASCVD (Group 3) and higher coronary disease among SGLT2i users in the same group, while HF patients (Group 4) showed the highest SGLT2i accuracy.

**Table 2** Explainable machine-learning predictors of GLP-1 receptor agonists (GLP-1RA) vsSGLT2 inhibitors (SGLT2i) prescriptions across cardio-renal phenotypes

| Variable | Relevance Score* | GLP1-RA † | SGLT2is | Threshold Values (ML) ‡ |
|---|---|---|---|---|
| **Group 1 (eGFR ≥ 60, no CVD, no HF):*N* = 76,302 (54.8%). Model reliability in predicting SGLT2is: 63.7% and GLP1-ra: 47.5**% | | | | |
| Age (years) | 0.444 | 63.2 (10.5) | 66.01 (10.04) | > 64 |
| HbA1c (%) | 0.384 | 7.99 (1.71) | 7.77 (1.47) | > 6.7 & <8.1 |
| eGFR (mL/min) | 0.262 | 88 (14) | 85 (14) | < 88 |
| LDL (mg/dL) | 0.163 | 99 (37) | 94 (36) | < 84 |
| Type of therapy at the visit preceding T0 (prescription of GLP1 or SGLT2) | 0.149 | § | § | OAD only, no insulin |
| Triglycerides (mg/dL) | 0.138 | 157 (106) | 144 (100) | < 100 |
| Visit interval (years) | 0.126 | § | § | ns |
| BMI (Kg/m$^2$) | 0.115 | 32.00 (6.27) | 28.69 (5.10) | < 30 |
| Sex (% Male) | 0.098 | 57 | 64 | Male |
| Microalbuminuria (n, % of total) (Yes/No)‖ | 0.097 | 3.820 (9% of 40.792) | 3.132 (9% of 35.510) | ns |
| Visits with insulin therapy before T0 (n) (Yes/No)‖ | 0.096 | § | § | < 1 |
| Macroalbuminuria (n, % of total) (Yes/No)‖ | 0.040 | 3,924 (10.3% of 40.792) | 2,140 (6% of 35.510) | YES |
| Neuropathy (n, % of total) (Yes/No)‖ | 0.015 | 1,622 (4% of 40.792) | 1,186 (3.3% of 35.510) | YES |
| Eye Disease (n, % of total) (Yes/No)‖ | 0.015 | 3,605 (9% of 40.792) | 2,378 (7% of 35.510) | ns |
| Time since diagnosis (years) | 0.015 | § | § | > 8.5 |
| **Group 2 (eGFR < 60, no CVD, no HF)*n* = 25,531 (18.3%). Model reliability in predicting SGLT2is: 69.5% and GLP1-ra: 54.1%** | | | | |
| BMI (kg/m$^2$) | 0.769 | 31.16 (5.89) | 28.65 (4.98) | < 28 |
| Albuminuria (mg/g) | 0.272 | 96.69 (261.51) | 113.32 (286.38) | ns |
| Type of therapy at the visit preceding T0 (prescription of GLP1 or SGLT2) | 0.263 | § | § | OAD only, no insulin |
| HbA1c (%) | 0.250 | 7.79 (1.49) | 7.39 (1.26) | > 5.5 & <7.5 |
| Age at Diagnosis (years) | 0.245 | 74.8 (8.7) | 75.3 (8.0) | > 72 & <82 |
| LDL (mg/dL) | 0.242 | 89 (34) | 87 (33) | > 55 & <76 |
| Triglycerides (mg/dL) | 0.232 | 160 (86) | 148 (84) | < 120 |
| Visit Interval (years) | 0.146 | § | § | ns |
| Statins Use (Yes/No)‖ | 0.131 | Yes | Yes | Presence of statins |
| Cardiovascular Conditions (including HNT and AF)‖ | 0.087 | 14,056 (85% of 16,451) | 7,601 (84% of 9,080) | AF and/or AF + HTN |
| Visits with insulin therapy before T0 (n)(Yes/No)‖ | 0.073 | † | † | < 1 |
| Kidney Disease (%Yes)‖ | 0.054 | 100% | 100% | microalbuminuria, macroalbuminuria, CKD + macroalbuminuria |
| eGFR (mL/min/1.73 m$^2$) | 0.050 | 44 (11) | 45 (10) | > 38 & <48 |
| Eye Disease (Yes/No)‖ | 0.027 | 2,057 (12.5% of 16,451) | 1,116 (12.3% of 9,080) | ns |
| Sex (% Male) | 0.026 | 49 | 58 | M |
| **Group 3 (Confirmed CVD and/or prior events, no HF)*n* = 20,003 (14.4%). Model reliability in predicting SGLT2is: 79.8% and GLP1-RA: 34.8%.** | | | | |
| Visit Interval (Years) | 0.522 | Not specified | Not specified | ns |
| BMI (kg/m$^2$) | 0.447 | 29.79 (5.23) | 27.94 (4.50) | < 27 |
| HbA1c (%) | 0.240 | 7.60 (1.37) | 7.37 (1.20) | > 5.8 & <7.3 |
| Type of therapy at the visit preceding T0 (prescription of GLP1 or SGLT2) (Yes/No)‖ | 0.239 | § | § | OAD only, no insulin |
| eGFR (mL/min) | 0.214 | 69 (22) | 67 (21) | > 33 & <63 |
| Age (Years) | 0.152 | 71.6 (9.3) | 72.5 (8.7) | > 72 |
| Triglycerides (mg/dL) | 0.136 | 141 (78) | 132 (76) | < 105 |
| Albuminuria (mg/g) | 0.114 | 73.22 (226.00) | 84.52 (244.02) | ns |

**Table 2** (continued)

| Variable | Relevance Score* | GLP1-RA † | SGLT2is | Threshold Values (ML) ‡ |
|---|---|---|---|---|
| Cerebrovascular disease(Yes/No)‖ | 0.113 | 3,150 (25% of 12.848) | 2,403 (34% of 7155) | ns |
| Risk Score (ScoreQ) (-) | 0.097 | § | § | < 26 |
| Sex (Male) (%) | 0.095 | 70% | 76% | M |
| Microalbuminuria (Yes/No)‖ | 0.070 | 1,727 (24% of 7.155) | 1,047 (15% of 7.155) | ns |
| Hypertension (Yes/No)‖ | 0.029 | 11,786 (91.7% of 12.848) | 6,497 (90.8% of 7155) | ns |
| Visits with insulin therapy before T0 (n) (Yes/No)‖ | 0.026 | § | § | < 1 |
| Macroalbuminuria (Yes/No)‖ | 0.026 | 2,586 (20% of 12.848) | 1,269 (18% of 7.155) | YES |
| **Group 4 (HF)*n* = 17,807, (12.51%). Model reliability in predicting SGLT2is: 83.1% and GLP1-RA: 31.6%.** | | | | |
| BMI (kg/m$^2$) | 0.463 | 30.91 (5.70) | 28.63 (5.07) | < 27.5 |
| HbA1c (%) | 0.288 | 7.65 (1.34) | 7.36 (1.15) | < 7.4 |
| eGFR (mL/min/1.73 m$^2$) | 0.207 | 65 ± 23 | 62 ± 21 | > 31 & < 59 |
| Type of therapy at the visit preceding T0 (prescription of GLP1 or SGLT2)(Yes/No)‖ | 0.155 | § | § | OAD only, no insulin |
| Kidney Disease (Yes/No)‖ | 0.142 | 7,282 (60% of 12.089) | 2,868 (54% of 5.277) | macroalbuminuria, CKD, CKD + microalbuminuria, CKD + macroalbuminuria |
| Age at date (years) | 0.112 | 73.1 (9.6) | 74.7 (8.6) | > 75 |
| Visit interval (years) | 0.108 | § | § | ns |
| NADMs | 0.095 | § | § | not present; lipid-lowering agents + antihypertensives (combined in the same therapy) |
| Cardiovascular Conditions (including CAD/MI, HNT, AF) (Yes/No)‖ | 0.095 | 11,599 (96% of 12.089) | 5,019 (95% of 5.277) | HF + one of the following: CAD/MI, FA, HTN. No HF alone |
| Risk Score (ScoreQ) (-) | 0.086 | § | § | < 26 |
| Visits with insulin therapy before T0 (n)(Yes/No)‖ | 0.067 | § | § | < 1 |
| Microalbuminuria (Yes/No)‖ | 0.055 | 1,709 (14% of 12.089) | 767 (15% of 5,277) | ns |
| Albuminuria (mg/g) | 0.050 | 71.75(214.68) | 83.77(238.25) | > 63 |
| LDL (mg/dL) | Not visible | 81 (31) | 79 (30) | < 65 |
| Triglycerides (mg/dL) | Not visible | 140 (80) | 131 (71) | < 105 |

The table shows the most relevant variables in descending order of Relevance Score, that the algorithm uses to define the classification rules. Data are expressed es mean (DS) or n (%) in both groups. The machine learning algorithm identified clear threshold values only for some variables. * The relevance score is a sensitivity measure that quantifies the degree of variation in the model's prediction based on the variable under consideration. Values are normalized between 0 and 1 to ensure a proportional representation of the relative contribution. §The thresholds for GLP1-RA prescriptions complement those for SGLT2is, but the models show low reliability in predicting GLP1-RA use. ‡The thresholds reported are exclusively for SGLT2is prescription and were validated by their respective averages across the GLP1-RA and SGLT2is groups. However, some variables with lower relevance did not exhibit well-defined thresholds, suggesting they may either contribute noise or indicate potential subpopulations within the analyzed group. § For the concomitant medications for each group see Table 1. ‖ the presence of the disease and/or condition is the variable in the model. IH, Insulin History. NS, Not Specified (There is not a specified Threshold Value); OAD, Oral Anti Diabetic medications; AF, Atrial Fibrillation; HTN, Hypertension; CKD, Chronic Kidney Disease; M, Males; Neuropathy, polyneuropathy, mononeuropathy, autonomic neuropathy; Eye Disease, any degree of diabetic retinopathy, macular edema, and other diabetes-related eye conditions; Kidney Disease, micro-macro albuminuria and/or eGFR < 60 ml/min/m2, dialysis, kidney transplantation; Cerebrovascular disease, Transient Ischemic Attack (TIA), revascularization of intracranial and neck vessels, pathology of the epiaortic vessels, ischemic/hemorrhagic stroke; CAD/MI, arterial hypertension, coronary artery disease, acute myocardial infarction, angina pectoris, coronary revascularization procedure. NADMs, Non Anti Diabetic Medications (all other medication not prescribed for hyperglycaemia, including lipid-lowering agents, antihypertensives, antiplatelets, thyroid medications); Group 1, eGFR ≥ 60 mL/min, no established coronary artery disease, no previous cardiovascular events (stroke/myocardial infarction), and no heart failure (HF), Group 2: eGFR < 60, no CAD, no previous events (stroke/myocardial infarction), and no heart failure; Group 3, Patients with confirmed CAD and/or previous events (stroke/myocardial infarction), but no heart failure; Group 4, Patients with heart failure

## Discussion

This machine learning analysis demonstrates that the use of SGLT2is and GLP-1RAs in real-world Italian diabetes care is influenced not only by cardiorenal risk profiles but also by demographic and anthropometric variables such as age, sex, and BMI. SGLT2i prescriptions showed high model reliability (63.7%–83.1%) and were consistently associated with key markers of cardiorenal vulnerability, such as reduced eGFR, intermediate HbA1c levels (5.5%–8.1%), history of atherosclerotic cardiovascular

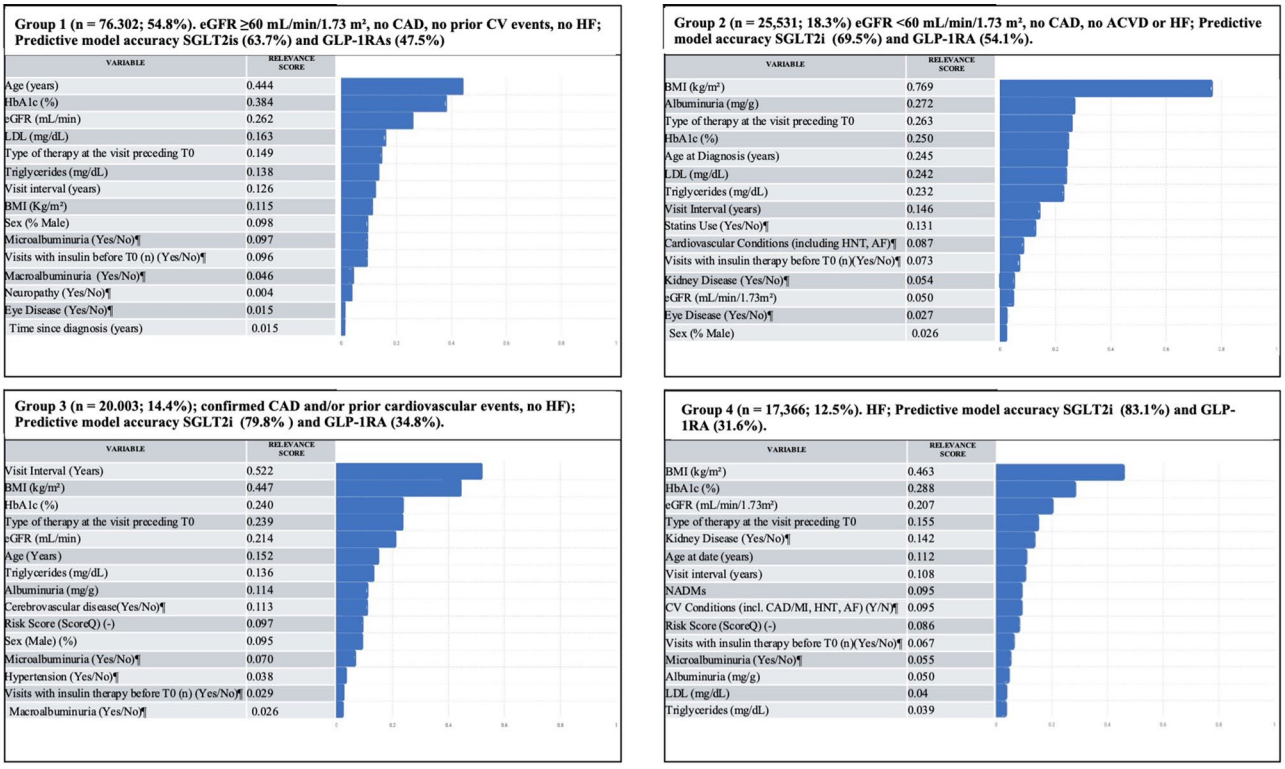



**Fig. 1** This figure shows the predictive reliability of machine learning models in identifying phenotypic patterns that influence the prescribing of SGLT2 inhibitors (SGLT2i) and GLP-1 receptor agonists (GLP1-RA) across four clinically stratified patient groups. The columns depict the reference score, a measure derived from the machine learning algorithm to quantify the contribution of each phenotypic feature in predicting treatment choices. Scores range from 0 to 1, with higher scores indicating stronger predictive relevance. The blue histogram overlays this data, highlighting the relative impact of key predictors, such as age, BMI, HbA1c levels, and renal function, on the prescription decision-making process

disease, and heart failure. The stability of these predictors across subgroups suggests alignment between physician decision-making and evidence-based risk stratification. SGLT2is were preferentially prescribed for individuals with overt or early renal impairment, consistent with their evidence from cardiorenal outcome trials and current guideline recommendations [5, 7]. Additionally, predictors such as shorter follow-up intervals and older age further distinguished patients receiving SGLT2is, indicating their use in individuals with closer clinical monitoring or progressive disease. Even in low-risk Group 1, SGLT2is use was common among older patients with moderate eGFR decline, reflecting early targeting of subclinical risk.

These findings corroborate previous analyses from the AMD Annals Initiative, which showed that the early introduction of SGLT2is may mitigate the long-term cardiovascular consequences of hyperglycemia [23]. They also align with evidence from DAPA-CKD, where early SGLT2i initiation significantly delayed CKD progression and improved survival outcomes [24]. The model's performance in Group 1 (accuracy: 63.7%) further supports its potential for informing individualized, risk-guided therapeutic decisions. In contrast, GLP-1RA prescription patterns were less consistently aligned with cardiovascular or renal profiles. Models showed lower predictive accuracy (31.6%–54.1%), with prescribing more strongly influenced by non-atherosclerotic features such as younger age and higher BMI, regardless of underlying cardiorenal status.

This study also indicates that despite guideline recommendations, patients with comparable cardiovascular or renal risk do not always have equal access to SGLT2is or GLP-1RAs.

The XAI analysis revealed that men were more likely to receive SGLT2is in lower-risk groups (1, 2, and 3), while women were less often treated, even though clinical trials show no increased UTI risk in women [25]. However, in Group 4, where heart failure is common, SGLT2is were used more evenly between sexes, likely due to their strong evidence in heart failure, leading to a more balanced gender distribution [26]. Treatment allocation patterns in this cohort indicated that BMI significantly influences prescribing decisions for SGLT2is and GLP-1RAs, often surpassing clinical indicators more directly associated with cardiovascular and renal outcomes. In Groups 2, 3, and 4, which include individuals with chronic kidney disease, previous cardiovascular events, or heart failure,

lower BMI remained a key predictor of SGLT2i use, with relevance scores of 0.769, 0.447, and 0.463, respectively (Table 2; Fig. 1). Conversely, traditional risk markers such as reduced eGFR, albuminuria, or older age had lower predictive significance. This implies clinicians may prioritize BMI over cardiorenal risk factors when choosing SGLT2is, potentially leading to underprescribing GLP-1RAs in leaner individuals, even when guideline-based indications exist.

GLP-1RAs were mainly prescribed to younger patients (< 72 years) with higher BMI (>30 kg/m²) and either very low (< 5.5%) or elevated (>8.1%) HbA1c, emphasising their well-established role in metabolic management. However, this narrow phenotypic focus may lead to their underuse in older patients and those with cardiorenal risk. Notably, prescriptions for GLP-1ras were less common in adults over 75 years, despite consistent evidence that reducing major adverse cardiovascular events (MACE) with GLP-1RAs remains effective in older populations [27]. Furthermore, individuals with CKD, a group at increased risk of cardiovascular morbidity, were less likely to receive GLP-1RAs when BMI was < 30 kg/m², despite evidence showing benefits independent of adiposity [15].

The lower predictive accuracy for GLP-1RAs prescriptions across all groups (31.6%–54.1%) may reflect the lack of structured criteria guiding their use in high-risk populations. These findings raise concerns that current prescribing practices could lead to missed cardiovascular and renal protection opportunities in patients outside traditional metabolic profiles. In a setting where both drug classes offer complementary benefits, ensuring equitable access based on clinical risk rather than age or body size remains crucial.

These findings highlight the need for a balanced, evidence-based approach in prescribing GLP-1RAs and SGLT2is, noting that while SGLT2is practices align with guidelines, there's room to improve GLP-1RA use in high-risk CKD populations [13, 15]. First, the benefits of these two drug classes, cardiorenal protection and glycemic and weight control, highlight the need for combination therapies for patients with overlapping risks [28, 29]. We did not analyze concomitant or sequential SGLT2i–GLP-1RA use, so patterns and demographic influences on combination therapy were not assessed. Furthermore, achieving a more balanced gender distribution in prescribing is crucial, especially given that women with obesity are more likely to develop heart failure with preserved ejection fraction (HFpEF) [30]. In this condition, the SGLT2is class has demonstrated significant benefits [31, 32], beyond those proven for GLP1-RAs in T2D [33]. Finally, GLP-1RAs offer anti-inflammatory and cardioprotective benefits, potentially independent of weight loss [34], and should be considered for patients with lower BMI, countering bias in current prescribing practices. AI tools could be developed to alert clinicians to potential disparities in real-time prescribing patterns, promoting more equitable decision-making [19].

### Limitations

This study has limitations, the study relied on EHR data within a cross-sectional design, which precludes causal inference and does not allow us to track longitudinal changes such as treatment switching or sequential use of drug classes. EHR data are also subject to incomplete or missing information, potential misclassification, and variability in data recording practices across centers, which may have influenced our analyses. Notably, albuminuria data were incomplete, with values available in fewer than 40% of patients across all groups (see Supplementary Table W). As a result, Group 3 only included the secondary prevention phenotype (Atherosclerotic Cardiovascular Disease), excluding the primary prevention phenotype of High CVD Risk, and Group 2's criteria were based solely on eGFR < 60 mL/min/1.73 m². In the subset of patients with available measurements, albuminuria was not independently associated with prescription patterns in multivariable models once age, BMI, HbA1c, and renal function were accounted for. Given both the extent of missingness and the absence of a robust independent effect, albuminuria was excluded from subgroup definitions. While methodologically justified, this decision limits the ability to assess its potential role in treatment allocation fully. The cross-sectional design precludes disentangling physician preference from patient-related factors (e.g., aversion to GLP-1RA injections) and did not allow longitudinal outcome assessment (MACE, CKD progression, mortality); thus, it remains uncertain whether observed disparities, such as BMI-driven underuse of GLP-1RAs, translate into long-term risk. We were also unable to characterise SGLT2i–GLP-1RA combination therapy or assess whether its use varies by demographic factors. Finally, although sex disparities in SGLT2i prescribing were identified, the study design does not permit evaluation of potential drivers, such as physician concern about urinary tract infections in women despite trial data showing no increased risk. Although these findings are broadly generalisable, the study population mainly consists of Caucasian individuals, which may restrict their relevance to other ethnic groups.

## Conclusions

SGLT2i prescribing generally aligned with guideline-based risk profiles and demonstrated high consistency across phenotypic subgroups. Nevertheless, disparities remain in certain high-risk groups, particularly women and individuals with lower BMI, who appeared less likely to receive SGLT2is despite clear cardiorenal indications.

Conversely, factors influencing GLP-1RA prescriptions were less aligned with current cardiovascular and renal guidelines, mainly driven by age and BMI rather than objective risk factors.

This analysis highlights the need for a more holistic, risk-focused approach to therapeutic decision-making in type 2 diabetes, with increased emphasis on cardiorenal protection and the judicious use of combination therapies. These findings highlight the potential for integration into clinical decision support systems, where explainable AI models could be embedded within EHR platforms to provide physicians with transparent, phenotype-driven recommendations at the point of care. By flagging potential mismatches between guideline-based eligibility and actual prescription patterns, such systems may help to reduce inequities and align therapeutic decisions with evidence-based priorities.

## Supplementary Information

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Supplementary Material 1

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**Author contributions**
G. Russo, S. De Cosmo and R. Zilich contributed to the conception, design, and data analysis of the study. D. Tuccinardi drafted the manuscript and contributed to the data analysis. P. Ponzani, N, Musacchio, V. Manicardi, A. Rocca, R. Pontremoli, P. Fioretto, G. A. Muscarà, Di Cianni, R. Candido critically revised it for important intellectual content. All authors reviewed and approved the final manuscript. R. Zilich is the guarantor of this work, having had full access to all the data and taking responsibility for the integrity of the data and the accuracy of the analysis.

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**Data availability**
The datasets analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

## Declarations

**Ethics approval and consent to participate**
This study was conducted in accordance with the principles of the Declaration of Helsinki and national guidelines on using anonymised healthcare data. Under national regulations for retrospective studies involving de-identified electronic health records, ethical approval and patient consent were waived.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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