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RESEARCH ARTICLE

Predictors of efficacy of Sodium-GLucose Transporter-2 inhibitors and Glucagon-Like Peptide 1 receptor agonists: A retrospective cohort study

Daniele Scoccimarro | Giacomo Cipani | Ilaria Dicembrini | Edoardo Mannucci

University of Florence, Diabetology and Metabolic Diseases, Careggi Hospital, Firenze, Italy

Correspondence
Edoardo Mannucci, Diabetology and Metabolic Diseases, Careggi Hospital; Department of Biomedical, Experimental and Clinical Sciences "Mario Serio", University of Florence, Largo Brambilla 3, Florence 50134, Italy.
Email: edoardo.mannucci@unifi.it

Abstract

Aims: The aim of the present study was to verify predictors of HbA1c reduction with Sodium-GLucose Transporter-2 (SGLT2) inhibitors and Glucagon-Like Peptide 1 (GLP1) receptor agonists in routine clinical practice.

Materials and Methods: A retrospective cohort study was performed, enrolling patients with type 2 diabetes aged ≥18 years who received a prescription of an SGLT2 inhibitor or a long-acting GLP1 receptor agonist with at least 6 months of persistence in therapy. Therapeutic success was defined as HbA1c reduction >10 mmol/mol or attainment of the recommended HbA1c target.

Results: Out of 236 patients receiving SGLT2 inhibitors, 148 were categorised as successes: successes had a mean lower age and higher estimated Glomerular Filtration Rate than failures, but only age retained statistical significance at multivariate analysis (Odds Ratio with 95% confidence interval: 0.94 [0.91–0.98], $p = 0.006$). In the GLP1 receptor agonists cohort ($N = 214$) there were 146 successes, showing a significantly shorter duration of diabetes even after adjusting for age, and baseline HbA1c (HR 0.96 [0.91–0.99], $p = 0.02$).

Conclusions: The present study is a preliminary exploration of factors associated with HbA1c response to SGLT2 inhibitors and GLP1 receptor agonists. Differences in predictors of HbA1c changes across different classes of drugs could be useful in identifying the most suitable drug in individual patients. SGLT2 inhibitors seem to be associated with a greater reduction of HbA1c in younger subjects, and GLP1 agonists in those with a shorter duration of diabetes.

KEYWORDS
GLP1 receptor agonists, HbA1c, SGLT2 inhibitors, type 2 diabetes

1 | INTRODUCTION

Sodium-GLucose Transporter-2 (SGLT2) inhibitors and Glucagon-Like Peptide 1 (GLP1) receptor agonists are widely used as second line or first-line[1,2] drugs in the treatment of type 2 diabetes. Current guidelines often offer a variety of therapeutic options without expressing a clear priority across different classes.[1–3] In clinical practice, the preference for one class over the other in individual patients is mainly based on the profile of action of different drugs, including the effects on parameters different from hyperglycemia (e.g., nephroprotection, cardiovascular risk reduction, weight loss, reduction of blood pressure, etc.), matched with patients' characteristics. For example, the American Diabetes Association/European Association for the Study of Diabetes Consensus documents recommend SGLT2 inhibitors in patients with predominant renal disease, and GLP1-receptor agonists in those with predominant cardiovascular disease.[1]

The effect of each drug on glucose control differs in individual patients; for instance, GLP1 receptor agonists, which are on average very effective on HbA1c, have been reported to fail to determine relevant improvement of this parameter approximately in 30% of patients.[4,5]

Several attempts have been made to discriminate the heterogeneity of patients with type 2 diabetes, which are possibly useful for the prediction of treatment response to different drugs. On the basis of some clinical parameters, a cluster approach allowed the identification of subgroups of patients at higher risk of needing insulin treatment[6]; to our knowledge, however, such clusters have never been used to predict the response to specific non-insulin treatments for type 2 diabetes. The effect of different drugs on blood glucose is moderated by some genetic factors: for example, specific alleles of some genes are associated with a greater response to metformin, sulfonylureas, pioglitazone, Dipeptidyl peptidase 4 inhibitors/GLP1-receptor agonists.[7] However, only a small fraction of the variability of response to treatment is predicted by genetic markers known to date[8]; as a consequence, genetic mapping cannot be considered, at present, a feasible strategy for the clinical characterisation of patients aimed at selecting the most appropriate drugs. The most straightforward approach for the identification of predictors of HbA1c response to a drug is the analysis of subgroups of patients enroled in clinical trials. Such analyses allowed, for example, the identification of impaired renal function as a predictor of poor response to SGLT2 inhibitors.[9] On the other hand, subgroup analyses are often missing in reports of phase III trials. The attempt at meta-analysing subgroups of patients from different clinical trials to gain some insight into predictors of reduction of HbA1c and body weight with GLP1 receptor agonists provided only partial results.[10] The enrolment in randomized trials of selected patients, with many exclusion criteria and an accurate follow-up procedure, could reduce the variability of response,[11] thus preventing the observation of relevant predictors. For this reason, observational studies may add relevant information.

The aim of the present study was to verify predictors of HbA1c reduction with SGLT2 inhibitors and GLP1 receptor agonists in routine clinical practice.

2 | MATERIALS AND METHODS

2.1 | Inclusion criteria

A retrospective cohort study was performed, enrolling patients with type 2 diabetes aged ≥18 years, referring to the Diabetes Outpatient Clinic of Careggi Hospital, Florence, between October 1st and 31 October 2020, who had received a prescription of an SGLT2 inhibitor or a long-acting GLP1 receptor agonist any time before 1 October 2018, with at least 6 months of persistence in therapy after the first prescription, and who provided their informed consent, with no other exclusion criteria. Persistence was defined as the maintenance of the same therapy according to current therapy recorded in clinical records based on follow-up visit interview.

2.2 | Retrieved data and outcomes

Demographic and clinical characteristics of patients at the date of prescription (age, gender, duration of diabetes, pharmacological treatments, comorbidities, diabetic complications, body mass index (BMI), blood pressure, HbA1c, lipid profile, creatinine, microalbuminuria) were retrieved from patients' clinical records; estimated Glomerular Filtration Rate (eGFR) was calculated using the CKD-EPI algorithm.[12] HbA1c levels after 6 months from the initiation of therapy were recorded for each patient. Treatment was considered as a success, with respect to glycaemic control, in case of either HbA1c reduction of at least 10 mmol/mmol, or when achieving HbA1c goals recommended by Italian Society of Diabetology/Medical Diabetologists Association (SID/AMD) standards of care.[13] Those goals were:

1. in patients not treated with antidiabetics capable of causing hypoglycemia (insulin, sulphonylureas/glinides), HbA1c ≤ 48 mmol/mol if aged ≤75 years, HbA1c ≤ 53 mmol/mol if aged >75 years or with multiple comorbidities;
2. in patients using drugs potentially causing hypoglycemia, HbA1c between 48 and 58 mmol/mol if aged ≤75 years, HbA1c between 53 and 64 mmol/mol if aged >75 years or with multiple comorbidities.

2.3 | Statistical analysis

Patients with missing data were excluded from each analysis. Success and failures were compared using two-tailed *t* tests and chi square tests for continuous and categorial variables, respectively. In addition, in order to adjust for confounders, a multivariate logistic regression analysis was performed, with success as the outcome, and age, and patients' characteristics significantly ($p < 0.05$) associated with success at univariate analysis as covariates. Statistical significance was set at $p < 0.05$. Statistical analysis was performed using IBM SPSS Statistics 25.0. Assuming a 30% proportion of failures, a

sample of 206 patients would have been sufficient to detect the effect of an evenly distributed categorial parameter with a relative risk of 1.66, with *a* and ß 0.05 and 0.80, respectively.

2.4 | Ethics and funding

The study protocol was approved by the local Ethical Board of Florence (Ref. 18526_oss/2020) and was performed as part of the institutional activity of the investigators with no specific funding. The study was reported following STROBE[14] recommendations (Table S1 of Supplementary Material).

3 | RESULTS

3.1 | Baseline characteristics

The characteristics of the samples enroled are summarised in Table 1, whereas the proportion with missing data for each variable is reported in Supplementary Table S2. Twelve patients were excluded because they did not provide their informed consent. None of the included patients received a combined treatment with SGLT2 inhibitors and GLP1 agonists, which had not yet been approved by regulatory authorities at the time of enrolment. The mean age, duration of diabetes and baseline HbA1c levels were similar in the two cohorts. The mean BMI was above 30 kg/m^2 in both the SGLT2 inhibitor and GLP1 receptor agonist cohorts.

3.2 | Response to Sodium-GLucose Transporter-2 inhibitors

In the SGLT2 inhibitor cohort, 88 patients were categorised as failures out of 236 participants. Failures had a mean higher age (67.1 ± 8.5 vs. 62.2 ± 10.2; $p < 0.05$) and lower eGFR (84.4 ± 18.8 vs. 89.5 ± 17.6; $p < 0.05$) than successes; no other significant difference was detected for any considered parameter, including the duration of diabetes (Table 1). At multivariate analysis (Figure 1 Panel A), which included age and eGFR, the association of success on HbA1c with lower age (Odds Ratio [OR] with 95% confidence interval: 0.94 [0.91–0.98] per year, $p = 0.006$), but not with reduced eGFR (OR 0.99 [0.97–1.01] per ml/min, $p = 0.61$), retained statistical significance.

3.3 | Response to Glucagon-Like Peptide 1 receptor agonists

In the GLP1 receptor agonist cohort ($N = 214$), there were 68 failures and 146 successes on HbA1c. Failures showed a significantly longer duration of diabetes (15.6 ± 8.7 vs. 12.1 ± 8.3; $p < 0.01$) and lower total cholesterol (164 ± 33 vs. 177 ± 41; $p < 0.05$) in comparison with successes; no significant difference was detected for age, BMI, or any other patients' feature (Table 2). The proportion of failures was not significantly different in patients with BMI below or above 30 kg/m^2 (37.7% vs. 24.2%, $p = 0.08$). At multivariate analysis (Figure 1 Panel B), which included age, duration of diabetes, baseline HbA1c and total cholesterol, success on HbA1c was associated with a shorter duration of diabetes (OR 0.96 [0.91–0.99] per year, $p = 0.02$), whereas the associations with age, baseline HbA1c and total cholesterol did not reach statistical significance (OR 0.99 [0.96–1.02] per year, $p = 0.52$, 1.01 [1.00–1.03] per mmol/mol, $p = 0.64$, and 1.02 [1.01–1.03] per mg/dL, $p = 0.31$, respectively).

4 | DISCUSSION

Many different drugs are currently available for the treatment of type 2 diabetes. The choice of the most suitable drug (or combination of drugs) for each patient is often mainly based on the effects of treatment other than the reduction of HbA1c, which may be particularly beneficial in some individuals, for example, reduction of major cardiovascular events in patients with high cardiovascular risk, nephroprotection in those with incipient nephropathy, weight loss in obese subjects, etc.[1] On the other hand, clinical trials show that the effects of drugs on HbA1c, which is still a major therapeutic target,[13] are heterogeneous. Although the initial glycaemic response to a drug could be a predictor of its longer-term efficacy on glucose control,[15] it would be clinically useful to identify predictors of response even before initiating a treatment.

Retrospective observational studies on cohorts of patients receiving different treatments could be a useful alternative source of information collected in routine clinical practice. In the present study, we identified some potential predictors of therapeutic success with respect to HbA1c for SGLT2 inhibitors and GLP1 agonists.

The higher risk of failure to SGLT2 inhibitors in patients with impaired renal function has already been observed in clinical trials.[16,17] In the present study, such an association was not significant at multivariate analysis after adjusting for confounders. However, SGLT2 inhibitors, which are now indicated in the treatment of chronic renal disease regardless of diabetes, were not approved or reimbursed for renally impaired patients at the time of enrolment; as a consequence, the whole sample was composed of individuals with relatively preserved renal function. This study cannot therefore provide reliable information on the effect of renal impairment on the efficacy of SGLT2 inhibitors. Interestingly, the proportion of success (with respect to the attainment of HbA1c targets) was smaller in older individuals. This association of a smaller reduction of HbA1c with SGLT2 inhibitors in older patients has not been previously described. Interestingly, the proportion of failures in the elderly retains statistical significance even after adjusting for estimated glomerular filtration; however, the estimation of glomerular filtration rate on the basis of serum creatinine is problematic in advanced age.[18] It should be noted that a greater proportion of failures on HbA1c in elderly patients does not necessarily imply that these drugs have a smaller nephroprotective effect in this population[19]; however,

TABLE 1 Baseline characteristics of patients treated successfully and not with Sodium-GLucose Transporter-2 (SGLT2)-inhibitors, and total sample.

	Treatment with SGLT-2 inhibitor			
Characteristics	**Total sample**	**Success**	**Failure**	***p*-value**
Number	236	148	88	-
Treatment (*n*, %)				
Empagliflozin	172 (72.9)	102 (68.9)	70 (79.5)	0.06
Dapagliflozin	51 (21.6)	34 (23.0)	17 (19.3)	
Canagliflozin	13 (5.5)	12 (8.1)	1 (1.1)	
Gender (female)	107 (45.3)	67 (45.3)	40 (45.5)	0.97
Age (years)	64.1 ± 9.9	62.2 ± 10.2	67.1 ± 8.5	<0.001
Age at diagnosis (years)	50.9 ± 10.6	50 ± 10.4	52.4 ± 10.7	0.10
Duration of diabetes (years)	13.2 ± 9.8	12.3 ± 9.8	14.6 ± 9.7	0.08
Medical history (*n*, %)				
Diabetic foot	5 (2.1)	2 (1.4)	3 (3.4)	0.29
Diabetic neuropathy	37 (20.1)	24 (20.6)	13 (19.4)	0.58
Diabetic retinopathy	26 (11.5)	13 (9.4)	13 (14.9)	0.20
Microalbuminuria	56 (25.5)	33 (24.6)	23 (26.7)	0.72
Ischemic heart disease	61 (26.0)	38 (25.9)	23 (26.1)	0.96
Stroke or TIA[a]	6 (2.5)	3 (2.0)	3 (3.4)	0.51
Cancer	33 (14.0)	23 (15.5)	10 (11.4)	0.25
Treatment (*n*, %)				
Metformin	198 (83.9)	124 (83.8)	74 (84.1)	0.95
Sulphonylurea	12 (5.1)	6 (4.1)	6 (6.8)	0.35
Pioglitazone	8 (3.4)	3 (2.0)	5 (5.7)	0.13
Acarbose	20 (8.5)	9 (6.1)	11 (12.5)	0.09
Insulin	91 (38.6)	60 (40.5)	31 (35.2)	0.42
Antihypertensive	188 (79.7)	113 (76.4)	75 (85.2)	0.10
Statin	154 (65.3)	90 (60.8)	64 (72.7)	0.06
Antiplatelet	113 (47.9)	65 (43.9)	48 (54.5)	0.11
BMI (kg/m^2)	31.4 ± 6.1	31.7 ± 6.2	31.0 ± 5.8	0.48
Systolic pressure (mmHg)	136 ± 16	137 ± 15	134 ± 16	0.20
Diastolic pressure (mmHg)	79 ± 9	79 ± 10	77 ± 8	0.17
HbA1c (mmol/mol)	64.3 ± 15.1	63.3 ± 17.2	65.9 ± 10.5	0.15
eGFR[b] (mL/min)	87.6 ± 18.2	89.5 ± 17.6	84.4 ± 18.8	<0.05
Total cholesterol (mg/dL)	171 ± 41	171 ± 43	170 ± 39	0.89
HDL cholesterol (mg/dL)	46 ± 14	46 ± 13	47 ± 15	0.76
Triglycerides (mg/dL)	161 ± 91	156 ± 77	170 ± 110	0.32

Note: Success is intended as HbA1c reduction of at least 10 mmol/mol or achieving HbA1c goals.
Data are expressed as *mean* ± *standard deviation* or *number* (%).

Abbreviation: BMI, body mass index.

[a]Transient ischaemic attack.

[b]estimated Glomerular Filtration Rate.

specific data on patients older than 75 years are not available.[19–21] Notably, in contrast with previous reports,[22,23] the reduction of HbA1c with SGLT2 inhibitors was not significantly associated with the duration of diabetes, despite a nonsignificant trend towards lower efficacy in patients with a longer duration of disease; the limited sample size might have prevented the detection of a

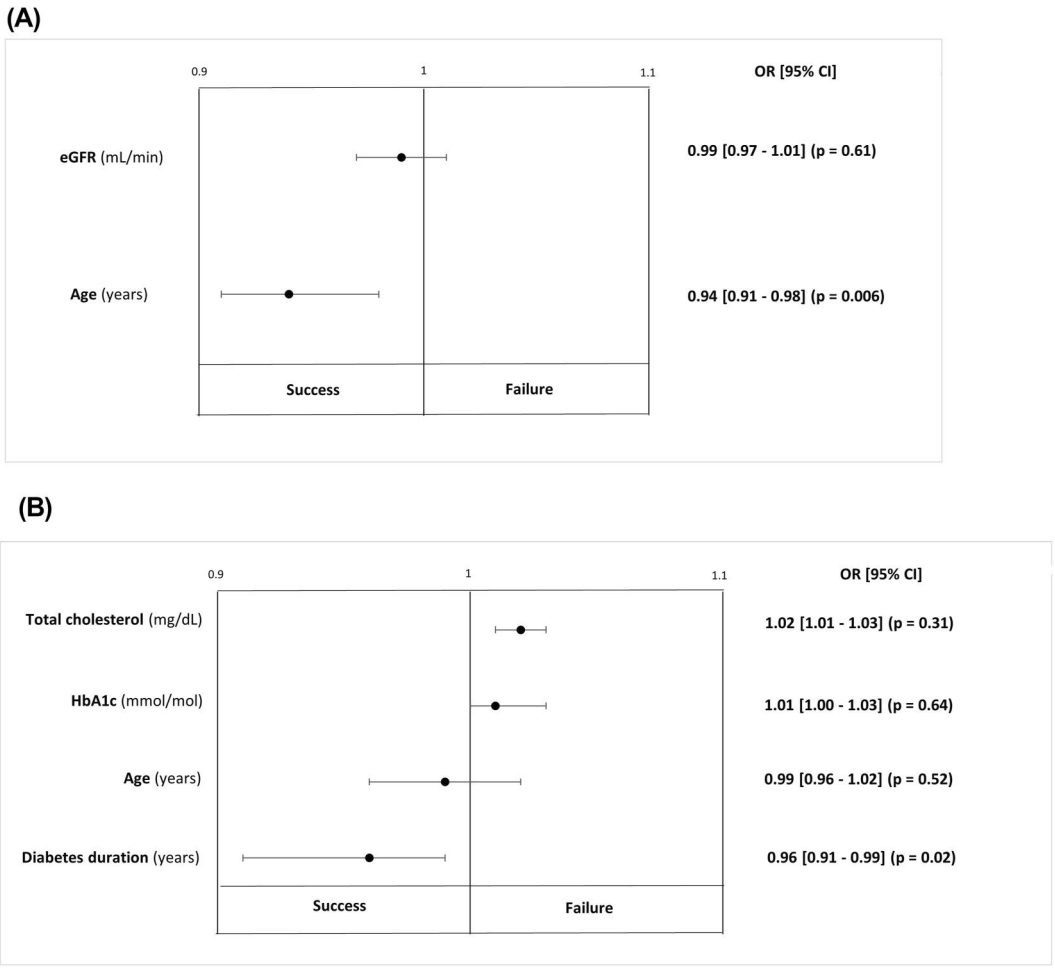

FIGURE 1 Panel A. Multivariate regression analysis for predictors of success with Sodium-GLucose Transporter-2 (SGLT2)-inhibitors. Panel B. Multivariate regression analysis for predictors of success with Glucagon-Like Peptide 1 (GLP1) receptor agonists. Success is intended as HbA1c reduction of at least 10 mmol/mol or achieving HbA1c goals. OR, Odds Ratio; eGFR, estimated Glomerular Filtration Rate.

significant difference. On the other hand, the reduction of HbA1c during treatment with GLP1 receptor agonists appears to be smaller in those with a long duration of diabetes, even after adjusting for confounders. This is not surprising, since the therapeutic action of these drugs is largely mediated by the stimulation of glucose-dependent insulin secretion[24]; the response to GLP1 and its analogues depends therefore on a sufficient ß cell functional mass, which declines with the duration of diabetes.[25] Conversely, the reduction of HbA1c with GLP1 receptor agonists was unaffected by patients' age. In addition, there is no moderating effect of BMI on HbA1c reduction with GLP1 receptor agonists, which appears to be similar in obese and lean patients. This latter result is in line with reports from randomized clinical trials[26] and cohort studies.[27] The effect of initial HbA1c on the incidence of treatment failure depends on the definition of success: if success is defined as the attainment of pre-defined target HbA1c levels, a higher HbA1c level should be expected to be associated with a higher proportion of failures; on the other hand, if success is defined as a pre-determined absolute reduction of HbA1c levels, such a target could be easier to reach in patients with higher baseline HbA1c. In the present study, with a combined definition of success, including both the attainment of treatment goals and/or a reduction of HbA1c of at least 10 mmol/mol, no significant association of treatment failure with baseline HbA1c levels was detected. The present study is intended to be a preliminary exploration of factors associated with HbA1c response to SGLT2 inhibitors and GLP1 receptor agonists. An observational study is inevitably affected by an allocation bias, which cannot be eliminated by statistical adjustments; therefore, the observed associations between changes in HbA1c levels after beginning therapy and clinical parameters could have been determined, at least partly, by undetected or unadjusted confounders. In fact, other characteristics of patients different from HbA1c, and most notably cardiovascular risk and renal impairment, can differentially affect prescription patterns for the two classes, irrespective of glucose control. The relatively small sample size could have prevented the observation of the relevant association. The size of the sample did not allow a specific analysis of the effects of changes in doses of the same drug. Changes in the doses of concurrent therapies could also have interfered with the results. Furthermore, since the data were retrospectively extracted from routine clinical records, the proportion of missing data was relevant

TABLE 2 Baseline characteristics of patients treated successfully and not with GLP1-RA, and total sample.

Characteristics	Treatment with GLP1-RA			
	Total sample	Success	Failure	*p*-value
Number	214	146	68	-
Treatment (*n*, %)				
Liraglutide	107 (50)	71 (48.6)	36 (52.9)	0.55
Dulaglutide	107 (50)	75 (51.4)	32 (47.1)	
Gender (female)	106 (49.5)	74 (50.7)	32 (47.0)	0.62
Age (years)	64.6 ± 10.0	63.9 ± 9.7	65.9 ± 10.7	0.18
Age at diagnosis (years)	51.6 ± 11.2	51.9 ± 10.4	50.8 ± 12.8	0.54
Duration of diabetes (years)	13.2 ± 8.6	12.1 ± 8.3	15.6 ± 8.7	<0.01
Medical history (*n*, %)				
Diabetic foot	4 (1.9)	4 (2.7)	0 (0.0)	0.12
Diabetic neuropathy	38 (17.7)	23 (15.7)	15 (22.0)	0.32
Diabetic retinopathy	31 (15.3)	18 (12.3)	13 (19.1)	0.17
Microalbuminuria	43 (21.8)	30 (20.5)	13 (19.1)	0.17
Ischemic heart disease	48 (22.4)	31 (21.2)	17 (25.0)	0.53
Stroke or TIA[a]	14 (6.5)	11 (7.5)	3 (4.4)	0.39
Cancer	22 (10.3)	13 (8.9)	9 (13.2)	0.33
Treatment (*n*, %)				
Metformin	190 (88.8)	127 (87.0)	19 (27.9)	0.22
Sulphonylurea	9 (4.2)	6 (4.1)	3 (4.4)	0.91
Pioglitazone	30 (14.0)	21 (14.4)	9 (13.2)	0.82
Acarbose	28 (13.1)	17 (11.6)	11 (16.2)	0.36
Insulin	67 (31.3)	100 (68.5)	46 (67.6)	0.93
Antihypertensive	162 (75.7)	109 (74.6)	53 (72.9)	0.60
Statin	139 (65.0)	94 (64.4)	45 (66.2)	0.80
Antiplatelet	98 (45.8)	64 (43.8)	34 (50.0)	0.40
BMI (kg/m^2)	32.5 ± 6.1	32.5 ± 5.4	32.4 ± 7.6	0.88
Systolic pressure (mmHg)	132 ± 16.0	131 ± 16	135 ± 16	0.13
Diastolic pressure (mmHg)	78 ± 10.0	77 ± 10	79 ± 12	0.51
HbA1c (mmol/mol)	65.5 ± 13.7	65.9 ± 15.7	64.6 ± 8.0	0.41
eGFR[b] (mL/min)	80.3 ± 22.0	81.2 ± 22.0	78.0 ± 22.0	0.34
Total cholesterol (mg/dL)	173 ± 39	177 ± 41	164 ± 33	<0.05
HDL cholesterol (mg/dL)	46 ± 11	46 ± 12	45 ± 10	0.49
Triglycerides (mg/dL)	157 ± 65	154 ± 67	156 ± 61	0.91

Note: Success is intended as HbA1c reduction of at least 10 mmol/mol or achieving HbA1c goals. Data are expressed as *mean* ± *standard deviation* or *number (%)*.

Abbreviation: BMI, body mass index.

[a]Transient ischaemic attack.

[b]estimated Glomerular Filtration Rate.

for some of the variables considered, in particular blood pressure. In addition, the sample studied, which was enroled in a Diabetes Outpatient Clinic of a University Hospital, cannot be considered representative of the whole population of patients with diabetes receiving a treatment with either SGLT2 inhibitors or GLP1 receptor agonists. Furthermore, potential differences in average efficacy on HbA1c between SGLT2 inhibitors and GLP1 receptor agonists could have affected results, since the same definition of success was

adopted for the two classes. Additionally, some parameters potentially affecting drug response (e.g., glucagon secretion for patients receiving SGLT2 inhibitors[28]) were not assessed. Finally, differences between reported and actually administered drugs could not be detected by the present study, in which current treatment was based on patients' interviews during follow-up visits; therefore, this study cannot incorporate data on compliance and/or adherence to the prescribed treatment.

In conclusion, differences in predictors of HbA1c changes across different classes of drugs could be useful for the identification of the most suitable drug in individual patients. SGLT2 inhibitors seem to be associated with a greater reduction of HbA1c in younger subjects, and GLP1 receptor agonists in those with a shorter duration of diabetes. Further studies on larger samples are needed to obtain greater details on possible predictors of therapeutic response to those two classes of drugs.

AUTHOR CONTRIBUTIONS

Daniele Scoccimarro was involved in the design, data collection, analysis, and writing of the manuscript. Giacomo Cipani was involved in data collection. Ilaria Dicembrini was involved in the analysis. Edoardo Mannucci was involved in the design, analysis, and writing of the manuscript. Daniele Scoccimarro and Edoardo Mannucci are the guarantors of this work, and as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST STATEMENT

Daniele Scoccimarro and Giacomo Cipani declare no conflicts of interest. Ilaria Dicembrini has received speaking fees from Novo Nordisk. Edoardo Mannucci has received consultancy fees from Merck and Novartis, speaking fees from AstraZeneca, Bristol Myers Squibb, Boehringer-Ingelheim, Eli-Lilly, Merck, Novo Nordisk, Sanofi and Novartis and research grants from Merck, Novartis and Takeda.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This material is the authors' own original work, which has not been previously published elsewhere. The paper is not currently being considered for publication elsewhere. The paper reflects the authors' own research and analysis in a truthful and complete manner. The paper properly credits the meaningful contributions of the co-authors and co-researchers. The results are appropriately placed in the context of prior and existing research. All sources used are properly disclosed (correct citation). All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

ORCID

Daniele Scoccimarro https://orcid.org/0000-0002-4493-517X
Ilaria Dicembrini https://orcid.org/0000-0001-9759-9408

PEER REVIEW

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REFERENCES

1. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American diabetes association (ADA) and the European association for the study of diabetes (EASD). *Diabetologia*. 2022;65(12):1925-1966. https://doi.org/10.1007/s00125-022-05787-2
2. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. 2020;41(2):255-323. PMID: 31497854. https://doi.org/10.1093/eurheartj/ehz486
3. *Type 2 Diabetes in Adults: Management*. : National Institute for Health and Care Excellence (UK); 2019. PMID: 32023018.
4. Nauck M, Frid A, Hermansen K, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. *Diabetes Care*. 2009;32(1):84-90. Epub 2008 Oct 17. PMID: 18931095; PMCID: PMC2606836. https://doi.org/10.2337/dc08-1355
5. Dungan KM, Povedano ST, Forst T, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. *Lancet*. 2014;384(9951):1349-1357. Epub 2014 Jul 10. Erratum in: Lancet. 2014 Oct 11:384(9951):1348. PMID: 25018121. https://doi.org/10.1016/S0140-6736(14)60976-4
6. Ahlqvist E, Storm P, Käräjämäki A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol*. 2018;6(5):361-369. Epub 2018 Mar 5. PMID: 29503172. https://doi.org/10.1016/S2213-8587(18)30051-2
7. Mannino GC, Andreozzi F, Sesti G. Pharmacogenetics of type 2 diabetes mellitus, the route toward tailored medicine. *Diabetes Metab Res Rev*. 2019;35(3):e3109. Epub 2019 Jan 7. PMID: 30515958; PMCID: PMC6590177. https://doi.org/10.1002/dmrr.3109
8. Nasykhova YA, Tonyan ZN, Mikhailova AA, Danilova MM, Glotov AS. Pharmacogenetics of type 2 diabetes-progress and prospects. *Int J Mol Sci*. 2020;21(18):6842. PMID: 32961860; PMCID: PMC7555942. https://doi.org/10.3390/ijms21186842
9. Zhang L, Zhang M, Lv Q, Tong N. Efficacy and safety of sodium-glucose cotransporter 2 inhibitors in patients with type 2 diabetes and moderate renal function impairment: a systematic review and meta-analysis. *Diabetes Res Clin Pract*. 2018;140:295-303. Epub 2018 Apr 9. PMID: 29649541. https://doi.org/10.1016/j.diabres.2018.03.047
10. Monami M, Dicembrini I, Nreu B, Andreozzi F, Sesti G, Mannucci E. Predictors of response to glucagon-like peptide-1 receptor agonists: a meta-analysis and systematic review of randomized controlled trials. *Acta Diabetol*. 2017;54(12):1101-1114. Epub 2017 Sep 20. PMID: 28932989. https://doi.org/10.1007/s00592-017-1054-2
11. He Z, Wang S, Borhanian E, Weng C. Assessing the collective population representativeness of related type 2 diabetes trials by

combining public data from ClinicalTrials.gov and NHANES. *Stud Health Technol Inf*. 2015;216:569-573.
12. Levey AS, Inker LA, Coresh J. GFR estimation: from physiology to public health. *Am J Kidney Dis*. 2014;63(5):820-834. Epub 2014 Jan 28. PMID: 24485147; PMCID: PMC4001724. https://doi.org/10.1053/j.ajkd.2013.12.006
13. Standard italiani per la cura del diabete mellito 2018. Cura del diabete.
14. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med*. 2007;147(8):573-577. Erratum in: Ann Intern Med. 2008 Jan 15;148(2):168. PMID: 17938396. https://doi.org/10.7326/0003-4819-147-8-200710160-00010
15. Guerci B, Trautmann ME, Lin T, Hardy E, Mudaliar SRD. Predictive factors associated with three years of response to HbA1c goals with exenatide QW or insulin glargine: post-hoc analysis of the DURATION-3 study. *Diabetes Obes Metab*. 2019;21(4):1049-1053. https://doi.org/10.1111/dom.13606
16. Cherney DZI, Cooper ME, Tikkanen I, et al. Pooled analysis of Phase III trials indicate contrasting influences of renal function on blood pressure, body weight, and HbA1c reductions with empagliflozin. *Kidney Int*. 2018;93(1):231-244. Epub 2017 Aug 30. PMID: 28860019. https://doi.org/10.1016/j.kint.2017.06.017
17. Dekkers CCJ, Wheeler DC, Sjöström CD, Stefansson BV, Cain V, Heerspink HJL. Effects of the sodium-glucose co-transporter 2 inhibitor dapagliflozin in patients with type 2 diabetes and Stages 3b-4 chronic kidney disease. *Nephrol Dial Transpl*. 2018;33(11):2005-2011. Erratum in: Nephrol Dial Transplant. 2018 Jul 1;33(7):1280. PMID: 29370424; PMCID: PMC6212718. https://doi.org/10.1093/ndt/gfx350
18. Raman M, Middleton RJ, Kalra PA, Green D. Estimating renal function in old people: an in-depth review. *Int Urol Nephrol*. 2017;49(11):1979-1988. Epub 2017 Sep 15. PMID: 28913589; PMCID: PMC5643354. https://doi.org/10.1007/s11255-017-1682-z
19. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. DAPA-CKD trial committees and investigators. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383(15):1436-1446. https://doi.org/10.1056/nejmoa2024816
20. Perkovic V, Jardine MJ, Neal B, et al. CREDENCE trial investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-2306. https://doi.org/10.1056/nejmoa1811744
21. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. 2019;393(10166):31-39. https://doi.org/10.1016/s0140-6736(18)32590-x
22. Lee JY, Cho Y, Lee M, et al. Predictors of the therapeutic efficacy and consideration of the best combination therapy of sodium-glucose Co-transporter 2 inhibitors. *Diabetes Metab J*. 2019;43(2):158-173. https://doi.org/10.4093/dmj.2018.0057
23. Cho YK, Lee J, Kang YM, et al. Clinical parameters affecting the therapeutic efficacy of empagliflozin in patients with type 2 diabetes. *PLoS One*. 2019;14(8):e0220667. https://doi.org/10.1371/journal.pone.0220667
24. Doyle ME, Egan JM. Mechanisms of action of glucagon-like peptide 1 in the pancreas. *Pharmacol Ther*. 2007;113(3):546-593. Epub 2006 Dec 28. PMID: 17306374; PMCID: PMC1934514. https://doi.org/10.1016/j.pharmthera.2006.11.007
25. Zangeneh F, Arora PS, Dyck PJ, et al. Effects of duration of type 2 diabetes mellitus on insulin secretion. *Endocr Pract*. 2006;12(4):388-393. PMID: 16939949. https://doi.org/10.4158/EP.12.4.388
26. Gentilella R, Sesti G, Vazquez L, et al. Dulaglutide is an effective treatment for lowering HbA1c in patients with type 2 diabetes regardless of body mass index. *Diabetes Obes Metab*. 2019;21(12):2660-2666. Epub 2019 Aug 28. PMID: 31392822. https://doi.org/10.1111/dom.13853
27. Chitnis AS, Ganz ML, Benjamin N, Langer J, Hammer M. Clinical effectiveness of liraglutide across body mass index in patients with type 2 diabetes in the United States: a retrospective cohort study. *Adv Ther*. 2014;31(9):986-999. Epub 2014 Sep 23. PMID: 25245811; PMCID: PMC4176953. https://doi.org/10.1007/s12325-014-0153-5
28. Fukui T, Ohara M, Yamagishi SI. Glucagon in type 1 diabetes patients receiving SGLT2 inhibitors: a Friend or Foe? *Diabetes Metab Res Rev*. 2021;37(5):e3415. https://doi.org/10.1002/dmrr.3415

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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