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ORIGINAL RESEARCH

Protective Effects of Home T2DM Treatment with Glucagon-Like Peptide-1 Receptor Agonists and Sodium-Glucose Co-transporter-2 Inhibitors Against Intensive Care Unit Admission and Mortality in the Acute Phase of the COVID-19 Pandemic: A Retrospective Observational Study in Italy

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ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) is a relevant risk factor for severe forms of COVID-19 (SARS coronavrus 2 [SARS-CoV-2] disease 2019), and calls for caution because of the high prevalence of T2DM worldwide and the high mortality rates observed in patients with T2DM who are infected with SARS-CoV-2. People with T2DM often take dipeptidyl peptidase-4 inhibitors (DPP-4is), glucagon-like peptide-1 receptor agonists (GLP-1ras), or sodium-glucose co-transporter-2 inhibitors (SGLT-2is),

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all of which have clear anti-inflammatory effects. The study aimed to compare (i) the severity and duration of hospital stay between patients with T2DM categorized by pre-hospitalization drug class utilization and (ii) the COVID-19-related death rates of those three groups.

Methods: We designed an observational, retrospective, multi-center, population-based study and extracted the hospital admission data from the health care records of 1916 T2DM patients over 18 years old who were previously on GLP-1ra, SGLT-2i, or DPP-4i monotherapy and were hospitalized for COVID-19 (diagnosis based on ICD.9/10 codes) between January 2020 and December 2021 in 14 hospitals throughout Italy. We analyzed general data, pre-admission treatment schedules, date of admission or transfer to the intensive care unit (ICU) (i.e., the index date; taken as a marker of increased COVID-19 disease severity), and death (if it had occurred). Statistics analyzed the impact of drug classes on in-hospital mortality using propensity score logistic regressions for (i) those admitted to intensive care and (ii) those not admitted to intensive care, with a random match procedure used to generate a 1:1 comparison without diabetes cohort replacement for each drug therapy group by applying the nearest neighbor method. After propensity score matching, we checked the balance achieved across selected variables if a balance was ever achieved. We then used propensity score matching between the three drug classes to assemble a sample in which each patient receiving an SGLT-2i was matched to one on a GLP-1ra, and each patient on a DPP-4i was matched to one on a GLP-1ra, adjusting for covariates. We finally used GLP-1ras as references in the logistic regression.

Results: The overall mortality rate (MR) of the patients was 14.29%. The MR in patients with COVID was 53.62%, and it was as high as 42.42% in the case of associated T2DM, regardless of any glucose-lowering therapy. In those on DPP-4is, there was excess mortality; in those treated with GLP-1ras and SGLT-2is, the death rate was significantly lower, i.e., almost a quarter of the overall mortality observed in COVID-19 patients with T2DM. Indeed, the odds ratio (OR) in the logistic regression resulted in an extremely high risk of in-hospital death in individuals previously treated with DPP-4is [incidence rate (IR) 4.02, 95% confidence interval (CI) 2.2–5.7) and only a slight, nonsignificantly higher risk in those previously treated with SGLT-2is (IR 1.42, 95% CI 0.6–2.1) compared to those on GLP-1ras. Moreover, the longer the stay, the higher the death rate, which ranged from 22.3% for $\leq$ 3-day stays to 40.3% for 4- to 14-day stays ($p < 0.01$ vs. the former) and 77.4% for over-14-day stays ($p < 0.001$ vs. both the others).

Discussion: Our data do not support a protective role of DPP-4is; indeed, this role has already been questioned due to previous observations. However, the data do show a strong protective effect of SGLT-2is and GLP-1ras. Beyond lowering circulating glucose levels, those two drug classes were found to exert marked anti-phlogistic effects: SGLT-2is increased adiponectin and reduced urate, leptin, and insulin concentrations, thus positively affecting overall low-grade inflammation, and GLP-1ras may also greatly help at the lung tissue level, meaning that their extra-glycemic effects extend well beyond those acknowledged in the cardiovascular and renal fields.

Conclusions: The aforedescribed observational clinical data relating to a population of Italian inpatients with T2DM suggest that GLP-1ras and SGLT-2is can be considered antidiabetic drugs of choice against COVID-19, and might even prove beneficial in the event of any upcoming pandemic that has life-threatening effects on the pulmonary and cardiovascular systems.

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Keywords: SARS-CoV-2–19; Diabetes mellitus; DPP-4is; GLP-1ras; SGLT-2is; Protective role

Key Points
Type 2 diabetes mellitus (T2DM) is a relevant risk factor for severe forms of COVID-19 (SARS coronavirus 2 [SARS-CoV-2] disease 2019).
A high prevalence was reported in Italian diabetic patients admitted to intensive care units (ICUs) for severe COVID-19.
dipeptidyl peptidase-4 inhibitors (DPP-4is) and glucagon-like peptide-1 receptor agonists (GLP-1ras) have anti-inflammatory effects which might help protect against COVID-19 and are typically associated with multiple organ inflammation and cytokine storming.
The use of sodium-glucose co-transporter-2 inhibitors (SGLT-2is) promotes encouraging COVID-19 clinical outcomes thanks to their anti-inflammatory effects.
The results of a head-to-head comparison of the effects of taking the three drugs before hospitalization on COVID-19-related hospital mortality clearly indicate that GLP-1ras and SGLT-2is have favorable effects but DPP-4is do not.
These results indicate that GLP-1ras and SGLT-2is are preferred therapeutic options in type 2 diabetics affected by COVID-19.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a relevant risk factor for severe forms of COVID-19 (SARS coronavirus 2 [SARS-CoV-2] disease 2019) [1], and calls for caution because of the high prevalence of T2DM worldwide and the high mortality rates observed in T2DM patients infected with SARS-CoV-2 [2].

According to various studies, a 5% to 36% prevalence of diabetes was estimated in COVID-19 patients [3], and a 17% prevalence of diabetes was reported in Italian patients admitted to intensive care units (ICUs) for severe COVID-19 [4]. In addition, cardiovascular diseases (CVDs) and obesity, which are frequently associated with T2DM, worsen COVID-19 clinical outcomes [5].

Both of the SARS coronaviruses (SARS-CoV-1 and SARS-CoV-2, the causative agent of COVID-19) invade the epithelial cells in the respiratory tract [6] by linking virion surface spike proteins to angiotensin-converting enzyme 2 (ACE2) receptors, which are also known for their role in determining micro- and macrovascular complications in people with diabetes [7].

MERS (Middle East respiratory syndrome) coronavirus, i.e., the second member of the coronavirus family in order of appearance, uses the enzyme dipeptidyl-peptidase-4 (DPP-4) [8] as a cell receptor. DPP-4 degrades glucagon-like peptide-1 (GLP-1), which is involved in the balance of insulin–glucagon secretion [9]; however, in the presence of T2DM, it does not always optimally control the glucose balance [10], thus inducing a chronic low-grade inflammatory condition, which, in turn, sets the stage for the severe expression of COVID-19 [11].

People with T2DM often take DPP-4 inhibitors (DPP-4is) or GLP-1 receptor agonists (GLP-1ras) [12]. All have anti-inflammatory effects, which might help against the multiple organ inflammation and cytokine storming typically associated with COVID-19 [13, 14].

Sodium-glucose co-transporter-2 inhibitors (SGLT-2is), i.e., another innovative class of anti-hyperglycemic drugs endowed with anti-inflammatory properties, have been proven to promote encouraging COVID-19 clinical outcomes through decreased exposure to pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) [15]. Several clinical and experimental studies have witnessed such effects, which apparently depend on decreased uric acid, insulin [16], and leptin blood concentrations [17], increased adiponectin secretion [18], suppression of the advanced glycation

end product (AGE) receptor (RAGE) axis [19]—notoriously responsible for the low-grade inflammation and oxidative stress associated with diabetes [20]—and polarization of monocyte-macrophage cells in the anti-inflammatory M2 phenotype [21].

Although home therapy with SGLT-2is was found to be associated with a lower risk for hospital mechanical ventilation [22], some authors have hypothesized that SGLT-2is may also enhance the expression of ACE-2 in the heart and the kidney [23] in such a way as to exert a favorable effect on SARS-CoV-2 infection. However, to further complicate matters, dapagliflozin recently failed to show any significant effects on the complication or mortality rate in patients with cardiovascular risk factors hospitalized for COVID-19 [24].

On the contrary, no conclusive data have been published on the effects of other hypoglycemic drugs on the clinical course of SARS-Cov-2 infection, except for metformin, which seems to help reduce both hospitalization and mortality risk [25], especially in obese women [26]. Moreover, the inpatient use of metformin or acarbose was associated with reduced COVID-19 mortality in T2DM [27]; however, their lower hypoglycemic potential and typical utilization in people with less severe T2DM forms [28] could have resulted in the selection of clusters of patients with less severe diabetes and related complications, thus introducing a bias into the overall assessment of the effect of hypoglycemic drugs in patients with COVID-19 and DM, and suggesting the need for further studies to dispel pending doubts about the safe in-hospital use and efficacy of those drugs.

In this article, we discuss the possible protective potential of GLP-1ras, SGLT-2is, and DPP-4is against subsequent COVID-19 hospitalization regarding disease course and mortality (death rate).

The aim of our paper was to compare:

1. The severity and duration of hospital stay between three groups of T2DM patients who were grouped based on the pre-hospitalization drug class they used: GLP-1ras, SGLT-2is, or DPP-4is
2. The COVID-19-related death rates of those three groups.

METHODS

Study Design

We designed the investigation as an observational, retrospective, multi-center, population-based study and extracted the hospital admission data from the health care records of the patients, none of whom were directly contacted.

We selected subjects with type 2 diabetes who were older than 18 years and hospitalized for COVID-19 (with the diagnosis based on ICD.9/10 codes) between January 2020 and December 2021 in 14 hospitals throughout Italy. We analyzed general data, pre-admission treatment schedules, date of admission or transfer to the intensive care unit (ICU) (i.e., the index date; taken as a marker of increased COVID-19 disease severity), and death (if it occurred) of only those who had been recorded as taking GLP-1ras, SGLT-2is, or DPP-4is as monotherapy at least twice (within a time interval of at least 6 months) before hospitalization.

We excluded those on other hypoglycemic drugs to reduce biases from expected confounding factors as follows: (i) insulin treatment could reflect greater clinical severity in T2DM; (ii) secretagogues carry potential cardiotoxicity or nephrotoxicity; and (iii) metformin might increase the risk for ketoacidosis in the case of respiratory disease, despite its beneficial effects on inflammation. Moreover, secretagogues and metformin have been limited to a secondary role in the latest American Diabetes Association (ADA) Standards of Care [28].

In particular, we need to remind the reader that, in the first months of the pandemic, COVID-19 cases dramatically increased within a few days, thus causing a severe shortage of hospital beds. Therefore, sub-intensive and intensive care wards were also used to cope with the high demand until beds became available again in ordinary wards. In general, patients

with severe COVID-19 could not be transferred to the ordinary wards again, and they stayed in sub-intensive or intensive care beds for over a certain number of days, which was suggestive of severe disease. Based on the average duration of hospital stays for non-severely ill patients before transfer to ordinary beds, we arbitrarily chose an over-3-day stay as a marker of disease severity.

We identified treatments using the Anatomical Therapeutic Chemical (ATC) drug classification: DDP-4is as ATC A10BH, GLP1-ras as ATC A10BJ, and SGLT-2is as ATC A10BK.

We classified comorbidities according to the ICD.9/10 codes. They included myocardial infarction, cardiac arrhythmias, cardiac valvulopathies, hypertension, congestive heart failure (CHF), peripheral vascular disease, stroke, chronic obstructive pulmonary disease (COPD), pulmonary circulation disorders, rheumatoid disease, peptic ulcer disease, liver disease, paralysis and other neurological disorders, chronic kidney disease, cancer with/without metastasis, and hypothyroidism. The Charlson comorbidity index (CCI), a prognostic, predictive index of severity and life expectancy in patients with multiple comorbidities, helped us to individually identify the overall impact of comorbidities, treatment, and hospital discharge [29]. We calculated the previous hospitalization rate ($\times$ 1000) as the number of in-hospital stays during the 2 years before the index date.

Ethical Approval

This study complied with good clinical practice standards and followed the ethical guidelines of the 1964 Declaration of Helsinki and its subsequent amendments. The study protocol was approved by the IRB (trial registration: Protocol n. 5, May 16, 2022), and the Ethical and Scientific Committee of the reference center, the Department of Endocrinology, San Raffaele Pisana Clinical Research Institute, Rome, Italy, served as the central reference ethical committee for the 14 affiliated hospitals contributing to the study. All subjects with T2DM who participated in the study signed an informed consent form before being included in the present investigation.

Statistical Analysis

We analyzed the data using SAS 9.1 software and assessed the impact of drug classes on in-hospital mortality using the double propensity score logistic regression: (i) intensive care admission and (ii) no-intensive care admission.

We considered potential confounders, i.e., variables associated with drug choice (age, gender, previous hospitalization, Charlson index), and used them to calculate the propensity score.

We used a random match procedure to generate a 1:1 comparison without diabetes cohort replacement for each drug therapy group by applying the nearest neighbor method. After propensity score matching, we checked the balance achieved across selected variables, if so, ever.

We then used propensity score matching between the three drug classes to assemble a sample in which each patient receiving an SGLT-2i was matched to one on a GLP-1ra, and each patient on a DPP-4i was matched to one on a GLP-1ra, adjusting for covariates, as shown in Table 1. We finally used GLP-1ras as references in the logistic regression.

We chose these matching goals to reflect the relative number of users in each group and matched patients without replacement based on the propensity score within a range of 0.025, i.e., $\sim$ 0.2 times the standard deviation of the propensity score. We obtained the estimated propensity scores from the logistic regression. We took an iterative approach to selecting confounders; a potential confounder was included in the model if this was required to ensure that the variable was balanced across treatment groups, as measured by the standardized mean difference. Imbalances of up to 0.2 were accepted.

We reported patient characteristics as mean $\pm$ standard deviation (SD) for continuous variables or number/percentage for categorical variables. We calculated, according to the Poisson regression model, the incidence rate (IR)

Table 1 General characteristics of the enrolled subjects divided up by treatment (DPP-4is, GLP-1ras, SGLT-2is), comorbidities, and summarized in-hospital outcomes

		DPP-4is	GLP-1RAs	SGLT-2is	DPP-4is vs. GLP1-ras	DPP-4is vs. SGLT-2is	GLP1-ras vs. SGLT-2is
n.		1,023	567	326			
Age at COVID-19 admission	M±SD	61±12	55±13	61±8	p<0.001	p=1.000	p<0.001
1st quartile	n	57	56	52	-	-	-
2nd quartile	n	66	64	62	-	-	-
3rd quartile	n	72	74	70	-	-	-
4th quartile	n	88	89	88	-	-	-
Male/Female ratio		0.8	0.8	0.9	p=0.559	p= 0.766	p= 0.491
BMI (kg/m^2)	M±SD range	29.5±2.5 27 - 33	30.1±1.8 27 - 34	29.8±1.7 28 - 34	p= 0.653	p= 0.734	p= 0,429
HbA1c (%)	M±SD range	7.9±1.5 7.1- 8.4	7.8±1.7 7.2 - 8.7	7.7±1.8 7.3 - 8.8	p= 0.765	p= 0.557	p= 0.527
Creatinine (mg/dl)	M±SD range	1.1±0.4 0.8 -1.4	1.1±0.6 0.8 -1.5	1.2±0.4 0.9 - 1.6	p= 0.874	p=881	p= 0.698
Previous Hospitalization	M±SD	8±3	5±3	6±5	p<0.001	p<0.001	p<0.001
COMORBIDITIES							
Heart Failure	%	3.9	3.2	3.3	p= 0.527	p = 0.725	p = 0.931
Cardio-Vascular Disease	%	7.7	7.9	7.5	p= 0.387	p= 0.441	p= 0.817
Lipid-lowering agents	%	70.5	72.2	70.6	p= 0.774	P = 0.867	p= 0.927
Stroke	%	6.6	3.2	5.5	p=0.063	p=0.413	p = 0.146
Hypertension	%	10.2	8.4	9.5	p= 0.265	p=0.755	p = 0.569
COPD	%	9.3	9.7	8.2	p= 0.806	p=0.912	p= 0.932
Hypothyroidism	%	8.2	6.1	3.3	p= 0.132	P=0.005	p = 0.082
Charlson Index	M±SD	8.7±5	9.2±4	8.6±4	p=0.409	p = 0.742	p = 0.031
High Charlson Index score	%	+19%	+18%	+25%	p= 0.692	p = 0.065	p = 0.048
SUMMARIZED IN-HOSPITAL OUTCOMES							
Intensive Care Admission	%	47.3	33.9	18.8	p<0.001	P = 0.151	p<0.001
Death Rate	per 1000 n	309 316	100 56	110 36	p<0.001	p<0.001	p = 0.601

DPP-4is dipeptidyl peptidase-4 inhibitors, *GLP-1ras* glucagon-like peptide-1 receptor agonists, *SGLT-2is* sodium-glucose co-transporter-2 inhibitors, *COPD* chronic obstructive pulmonary disease, High CharlsonIndex score: over 13

within the 95% confidence interval (95% CI) for several parameters expressed as the number or percent. We used, as appropriate, analysis of variance (rANOVA) supplemented by the two-tailed paired Student's *t*-test with 95% confidence intervals for parametric variables and the Mann–Whitney U test for nonparametric variables. We implemented the χ^2 test with Yates's correction or Fisher's exact test to achieve categorical variable differentiation. Finally, we considered all p values < 0.05 to be statistically significant.

When writing this manuscript, we followed STROBE (Strengthening the Reporting of Observational Studies in Epidemiology)

guidelines for observational study reporting (see the supplementary material).

RESULTS

The cohort analyzed in the present study pertains to the whole registry, including all hospitalizations in the 14 participating structures, as seen from the flowchart shown in Fig. 1.

Figure 2 depicts the main parameters indicative of COVID-19-related mortality by hypoglycemic class, using DDP-4is as the comparator. The overall mortality rate (MR) of the patients was 14.29%. The MR in COVID patients was 53.62%, and it was as high as 42.42% in the case of associated T2DM regardless of any glucose-lowering therapy. In those on DPP-4is, there was excess mortality. At the same time, in those treated with GLP-1ras and SGLT-2is, the death rate was significantly lower, i.e., almost a quarter of the overall mortality observed in COVID-19 patients with T2DM.

Therefore, according to the inclusion criteria, we enrolled 1,916 patients (Table 1), who were divided into a DPP-4is group (n = 1023; 41%), a GLP-1ras group (n = 567; 22%), and a SGLT-2is group (n = 326; 37%).

Figure 3 depicts the pre-hospitalization distribution by age quartile, which shows no differences among drug classes. Patients in the GLP-1ras group were younger than the others (GLP-1ras: 55 years, DPP-4is and SGLT-2is: 61 years) but displayed the highest prevalence of a high Charlson index score (DPP-4is: 8.7, GLP-1ras: 9.2, SGLT-2is: 8.6) despite a lower, non-significant prevalence of heart failure, stroke, and hypertension, and thus had a higher prevalence of intensive care admission (60%) than the others.

The all-cause mortality rate in the DDP-4is group was the highest (DPP-4is: 309 units of death per 1,000 individuals, GLP-1ras: 100 units of death per 1000 individuals, SGLT-2is: 110 units of death per 1000 individuals). Figures 4 and 5 display the COVID-19-related death rate

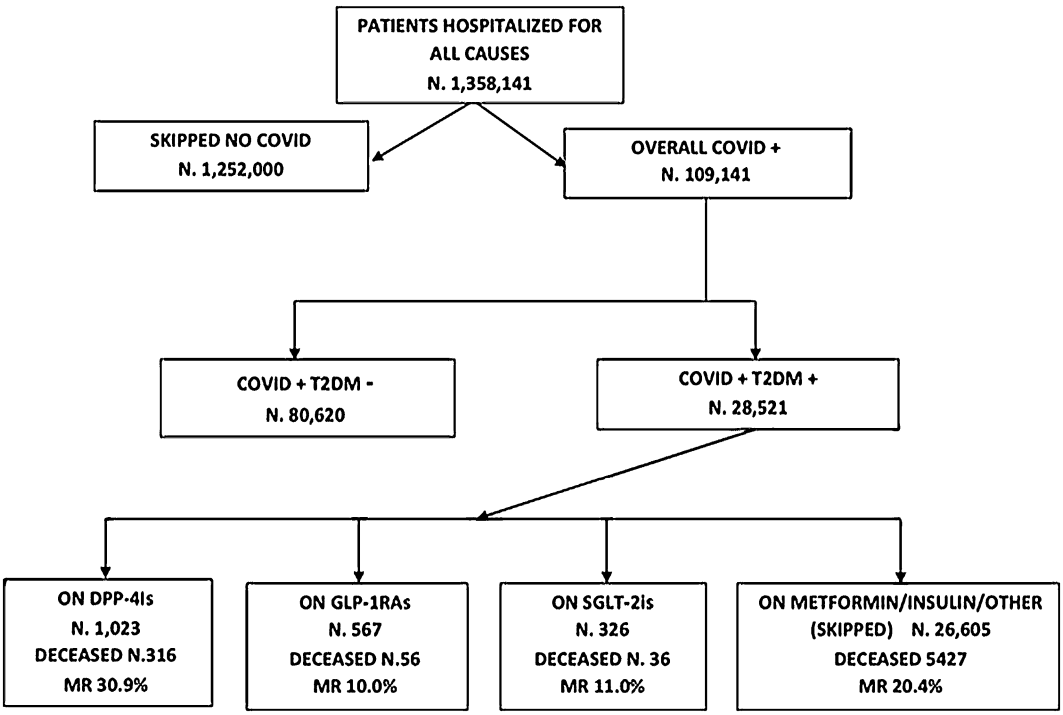

Fig. 1 Flowchart of the enrollment procedure. *MR* percentage mortality rate, *T2DM* type 2 diabetes mellitus, *DPP-4is* dipeptidyl peptidase-4 inhibitors, *GLP-1ras* glucagon-like peptide-1 receptor agonists, *SGLT-2is* sodium-glucose co-transporter-2 inhibitors

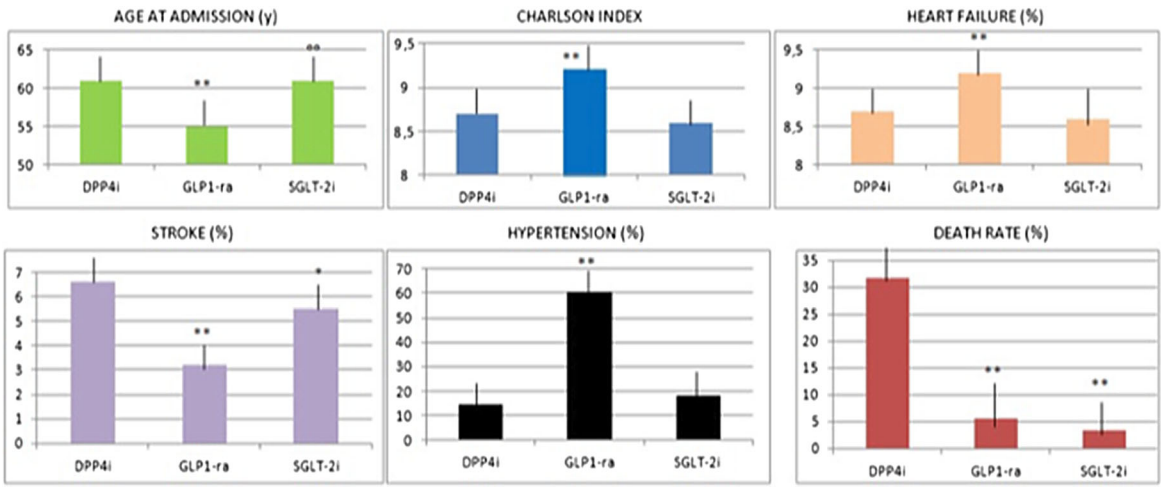

Fig. 2 Graphs of the main parameters indicative of COVID-19-related mortality by hypoglycemic class, using DDP-4is as the comparator. $^{**}p < 0.001$ vs. DPP-4is; $^{*}p < 0.05$ vs. DPP-4is, $^{\circ\circ}p < 0.001$ vs. GLP-1ras. *DPP-4is* dipeptidyl peptidase-4 inhibitors, *GLP-1ras* glucagon-like peptide-1 receptor agonists, *SGLT-2is* sodium-glucose co-transporter-2 inhibitors

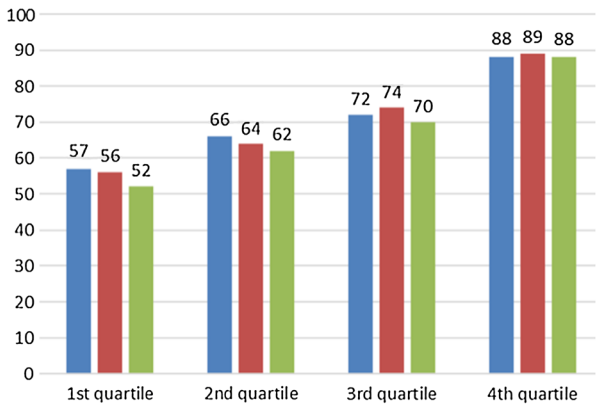

Fig. 3 Pre-hospitalization distribution by age quartile and drug utilization; *blue bars* DDP-4is, *red bars* GLP-1ras, *green bars* SGLT-2is, *DPP-4is* dipeptidyl peptidase-4 inhibitors, *GLP-1ras* glucagon-like peptide-1 receptor agonists, *SGLT-2is* sodium-glucose co-transporter-2 inhibitors

in hospitalized patients with T2DM in relation to the length of stay in the ICU and previous home treatment, respectively.

We adopted two metrics to assess how well a logistic regression model fits a dataset, i.e., sensitivity and specificity. Sensitivity is the probability that the model predicts a positive outcome for a specific observation when the outcome is positive, also called the "true positive rate." Specificity is the probability that the model predicts a negative outcome for a specific observation when the outcome is negative, also called the "true negative rate." One way to visualize and summarize these two metrics is to plot a ROC (receiver operating characteristic) curve, i.e., a plot that displays the sensitivity along the *y* axis and (1 − specificity) along the *x* axis. One way to quantify how well the logistic regression model classifies the data is to calculate the AUC, which stands for the "area under the curve." The AUC value ranges from 0 to 1. A model with an AUC of 1 can perfectly classify observations, while a model with an AUC of 0.4 does no better than random guessing. The AUC of the designed propensity score model was 0.52 in all the cohorts.

The odds ratio (OR) in the logistic regression resulted in an extremely high risk of in-hospital death in individuals previously treated with DPP-4is (Table 2; IR 4.02, 95% CI 2.2–5.7), and only a slight and non-significantly higher risk in those previously treated with SGLT-2is (IR 1.42, 95% CI 0.6–2.1) compared to those on GLP-1ras.

Table 3 summarizes the results of the multivariate analysis comparing death rates adjusted

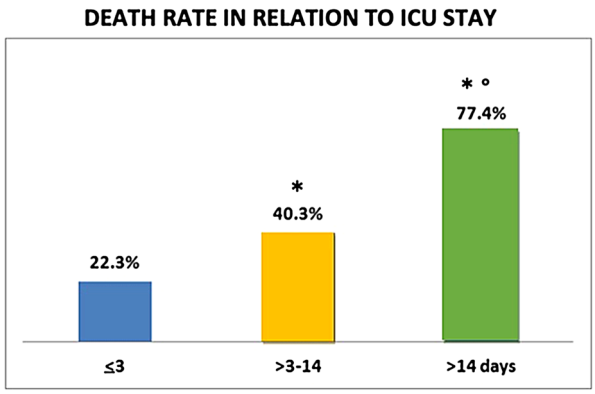

Fig. 4 The COVID-19-related death rate in hospitalized patients with type 2 diabetes mellitus (T2DM) in relation to the length of stay in the intensive care unit (ICU). $^{*}p < 0.01$ vs. ≤ 3 days; $^{\circ}p < 0.05$ vs. > 3–14 days

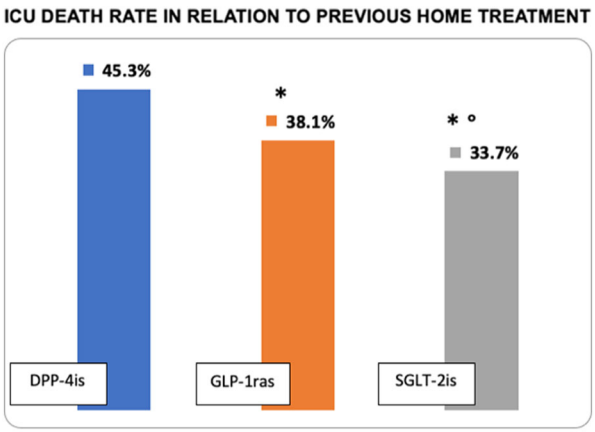

Fig. 5 The COVID-19-related death rate in hospitalized patients with type 2 diabetes mellitus (T2DM) in relation to previous home treatment. $^{*}p < 0.001$ vs. DPP-4is; $^{\circ}p < 0.001$ vs. GLP-1ras. *ICU* intensive care unit, *DPP-4is* dipeptidyl peptidase-4 inhibitors, *GLP-1ras* glucagon-like peptide-1 receptor agonists, *SGLT-2is* sodium-glucose co-transporter-2 inhibitors

for confounding factors between paired drug classes stratified by propensity score matching.

Table 4 displays the distribution of the COVID-19-related duration of stay in the ICU in absolute numbers and by pre-hospitalization anti-hyperglycemic drug class. It clearly shows that the longer the stay, the higher the death rate. The latter, indeed, went from 22.3% in ≤ 3-day stays to 40.3% in 4- to 14-day stays ($p < 0.01$ vs. the former) and 77.4% in over 14-day stays ($p < 0.001$ vs. both the others) (as also seen in Fig. 3). After dividing up the cases by treatment class, we observed a lower death rate in those administered GLP-1ras or SGLT-2is (virtually superimposable levels, i.e., 38.1% and 33.7%, respectively, p was n.s.) than in those administered DPP-4is (45.3%; $p < 0.001$ vs. GLP1-ras and SGLT-2is), as also seen in Fig. 4. Indeed, the number of subjects on DPP-4is was significantly higher than the number on GLP-1ras (47.3% vs. 33.9%, $p < 0.01$, respectively) and, especially, the number on SGLT-2is (47.3% vs. 18.8%, $p < 0.001$).

DISCUSSION

Beyond lowering circulating glucose levels, DPP-4is and GLP1-ras exert marked anti-phlogistic effects by promoting blood and tissue monocyte-macrophagic cell polarization into the anti-inflammatory M2 phenotype [30] and blunting inflammatory cytokine secretion [14].

The established GLP-1ras anti-inflammatory effects [11] mainly rely on macrophage-derived nuclear factor (NF)-κB pathway inhibition [31] and related insulin resistance attenuation [32]. Therefore, GLP-1ras could act positively in different phases of COVID-19 by reducing risk factors contributing to the development of detrimental comorbidities before exposure to the virus and by mitigating lung damage and metabolic derangement in the acute phase of the disease [33].

Moreover, these drugs may contribute to a novel therapeutic strategy to counteract the pulmonary arterial hypertension (PAH) condition often observed after COVID-19 infection [34].

In addition, many pulmonary diseases, including asthma, chronic obstructive pulmonary disease (COPD), nosocomial pneumonitis, and pulmonary fibrosis, might benefit from GLP-1-based therapies [35]. Therefore, it is conceivable that incretin-based therapies greatly help at the lung tissue level, thus extending their extra-glycemic effects well beyond those acknowledged in the cardiovascular and renal fields [36]. Moreover, as

Table 2 COVID-19-related mortality among hospitalized patients during the index period

	Mortality rate (× 1000)	95% confidence interval
General population	1.9	1.8–2.0
Patients with T2DM (overall)	150	80–630
Patients with T2DM on DPP-4is	309	270–348
Patients with T2DM on GLP-1ras	100	81–120
Patients with T2DM on SGLT-2is	110	96–124

T2DM type 2 diabetes mellitus, *DPP-4is* dipeptidyl peptidase-4 inhibitors, *GLP-1ras* glucagon-like peptide-1 receptor agonists, *SGLT-2is* sodium-glucose co-transporter-2 inhibitors

Table 3 Results of the multivariate analysis comparing death rates adjusted for confounding factors between paired drug classes stratified by propensity score matching

	OR	95% CI
DPP-4is vs. GLP-1ras	4.81	2.6–6.1
SGLT2-is vs. GLP-1ras	1.42	0.6–2.1
DPP-4is vs. SGLT-2is	2.45	1.01–3.84

OR odds ratio, *CI* confidence interval, *DPP-4is* dipeptidyl peptidase-4 inhibitors, *GLP-1ras* glucagon-like peptide-1 receptor agonists, *SGLT-2is* sodium-glucose co-transporter-2 inhibitors

endotoxin-induced GLP-1 secretion is blunted in IL-6 knockout (KO) mice, IL-6 is thought to be needed to directly stimulate GLP-1 production and release [37], so GLP-1ras may also reverse the inhibitory effects of biological anti-IL-6 treatment regimes on GLP-1 secretion.

Several clinical and experimental investigations have shown that SGLT-2is also counteract typical diabetes-associated low-grade inflammation and oxidative stress [20] by polarizing monocyte-macrophage cells into the anti-inflammatory M2 phenotype [21] and blunting the release of the pro-inflammatory cytokines TNF-α, interleukin-6 (IL-6), and C-reactive protein (CRP) [15] by increasing adiponectin [18] and reducing urate, leptin, and insulin [16] concentrations. SGLT-2is exert many favorable effects on COVID-19 outcome as well [38], conceivably due to their well-known anti-inflammatory properties [15]. In line with that, a retrospective observational study of 76 T2DM patients with T2DM in Singapore showed that home therapy with SGLT-2is was associated with a lower risk of mechanical ventilation [22].

Before our study, the abilities of those three drug classes to reduce COVID-19 severity, length of stay, and mortality had not been compared head to head. Our study did that for the first time using a random match procedure to generate a 1:1 comparison for each of them. For this purpose, we used the Charlson index to stratify diabetes and comorbidities severity and limited our study to patients on DPP-4i, GLP-1ra, or SGLT-2i monotherapy to eliminate possible confounding effects due to other hypoglycemic treatments. As expected, of the 1916 selected subjects, most (41%) were on DPP-4is, and 22% and 37% were on the other two drug classes, respectively.

As easily observed in Table 1 and Fig. 2, patients on GLP-1ras displayed a significantly increased Charlson index and were more frequently affected by arterial hypertension and heart failure than the other two groups, which turned out to be quite similar in those terms. The age quartile partition was almost superimposable among all drug groups (Fig. 3). However, subjects treated with DPP-4is had been more frequently hospitalized (Table 1), were more often moved to the ICU and stayed there longer (Table 4), and displayed a higher COVID-19-related death rate (Tables 2, 3, and 4) than the other two groups. Interestingly, their death rate was higher whether calculated globally or in terms of ICU stay (ward stay + ICU stay = 309 per 1000 vs. 100 per 1000 and 110 per 1000, respectively, ; $p < 0.001$).

In general, the death rate correlated significantly with ICU stay independently of drug class (22.3% in ≤ 3-day stays, 40.3% in 4- to

Table 4 Distribution of the COVID-19-related duration of stay of the diabetes patient in the intensive care unit (ICU) by number and pre-hospitalization drug class

ICU stay (days)	Overall			DPP-4is (*n* = 1023)			GLP1-ras (*n* = 567)			SGLT-2is (*n* = 326)		
	N	Average stay (days) Mean, range	Deaths *N* (%)	*N*	Average stay (days) Mean, range	Deaths *N* (%)	*N*	Average stay (days) Mean, range	Deaths *N* (%)	*N*	Average stay (days) Mean, range	Deaths *N* (%)
≤ 3	138	2	31 (22.3)	71	2	20 (28.1)	39	2	7	28	2	4 (14.2)
		1–3			1–3			1–3	(17.9)		1–3	
4–14	263	11	106	122	12	53 (43.4)	93	11	35 (39.7)	48	10	18
		4–14	(40.3)		4–14			4–14			4–14	(37.5)
> 14	71	18	55 (77.4)	30	19	28	28	20	19	13	18	8
		14–41			14–40	(93.3)		14–41	(69.0)		14–38	(61.5)
Overall	472		192	223		101	160		61 (38.1)	89		30 (33.7)
			(40.7)	(47.3)		(45.3)	(33.9)			(18.8)		

DPP-4is dipeptidyl peptidase-4 inhibitors, *GLP-1ras* glucagon-like peptide-1 receptor agonists, *SGLT-2is* sodium-glucose co-transporter-2 inhibitors

14-day stays ($p < 0.001$ vs. the shorter stays), and 77.4% in > 14-day stays ($p < 0.001$ vs. both shorter stays) (Fig. 4).

However, when stratifying drug classes by length of stay in the ICU, we found patients on DPP-4is to have a higher death rate (i.e., 45.3%) than those on GLP-1ras (38.1%, $p < 001$) and on SGLT-2is (33.7%, $p < 0.01$) (Fig. 5).

Our data do not support a protective role for DPP-4is. Such a role has already been questioned due to previous observations [39, 40] against a single multinational systematic review and meta-analysis showing reduced mortality in inpatients with COVID-19 (odds ratio [OR] 0.75) treated by DPP-4is [41]. The excess mortality we observed in those taking DPP-4is before hospitalization remains to be explained.

Bearing in mind that we only selected patients on monotherapy with DPP-4is, GLP-1ras, and SGLT-2is to avoid the risk for hospitalization and COVID severity described for other hypoglycemic drugs, some additional considerations should be made regarding the role of pre-hospitalization therapy with DPP-4is, as—differently from the other two drug classes—pre-hospitalization DPP-4is were associated with excess COVID-related mortality in people with T2DM in one study [42], while in-hospital DPP-4is utilization seemed to have a protective effect during the clinical course of COVID [43, 44]. So, the topic remains debated: insufficient data have been collected so far, and further research is needed in this specific field [45].

In contrast, our results showed a favorable effect of GLP-1ras and SGLT-2is home therapy on COVID-19 severity, length of hospital stay (especially in the ICU), and COVID-related deaths, thus confirming results in the literature that—although not based on a direct head-to-head comparison among drug classes—strongly suggest an almost superimposable protective role for GLP-1ras and SGLT-2is in patients with T2DM hospitalized for COVID-19 [46]. In particular, our study demonstrated a positive effect of pre-admission SGLT-2is utilization on COVID-19 outcomes in hospitalized patients with T2DM. This result is in line with a recent meta-analysis showing that pre-admission SGLT-2i utilization was associated with reduced COVID-19 mortality (OR 0.69; 95% CI: 0.56–0.87, $p = 0.001$, $I^2 = 91\%$) and severity (OR 0.88; 95% CI: 0.80–0.97, $p = 0.008$, $I^2 = 13\%$) independently of confounding factors like age ($p = 0.2335$), gender ($p = 0.2742$), BMI ($p = 0.1797$), HbA1c level ($p = 0.4924$), diabetes duration ($p = 0.7233$), hypertension ($p = 0.2165$), heart failure ($p = 0.1616$), and metformin utilization ($p = 0.6617$) [47].

LIMITATIONS

Our study has some limitations. One is the arbitrary choice, justified by clinical experience, of the 3-day cutoff for the length of stay in the ICU as a criterion for disease severity. Another one is the utilization of hospital discharge records, which, by definition, lack several clinical parameters that would be extremely helpful for an extensive, in-depth interpretation of our results, including antiviral, antibiotic, anticoagulant, corticosteroid, and immune-based therapies and the need for mechanical ventilation. Indeed, as ours was a retrospective, observational study, we had to rely only on the above-mentioned records and pre-hospitalization health care data. Therefore, we could not rule out possible influences of risk factors other than those available and reported in the manuscript on the favorable effects of GLP-1ras and SGLT-2is on COVID-related hospital mortality. In other words, such effects might not be independent of risk factors other than those we could statistically analyze. Nevertheless, hospital discharge records have the great merit of providing certified and uniform data according to ICD9/10-CM criteria and allowing us to follow individual patients during their shifts in and out of different hospital wards in a head-to-head extra-glycemic effect comparison of DPP-4is, GLP-1ras, and SGLT-2is.

CONCLUSIONS

Based on the aforedescribed observational clinical data relating to an Italian T2DM inpatient population, our study suggests that GLP-1ras and SGLT-2is can be considered antidiabetic drugs of choice in COVID-19 and might,

therefore, even prove beneficial in the event of any upcoming pandemic that has life-threatening effects on the pulmonary and cardiovascular systems. However, the role of DPP-4is remains debated, and further studies are needed on this drug class regarding the specific topic of our investigation .

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Data Availability. The datasets analyzed during the present study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest. Vincenzo M. Monda, Claudio Voci, Felice Strollo, Angela Passaro, Salvatore Greco, Marcello Monesi, Renato Bigoni, Francesca Porcellati, Daniela Piani, Ersilia Satta, and Sandro Gentile have no financial interests to declare concerning the present study.

Ethical Approval. This study complied with good clinical practice standards and followed the ethical guidelines of the 1964 Declaration of Helsinki and its subsequent amendments. The study protocol was approved by the IRB (trial registration: Protocol n. 5, May 16, 2022) and the Ethical and Scientific Committee of the reference center, the Department of Endocrinology, San Raffaele Pisana Cliical Research Institute, Rome, Italy, served as the central reference ethical committee for all of the participating affiliated medical units. All subjects with T2DM who participated in the study signed an informed consent form before being included in the present investigation.

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