Diabetes, Drug Treatment, and Mortality in COVID-19: A Multinational Retrospective Cohort Study

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Patients with type 2 diabetes mellitus (T2DM) are at increased risk of severe coronavirus disease 2019 (COVID-19) outcomes possibly because of dysregulated inflammatory responses. Glucose-regulating medications, such as glucagon-like peptide 1 receptor (GLP-1R) agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, and pioglitazone, are known to have anti-inflammatory effects that may improve outcomes in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. In a multinational retrospective cohort study, we used the TriNetX COVID-19 Research Network of 56 large health care organizations to examine these medications in relation to the incidence of hospital admissions, respiratory complications, and mortality within 28 days after a COVID-19 diagnosis. After matching for age, sex, race, ethnicity, BMI, and significant comorbidities, use of GLP-1R agonists and/ or pioglitazone was associated with significant reductions in hospital admissions (GLP-1R: 15.7% vs. 23.5%, risk ratio [RR] 0.67 [95% CI 0.57–0.79; *P* < 0.001]; pioglitazone: 20.0% vs. 28.2%; RR 0.71 [95% CI 0.54–0.93; *P* = 0.01]). Use of GLP-1R agonists was also associated with reductions in respiratory complications (15.3% vs. 24.9%, RR 0.62 [95% CI 0.52–0.73]; *P* < 0.001) and incidence of mortality (1.9% vs. 3.3%, RR 0.58 [95% CI 0.35–0.97]; *P* = 0.04). Use of DPP-4 inhibitors was associated with a reduction in respiratory complications (24.0% vs. 29.2%, RR 0.82 [95% CI 0.74–0.90]; *P* < 0.001), and continued use of DPP-4 inhibitors after hospitalization was associated with a decrease in mortality compared with those who discontinued use (9% vs. 19%, RR 0.45 [95% CI 0.28–0.72]; *P* < 0.001). In conclusion, use of

glucose-regulating medications, such as GLP-1R agonists, DPP-4 inhibitors, or pioglitazone, may improve COVID-19 outcomes for patients with T2DM; randomized clinical trials are needed to further investigate this possibility.

As of 14 April 2021, there were 137,811,552 confirmed cases and 2,964,835 (2.2%) deaths worldwide as a result of coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). These figures include 31,375,111 confirmed cases and 563,873 (1.8%) deaths in the U.S. alone (1). Given the time required to distribute a vaccine, an expedient solution to reduce morbidity and mortality as a result of COVID-19 is to rapidly identify therapeutics utilizing highly scalable agents that show promise. A randomized placebo-controlled trial found that remdesivir, a broad-spectrum antiviral with activity against SARS-CoV-2, reduced median recovery time from 15 to 11 days but did not reduce mortality (2,3). An open-label trial with the synthetic glucocorticoid dexamethasone suggested a reduction in mortality by one-third in patients requiring ventilator support and by one-fifth in patients requiring oxygen (4). Together, these interventions are proving helpful; however, the number of deaths as a result of COVID-19 continues to climb in the U.S. and around the world (1). Moreover, mortality for at-risk populations, such as those with type 2 diabetes mellitus (T2DM), is much higher (5–7). In China, risk of mortality was reported to be 7.2% for patients with T2DM (8), and a recent study in England found that patients

COMPLICATIONS

with T2DM made up 31.4% of the COVID-19–related deaths (9). One hypothesis is that patients with T2DM are more susceptible to a dysregulated inflammatory response, or cytokine storm, which has been hypothesized to lead to severe outcomes in a subset of patients with COVID-19 (10,11). Additionally, recent data indicate dysregulation of glycometabolic control in patients with COVID-19 (12).

Because SARS-CoV-2 uses ACE2 as its receptor, we selected medications that are used to treat T2DM and that have been shown to increase ACE2 and have anti-inflammatory effects. The glucagon-like peptide 1 (GLP-1) agonist liraglutide has been shown to increase ACE2 expression in the lungs of rats and reduce acute lung injury caused by influenza virus in mice, which is particularly relevant to COVID-19–induced pulmonary disease (13–16). Dipeptidyl peptidase 4 (DPP-4) inhibitors may have similar effects as they increase endogenous GLP-1 levels by inhibiting the breakdown of GLP-1 by the DPP-4 enzyme. The DPP-4 inhibitor linagliptin has been shown to increase ACE2 activity and has the potential to exert anti-inflammatory effects (17). Finally, thiazolidinediones (TZDs) were selected because they have been shown to increase ACE2 levels in the aorta, liver, adipose tissue, and skeletal muscle (18,19). Because GLP-1 agonists, DPP-4 inhibitors, and TZDs increase ACE2, we hypothesized that these drugs would have protective effects in patients with COVID-19 and diabetes. Increased ACE2 leads to increased production of angiotensin-(1–7), which exhibits anti-inflammatory effects and prevents end-organ damage as a result of diabetes and may also potentially prevent end-organ damage caused by COVID-19.

Several medications used to regulate blood glucose have been hypothesized to improve COVID-19–related outcomes in patients with T2DM (20–28); however, no data currently support these hypotheses or provide rationale for a randomized trial. The objective of this multinational, retrospective cohort study was to investigate whether the use of T2DM medications is associated with improved outcomes in patients with COVID-19 and T2DM. One such class of medications includes GLP-1 receptor (GLP-1R) agonists. GLP-1 is a hormone produced by L cells in the small intestine that increases insulin release, decreases glucagon release, and decreases gastric emptying (29). GLP-1R agonists are an approved and effective treatment for obesity and T2DM (30–32) and may have a protective effect for severe outcomes of COVID-19 in patients with fatty liver disease (33). In patients with T2DM, GLP-1R agonists control blood glucose, reduce elevated glycated hemoglobin (HbA$_{1c}$), and decrease both cardiovascular risk (34) and the frequency of major adverse cardiac events (35,36). GLP-1R agonists also have positive effects on body weight, BMI, blood pressure, and cholesterol (29,37). Of particular interest, GLP-1R agonists have been shown to decrease inflammatory cytokines in animals (38) and humans (37,39). Other medications for T2DM that have anti-inflammatory

effects include DPP-4 inhibitors, which block the breakdown of GLP-1 and have been shown to regulate other coronaviruses (40), and pioglitazone, which is a TDZ (23,41). We hypothesized that the use of GLP-1R agonists, DPP-4 inhibitors, or pioglitazone within 6 months before the diagnosis of COVID-19 would reduce hospital admissions, respiratory complications, and mortality within 28 days after the diagnosis of COVID-19 in patients with T2DM.

RESEARCH DESIGN AND METHODS

To determine whether treatment with GLP-1R agonists, DPP-4 inhibitors, or pioglitazone in patients with COVID-19 and T2DM was associated with better outcomes, we conducted a retrospective analysis of the TriNetX COVID-19 Research Network. This global federated research network provides access to statistics in electronic medical records (EMRs) across 56 large health care organizations predominately in the U.S. TriNetX provides aggregated counts and statistical summaries of deidentified information but no protected health information. Further details of the TriNetX networks have been previously described (42,43). All analyses were conducted using the browser-based real-time analytics feature of TriNetX.

We analyzed the EMRs of 64,936,797 patients with a diagnostic code for COVID-19 or positive laboratory test results for SARS-CoV-2 between 1 January 2020 and 1 September 2020. Analyses included patients with a diagnostic code for T2DM any time within 6 months preceding the first record of COVID-19 (Fig. 1). Because treatment for type 1 diabetes has some, but not total, overlap with T2DM treatment, patients with type 1 diabetes were excluded from analyses. There were 29,516 patients with T2DM included in the analyses. These patients were divided into cohorts based on medications listed in their EMR within 6 months preceding the first record of COVID-19 (see Supplementary Tables 1–3 for a comprehensive list of medications). These patient subsets included 1,774 patients treated with GLP-1R agonists only (dulaglutide, exenatide, liraglutide, semaglutide, or lixisenatide), 2,264 treated with DPP-4 inhibitors only (alogliptin, linagliptin, saxagliptin, or sitagliptin), and 469 patients treated with pioglitazone only. There were two control groups: The first consisted of 23,714 patients with T2DM who had none of the medications of interest (No-G/D/P cohort), and the second included 5,606 patients with T2DM who had more than one of the medications of interest (Any Med cohort) any time within 6 months preceding the first record of COVID-19.

The primary outcome was mortality and defined as the presence of the term deceased in the EMR up to 28 days after the first record of COVID-19. Hospitalization and respiratory complications were secondary outcomes. Hospitalization was defined as a direct admission to inpatient care or observation in the EMR up to 28 days after the first record of COVID-19. Respiratory complications were
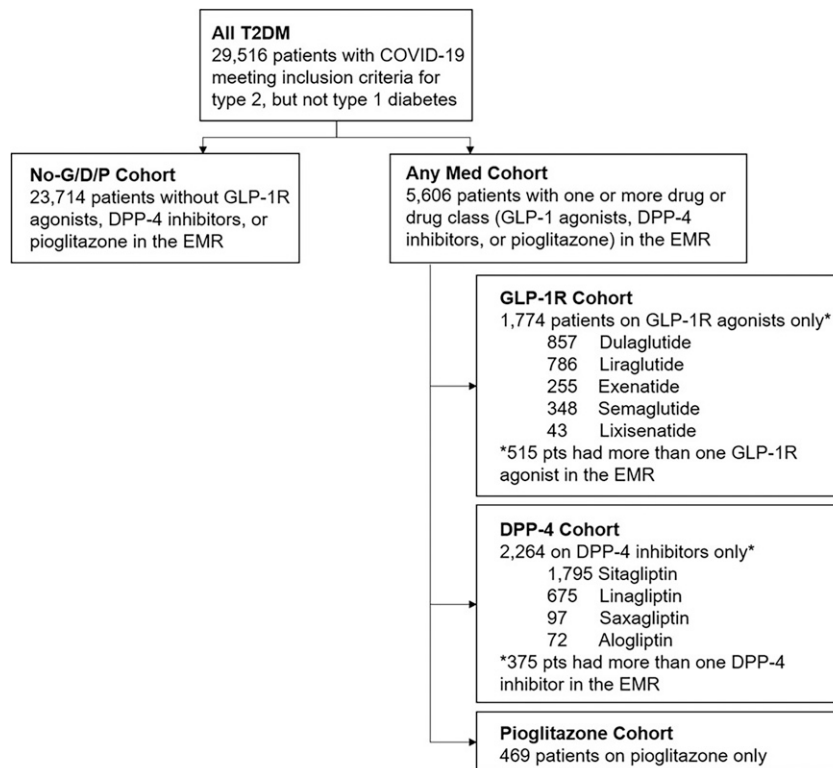
All T2DM
29,516 patients with COVID-19 meeting inclusion criteria for type 2, but not type 1 diabetes

No-G/D/P Cohort
23,714 patients without GLP-1R agonists, DPP-4 inhibitors, or pioglitazone in the EMR

Any Med Cohort
5,606 patients with one or more drug or drug class (GLP-1 agonists, DPP-4 inhibitors, or pioglitazone) in the EMR

GLP-1R Cohort
1,774 patients on GLP-1R agonists only*
   857   Dulaglutide
   786   Liraglutide
   255   Exenatide
   348   Semaglutide
   43   Lixisenatide
*515 pts had more than one GLP-1R agonist in the EMR

DPP-4 Cohort
2,264 on DPP-4 inhibitors only*
   1,795 Sitagliptin
   675   Linagliptin
   97   Saxagliptin
   72   Alogliptin
*375 pts had more than one DPP-4 inhibitor in the EMR

Pioglitazone Cohort
469 patients on pioglitazone only

Figure 1—Study flowchart. pts, patients.

defined as the presence of diagnostic codes for acute respiratory distress syndrome, acute and chronic respiratory failure, dependence on mechanical ventilation, acute respiratory distress, or respiratory arrest in the EMR within 28 days after the first record of COVID-19.

Risks for hospital admissions, respiratory complications, and mortality were first assessed for each patient cohort compared with the No-G/D/P cohort before propensity matching. Subsequent analyses were propensity matched for age, sex, race, ethnicity, BMI, and the presence of diagnostic codes for the following comorbidities: hypertension, ischemic heart disease, cerebrovascular disease, heart failure, chronic kidney disease, and overweight or obesity in the EMR within 6 months of the first record of COVID-19. Sex was used for propensity matching throughout these analyses and, thus, not considered a factor for comparison. Propensity scoring was calculated using logistic regression implemented by the function *LogisticRegression* of the scikit-learn package in Python version 3.7. The propensity score 1:1 matching used a greedy nearest neighbor matching approach, with a caliper distance of 0.1 pooled SDs of the logit of the propensity score. All laboratory values are the most recent value in the EMR within the designated time period unless otherwise stated. After propensity matching, the risks of hospital admissions, respiratory complications, and mortality were calculated for each patient cohort compared with the No-G/D/P cohort. Additionally, hospitalized patients who remained on their respective medications were compared with those whose medications were discontinued within each cohort.

Data and Resource Availability

The data that support the findings of this study are available from TriNetX, but restrictions apply to the availability of these data, which were used under license for the current study and, therefore, are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of TriNetX.

RESULTS

Of the 229,809 patients with a diagnostic code for COVID-19 or positive laboratory result for SARS-CoV-2 present in the database, 2.2% were deceased within 28 days of the first record of COVID-19 (Table 1). Patients with a diagnosis of T2DM were more than four times as likely to be deceased (6.5%) within 28 days compared with those without a diagnosis of T2DM (1.6%). This increase in mortality was observed across all age-groups, with the greatest increase (22.8-fold) in patients <30 years of age. Group characteristics were first assessed for all patients with T2DM with COVID-19 who were alive at 28 days compared with those who were deceased at 28 days after the first record of COVID-19. Those who were deceased were older, more likely to be male, and had higher blood glucose, lower oxygen saturation, and lower blood pressure (Table 2).

Table 1—Cohort statistics

	No. of patients in database	Percent of database	Positive for SARS-CoV-2		Deceased at 28 days*	
			n	%	n	%
Without T2DM	64,936,797	94.2	200,293	0.3	3,209	1.6
With T2DM	4,022,267	5.8	29,516	0.7	1,921	6.5
Total	68,959,064	—	229,809	0.3	5,130	2.2

	Patients with COVID-19 without T2DM			Patients with COVID-19 with T2DM			
Age, years	Deceased at 28 days, n (%)	Alive at 28 days, n	Total, n	Deceased at 28 days, n (%)	Alive at 28 days, n	Total, n	Fold increase in risk for T2DM
<30	44 (0.07)	63,162	63,206	10 (1.59)	619	629	22.8
30–40	63 (0.17)	36,252	36,315	26 (1.49)	1,715	1,741	8.6
40–50	128 (0.41)	31,333	31,461	54 (1.36)	3,931	3,985	3.3
50–60	272 (0.95)	28,383	28,655	231 (3.38)	6,611	6,842	3.6
60–70	525 (2.65)	19,260	19,785	388 (5.28)	6,954	7,342	2.0
70–80	793 (7.25)	10,138	10,931	587 (10.77)	4,863	5,450	1.5
80–90	959 (13.81)	5,986	6,945	496 (17.45)	2,346	2,842	1.3
>90	425 (14.19)	2,570	2,995	129 (18.83)	556	685	1.3
Total	3,209 (1.60)	197,084	200,293	1,921 (6.51)	27,595	29,516	4.1

*Patients with the term "deceased" in the medical record within 28 days of a diagnosis of COVID-19 or positive test results for SARS-CoV-2 were included in the deceased group, while all others were assigned to the alive group.

Additionally, patients with T2DM who were deceased within 28 days had a greater incidence of hypertension, ischemic heart disease, cerebrovascular disease, heart failure, chronic kidney disease, and overweight and obesity. Consequently, these factors were used for propensity matching in subsequent analyses (see Table 3 for baseline patient characteristics by drug cohort).

Hospital Admissions

Collectively, 27.3% of all patients with T2DM with COVID-19 were admitted to the hospital within 28 days of the first record of COVID-19 (Table 4). Among patients with T2DM in the No-G/D/P cohort, 28.4% were admitted, reflecting a 4.3% relative increase in incidence of hospital admissions compared with all patients with T2DM (risk ratio [RR] 1.04 [95% CI 1.01–1.07]; $P = 0.004$). Compared with the No-G/D/P cohort, there was a 47.1% relative reduction in hospitalizations for the GLP-1R cohort (15.1% vs. 28.4%, RR 0.53 [95% CI 0.47–0.59]; $P < 0.001$), 19.0% relative reduction for the pioglitazone cohort (23.0% vs. 28.4%, RR 0.81 [95% CI 0.69–0.96]; $P = 0.01$), and 21.0% relative reduction for the Any Med cohort (22.5% vs. 28.4%, RR 0.79 [95% CI 0.75–0.83]; $P < 0.001$). These cohorts maintained significant reductions in hospitalizations after propensity matching, with the GLP-1R cohort showing a 33.0% relative decrease (15.7% vs. 23.5%, RR 0.67 [95% CI 0.57–0.79]; $P < 0.001$) followed by the pioglitazone cohort, which had a 29.2% relative decrease (20.0% vs. 28.2%, RR 0.71 [95% CI 0.54–0.93]; $P = 0.01$), and the Any Med cohort, which had a 16.2% relative decrease in hospitalizations (22.3%

vs. 26.6%, RR 0.84 [95% CI 0.78–0.90]; $P < 0.001$). Patients in the DPP-4 cohort did not differ from the No-G/D/P cohort before propensity matching (29.5% vs. 28.4%, RR 1.04 [95% CI 0.97–1.11]; $P = 0.30$) or after propensity matching (29.5% vs. 30.2%, RR 0.98 [95% CI 0.89–1.07]; $P = 0.63$).

Incidence of Respiratory Complications

Of all patients with T2DM, 25.7% experienced respiratory complications within 28 days of the first record of COVID-19 (Table 4). Patients in the No-G/D/P cohort had a 5.7% relative increase in incidence compared with all patients with T2DM (27.1% vs. 25.7%, RR 1.06 [95% CI 1.03–1.09]; $P < 0.001$). Compared with the No-G/D/P cohort, there was a 44.1% relative decrease in respiratory complications for the GLP-1R cohort (15.2% vs. 27.1%, RR 0.56 [95% CI 0.50–0.63]; $P < 0.001$), 11.6% relative decrease for the DPP-4 cohort (24.0% vs. 27.1%, RR 0.88 [95% CI 0.82–0.95]; $P = 0.001$), and 27.6% relative decrease for the Any Med cohort (19.6% vs. 27.1%, RR 0.72 [95% CI 0.68–0.77]; $P < 0.001$). These cohorts maintained significant reductions in respiratory complications after propensity matching. The GLP-1R cohort had a 38.4% relative decrease (15.3% vs. 24.9%, RR 0.62 [95% CI 0.52–0.73]; $P < 0.001$), the DPP-4 cohort had a 18.0% relative decrease (24.0% vs. 29.2%, RR 0.82 [95% CI 0.74–0.90]; $P < 0.001$), and the Any Med cohort had a 27.2% relative decrease (19.6% vs. 27.0%, RR 0.73 [95% CI 0.68–0.78]; $P < 0.001$) in respiratory complications. Patients in the pioglitazone cohort did not differ from the No-G/D/P cohort before propensity matching (23.0% vs.

Table 2—Baseline characteristics for all patients with T2DM with a diagnosis of COVID-19 or positive SARS-CoV-2 test results

Characteristic	All T2DM (n = 29,516)	Alive at 28 days* (n = 27,595)	Deceased at 28 days (n = 1,921)	P	SMD
Age,† years, mean (SD)	60.9 (15.0)	60.0 (14.8)	71.7 (12.8)	<0.001	0.78
Sex, n (%)					
Female	15,289 (51.8)	14,518 (52.6)	771 (40.1)	<0.001	
Male	14,227 (48.2)	13,077 (47.4)	1,149 (59.8)	<0.001	
Race, n (%)					
White	14,138 (47.9)	13,356 (48.4)	782 (40.7)	<0.001	
Black or African American	7,527 (25.5)	6,014 (25.4)	513 (26.7)	0.14	
Asian	915 (3.1)	840 (3.0)	75 (3.9)	0.16	
Unknown	5,903 (20.0)	5,367 (19.4)	536 (27.9)	<0.001	
Ethnicity, n (%)					
Hispanic or Latino	5,490 (18.6)	5,338 (19.3)	152 (7.9)	<0.001	
Not Hispanic or Latino	12,898 (43.7)	12,198 (44.2)	700 (36.4)	<0.001	
Unknown	11,128 (37.7)	10,059 (36.5)	1,069 (55.6)	<0.001	
Vitals and key laboratory findings,‡ mean (SD)					
BMI, kg/m^2	32.8 (8.9)	32.7 (8.8)	30.8 (8.7)	<0.001	0.21
Glucose, mg/dL	155.0 (78.6)	155.0 (77.1)	163.0 (85.1)	<0.001	0.10
HbA$_{1c}$				0.65	0.05
%	7.7 (2.1)	7.7 (2.1)	7.8 (2.0)		
mmol/mol	61 (23)	61 (23)	62 (21.9)		
Oxygen saturation, %	81.9 (22.3)	83.1 (20.9)	79.4 (21.9)	<0.001	0.17
Blood pressure, mmHg					
Systolic	128.0 (21.5)	130.0 (21.0)	109.0 (31.4)	<0.001	0.98
Diastolic	73.3 (13.4)	74.4 (12.8)	57.7 (18.1)	<0.001	1.25
Comorbidities,§ n (%)					
Essential (primary) hypertension	14,079 (47.7)	12,901 (46.8)	1,178 (61.3)	<0.001	
Overweight and obesity	5,726 (19.4)	5,190 (18.8)	536 (27.9)	<0.001	
Ischemic heart disease	4,457 (15.1)	3,708 (13.4)	749 (39.0)	<0.001	
Heart failure	3,512 (11.9)	2,868 (10.3)	644 (33.5)	<0.001	
Cerebrovascular disease	1,800 (6.1)	1,485 (5.4)	315 (16.4)	<0.001	
Chronic kidney disease	4,575 (15.5)	3,799 (13.8)	776 (40.4)	<0.001	

P values indicate significance between alive and deceased groups. SMD, standardized mean difference between alive and deceased groups. *Patients with the term "deceased" in the medical record within 28 days of a diagnosis of COVID-19 or positive test results for SARS-CoV-2 were included in the deceased group, while all others were assigned to the alive group. †Age is defined as the age of the patient at the time of diagnosis of COVID-19 or positive test results for SARS-CoV-2. ‡Vitals and key laboratory findings are the most recent value recorded in the EMR within 6 months up to the time of diagnosis of COVID-19 or positive test results for SARS-CoV-2. §Comorbidities are assessed as presence of a diagnostic code for the six major comorbidities within the EMR within 6 months up to the time of diagnosis of COVID-19 or positive test results for SARS-CoV-2.

27.1%, RR 0.88 [95% CI 0.75–1.04]; *P* = 0.12) or after propensity matching (25.0% vs. 28.2%, RR 0.89 [95% CI 0.70–1.14]; *P* = 0.34).

Mortality

Among all patients with T2DM and COVID-19, 6.5% died within 28 days of the first record of COVID-19 (Fig. 2 and Table 4). Patients with T2DM in the No-G/D/P cohort did not differ significantly from all patients with T2DM (6.1% vs. 6.5%) in risk for mortality. Compared with the No-G/D/P cohort, patients with T2DM on GLP-1R agonists had a 59.2% relative decrease in risk of mortality (2.5% vs. 6.1%, RR 0.41 [95% CI 0.30–0.55]; *P* < 0.001), and those in the Any Med cohort had a 22.0% relative decrease in risk for mortality (4.7% vs. 6.1%, RR 0.78 [95% CI 0.69–0.89]; *P* = 0.001). After propensity matching, both cohorts had a significant relative reduction in risk for

mortality, with statistically significant reductions of 42.1% for the GLP-1R (1.9% vs. 3.3%, RR 0.58 [95% CI 0.35–0.97]; *P* = 0.04) and 15.1% for the Any Med (4.6% vs. 5.4%, RR 0.85 [95% CI 0.72–1.00]; *P* = 0.05) cohorts. The DPP-4 cohort had a significant 22.7% relative increase in mortality risk (7.5% vs. 6.1%, RR 1.23 [95% CI 1.05–1.43]; *P* = 0.009); however, this was not significant after propensity matching (7.5% vs. 7.2%, RR 1.03 [95% CI 0.84–1.26]; *P* = 0.78). Patients in the pioglitazone cohort did not differ from those in the No-G/D/P cohort before propensity matching (4.5% vs. 6.1%, RR 0.74 [95% CI 0.48–1.12]; *P* = 0.15) or after propensity matching (5.0% vs. 4.7%, RR 1.06 [95% CI 0.55–2.07]; *P* = 0.86).

Continuation of Medication After Hospital Admission

In a follow-up analysis, hospitalized patients within each cohort who remained on their respective medications

Table 3—Baseline characteristics for patients with T2DM with a COVID-19 diagnosis or positive SARS-CoV-2 test results by medication cohort

Characteristic	No-G/D/P* (n = 23,714)	GLP-1 (n = 1,774)	P	SMD	DPP-4 (n = 2,264)	P	SMD	Pioglitazone (n = 469)	P	SMD	Any Med† (n = 5,606)	P	SMD
Age,‡ years, mean (SD)	60.9 (15.3)	55.0 (12.7)	<0.001	0.39	64.6 (13.5)	<0.001	0.25	63.1 (13.5)	0.003	0.15	60.2 (13.5)	0.006	0.05
Sex, n (%)													
Female	12,142 (51.2)	1,079 (60.8)	<0.001		1,152 (50.9)	0.80		219 (46.7)	0.19		3,066 (54.7)	<0.001	
Male	11,572 (48.8)	695 (39.2)	<0.001		1,112 (49.1)	0.79		250 (53.3)	0.19		2,540 (45.3)	<0.001	
Race, n (%)													
White	11,792 (49.7)	609 (52.3)	0.46		1,114 (49.2)	0.64		178 (52.4)	0.32		2,790 (50.5)	0.18	
Black or African American	5,874 (24.8)	334 (28.7)	<0.001		603 (26.6)	0.05		79 (23.2)	0.06		1,669 (30.2)	<0.001	
Asian	783 (3.3)	10 (0.9)	<0.001		116 (5.1)	<0.001		12 (3.5)	0.85		170 (3.1)	0.36	
Unknown	4,808 (20.3)	200 (17.2)	<0.001		409 (18.1)	0.01		63 (18.5)	0.005		830 (15.0)	<0.001	
Ethnicity, n (%)													
Hispanic or Latino	4,755 (20.1)	239 (20.5)	0.17		354 (15.6)	<0.001		85 (25.0)	0.72		929 (16.8)	<0.001	
Not Hispanic or Latino	10,407 (43.9)	659 (56.6)	<0.001		1,076 (47.5)	<0.001		172 (50.6)	<0.001		2,679 (48.5)	<0.001	
Unknown	8,552 (36.1)	266 (22.9)	<0.001		834 (36.8)	0.46		83 (24.4)	<0.001		1,912 (34.6)	0.01	
Vitals and key laboratory findings,§ mean (SD)													
BMI, kg/m²	32.3 (8.7)	37.5 (9.3)	<0.001	0.58	31.4 (8.1)	0.02	0.10	31.9 (8.0)	0.82	0.04	34.3 (9.0)	<0.001	0.22
Glucose, mg/dL	152.0 (77.5)	168.0 (81.4)	<0.001	0.20	167.0 (80.2)	<0.001	0.19	159.0 (79.9)	0.40	0.09	168.0 (81.2)	<0.001	0.20
HbA$_{1c}$													
%	7.5 (2.1)	8.4 (2.2)	<0.001	0.43	8.0 (2.0)	<0.001	0.24	7.8 (2.0)	0.16	0.14	8.2 (2.0)	<0.001	0.33
mmol/mol	58 (23)	68 (24)			64 (21.9)			62 (21.9)			66 (21.9)		
Blood pressure, mmHg													
Systolic	129.0 (22.0)	129.0 (19.7)	0.03	0.00	130.0 (21.3)	0.06	0.05	128.0 (23.0)	0.72	0.05	130.0 (20.4)	0.03	0.05
Diastolic	73.3 (13.4)	75.8 (12.8)	<0.001	0.19	71.7 (13.5)	<0.001	0.12	71.8 (14.6)	0.19	0.11	74.1 (13.1)	0.009	0.06
Comorbidities,¶ n (%)													
Essential (primary) hypertension	10,648 (44.9)	651 (55.9)	<0.001		1,266 (55.9)	<0.001		177 (52.1)	0.003		3,166 (57.4)	<0.001	
Overweight and obesity	4,161 (17.5)	416 (35.7)	<0.001		416 (18.4)	0.32		71 (20.9)	0.13		1,444 (26.2)	<0.001	
Ischemic heart disease	3,521 (14.9)	161 (13.8)	0.17		451 (19.9)	<0.001		51 (15.0)	0.99		881 (16.0)	0.04	
Heart failure	2,786 (11.7)	99 (8.5)	<0.001		344 (15.2)	<0.001		32 (9.4)	0.18		613 (11.1)	0.18	
Cerebrovascular disease	1,467 (6.2)	37 (3.2)	<0.001		177 (7.8)	0.002		22 (6.5)	0.83		307 (5.6)	0.11	
Chronic kidney disease	3,528 (14.9)	150 (12.9)	0.06		508 (22.4)	<0.001		59 (17.4)	0.22		941 (17.0)	<0.001	

P values indicate significance compared with the No-G/D/P cohort. SMD, standardized mean difference between drug cohorts and the No-G/D/P cohort. *The No-G/D/P cohort consisted of patients with T2DM with a diagnosis of COVID-19 or positive test results for SARS-CoV-2 who did not have any GLP-1R agonists, DPP-4 inhibitors, or pioglitazone in the EMR. †The Any Med cohort consisted of patients with T2DM with a diagnosis of COVID-19 or positive test results for SARS-CoV-2 who had GLP-1R agonists, DPP-4 inhibitors, and/or pioglitazone in the EMR. ‡Age is defined as the age of the patient at the time of diagnosis of COVID-19 or positive test results for SARS-CoV-2. §Vitals and key laboratory findings are the most recent values recorded in the EMR within 6 months up to the time of diagnosis of COVID-19 or positive test results for SARS-CoV-2. ¶Comorbidities are the presence of a diagnostic code for the six major comorbidities within the EMR within 6 months up to the time of diagnosis of COVID-19 or positive test results for SARS-CoV-2.

Table 4—Risk of adverse outcomes within 28 days after COVID-19 diagnosis or positive SARS-CoV-2 test results

	Before propensity matching					After propensity matching*			
	n (%)	RR (95% CI)	P	Relative change, %	n after matching	n (%)	RR (95% CI)	P	Relative change, %
Hospital admissions									
No-G/D/P† (n = 23,714)	6,741 (28.4)								
All T2DM (n = 29,516)	8,046 (27.3)	1.04 (1.01–1.07)	0.004	4.3					
GLP-1 (n = 1,774)	267 (15.1)	0.53 (0.47–0.59)	<0.001	−47.1	1,163	183 (15.7)			
No-G/D/P† (n = 23,714)	6,741 (28.4)				1,163	273 (23.5)	0.67 (0.57–0.79)	<0.001	−33.0
DPP-4 (n = 2,264)	667 (29.5)	1.04 (0.97–1.11)	0.30	3.6	2,264	667 (29.5)			
No-G/D/P† (n = 23,714)	6,741 (28.4)				2,264	684 (30.2)	0.98 (0.89–1.07)	0.63	−2.5
Pioglitazone (n = 469)	108 (23.0)	0.81 (0.69–0.96)	0.01	−19.0	340	68 (20.0)			
No-G/D/P† (n = 23,714)	6,741 (28.4)				340	96 (28.2)	0.71 (0.54–0.93)	0.01	−29.2
Any Med‡ (n = 5,606)	1,259 (22.5)	0.79 (0.75–0.83)	<0.001	−21.0	5,520	1,229 (22.3)			
No-G/D/P† (n = 23,714)	6,741 (28.4)				5,520	1,467 (26.6)	0.84 (0.78–0.90)	<0.001	−16.2
Respiratory complications									
No-G/D/P† (n = 23,714)	6,432 (27.1)								
All T2DM (n = 29,516)	7,577 (25.7)	1.06 (1.03–1.09)	<0.001	5.7					
GLP-1 (n = 1,774)	269 (15.2)	0.56 (0.50–0.63)	<0.001	−44.1	1,163	178 (15.3)			
No-G/D/P† (n = 23,714)	6,432 (27.1)				1,163	289 (24.9)	0.62 (0.52–0.73)	<0.001	−38.4
DPP-4 (n = 2,264)	543 (24.0)	0.88 (0.82–0.95)	0.001	−11.6	2,264	543 (24.0)			
No-G/D/P† (n = 23,714)	6,432 (27.1)				2,264	662 (29.2)	0.82 (0.74–0.90)	<0.001	−18.0
Pioglitazone (n = 469)	112 (23.0)	0.88 (0.75–1.04)	0.12	−12.0	340	85 (25.0)			
No-G/D/P† (n = 23,714)	6,432 (27.1)				340	96 (28.2)	0.89 (0.70–1.14)	0.34	−11.5
Any Med‡ (n = 5,606)	1,101 (19.6)	0.72 (0.68–0.77)	<0.001	−27.6	5,520	1,083 (19.6)			
No-G/D/P† (n = 23,714)	6,432 (27.1)				5,520	1,488 (27.0)	0.73 (0.68–0.78)	<0.001	−27.2
Mortality									
No-G/D/P† (n = 23,714)	1,443 (6.1)								
All T2DM (n = 29,516)	1,921 (6.5)	1.04 (0.98–1.12)	0.21	−6.5					
GLP-1 (n = 1,774)	44 (2.5)	0.41 (0.30–0.55)	<0.001	−59.2	1,163	22 (1.9)			
No-G/D/P† (n = 23,714)	1,443 (6.1)				1,163	38 (3.3)	0.58 (0.35–0.97)	0.04	−42.1
DPP-4 (n = 2,264)	169 (7.5)	1.23 (1.05–1.43)	0.009	22.7	2,264	169 (7.5)			
No-G/D/P† (n = 23,714)	1,443 (6.1)				2,264	164 (7.2)	1.03 (0.84–1.26)	0.78	3.1
Pioglitazone (n = 469)	21 (4.5)	0.74 (0.48–1.12)	0.15	−26.4	340	17 (5.0)			
No-G/D/P† (n = 23,714)	1,443 (6.1)				340	16 (4.7)	1.06 (0.55–2.07)	0.86	6.3
Any Med‡ (n = 5,606)	266 (4.7)	0.78 (0.69–0.89)	<0.001	−22.0	5,520	254 (4.6)			
No-G/D/P† (n = 23,714)	1,443 (6.1)				5,520	299 (5.4)	0.85 (0.72–1.00)	0.05	−15.1

P values indicate significance compared with the No-G/D/P cohort. *Propensity matching balanced cohorts according to age, sex, race, ethnicity, BMI, and the presence of essential (primary) hypertension, ischemic heart disease, cerebrovascular disease, heart failure, chronic kidney disease, or overweight and obesity in the EMR within 6 months before COVID-19 diagnosis. †The No-G/D/P cohort consisted of patients with T2DM with a diagnosis of COVID-19 or positive test results for SARS-CoV-2 who did not have any GLP-1R agonists, DPP-4 inhibitors, or pioglitazone in the EMR. ‡The Any Med cohort consisted of patients with T2DM with a diagnosis of COVID-19 or positive test results for SARS-CoV-2 who had GLP-1R agonists, DPP-4 inhibitors, and/or pioglitazone in the EMR.
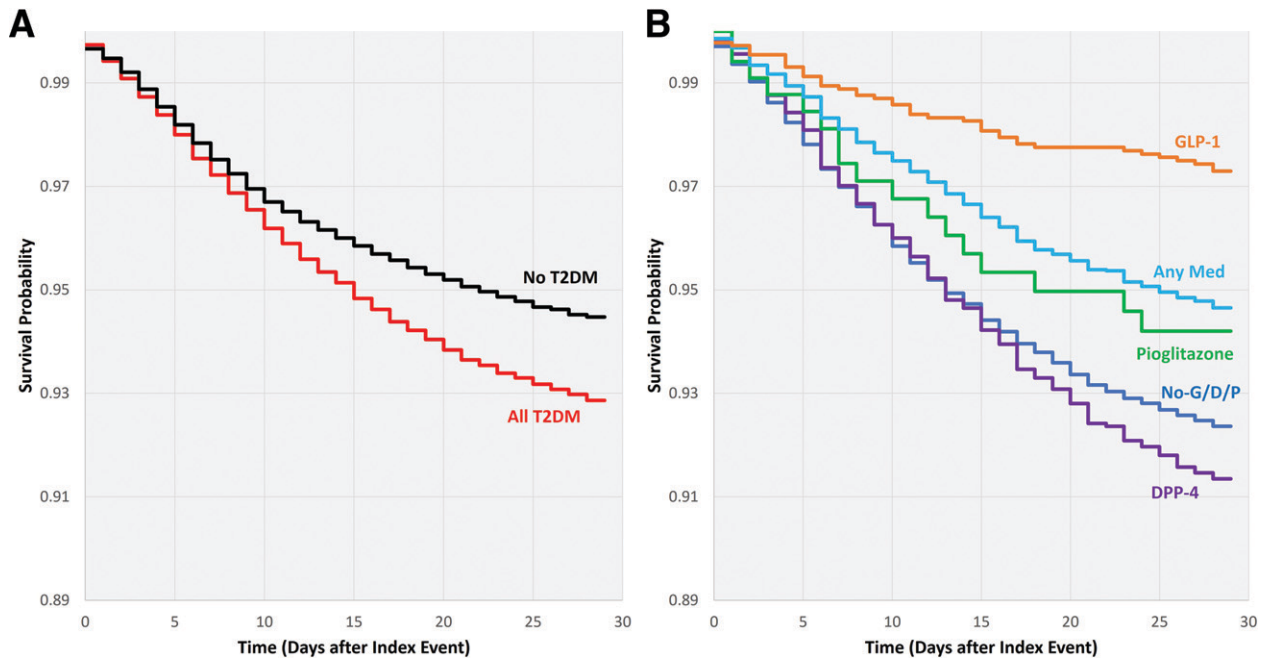
Figure 2—Survival probability by cohort up to 28 days after the first record of COVID-19 (diagnosis code for COVID-19 or positive test results for SARS-CoV-2). A: All patients without T2DM (n = 200,293) and all patients with T2DM (n = 29,516). B: Patients in the drug comparison cohorts (No-G/D/P, n = 23,714; GLP-1R agonists, n = 1,774; DPP-4 inhibitors, n = 2,264; pioglitazone, n = 469; Any Med, n = 5,606).

were compared with those whose medications were discontinued (Table 5). Of those who were hospitalized, 35.2% (94 of 267) in the GLP-1 cohort, 39.6% (264 of 667) in the DPP-4 cohort, 39.8% (43 of 108) in the pioglitazone cohort, and 38.6% (486 of 1,259) of the Any Med cohort remained on their respective medications (see Supplementary Table 4 for baseline patient characteristics and Supplementary Tables 4 and 5 for laboratory values at admission and during hospitalization). There were no differences in the incidence of respiratory complications for patients who continued compared with those who discontinued GLP-1R agonists or pioglitazone both before (GLP-1R: 39% vs. 44%, RR 0.87 [95% CI 0.65–1.18; P = 0.37]; pioglitazone: 36% vs. 51%, RR 0.70 [95% CI 0.44–1.11; P = 0.11]) and after (GLP-1R: 46% vs. 54%, RR 0.86 [95% CI 0.61–0.1.21; P = 0.39]; pioglitazone: 43% vs. 47%, RR 0.93 [95% CI 0.53–1.63; P = 0.80]) propensity matching (Table 6). Hospitalized patients in the DPP-4 cohort and Any Med cohort who remained on their medications had a 59% and 52% relative decrease in the incidence of mortality compared with patients who discontinued their medication (DPP-4: 9% vs. 21%, RR 0.42 [95% CI 0.27–0.64; P < 0.001]; Any Med: 8% vs. 16%, RR 0.48 [95% CI 0.34–0.69; P < 0.001]). This maintained significance after propensity matching, with the DPP-4 cohort having a 55% relative reduction (9% vs. 19%, RR 0.45 [95% CI 0.28–0.72; P < 0.001) and the Any Med cohort having a 49% reduction in mortality (8% vs. 15%, RR 0.51 [95% CI 0.35–0.73; P < 0.001). Differences in mortality as a function of the continuation of medication could not be compared within the GLP-1R or pioglitazone cohorts following propensity matching because of small group size.

DISCUSSION

Of the 68,959,064 patients in the database, 1.6% of patients without T2DM and 6.5% of patients with T2DM died within 28 days after the first record of COVID-19. This reflects a fourfold increase in mortality for patients positive for COVID-19 with a comorbid condition of T2DM. Similar data were reported in a large study conducted in England, where 31.4% of all in-hospital COVID-19 deaths occurred in patients diagnosed with T2DM (9). In the current study, risk for mortality varied across the life span and was increased in each decade in patients with a comorbid diagnosis of T2DM. For those aged ≥30 years, a diagnosis of T2DM was associated with a 2.9-fold relative increase in risk for mortality. This finding is consistent with the twofold increase in mortality reported for adult (mean age 52.6 ± 17.4 years) patients positive for COVID-19 with T2DM (44). For patients <30 years of age, we found a stunning 22.8-fold relative increase in mortality for those with T2DM. With the incidence of diabetes (in particular T2DM) increasing for younger adults around the globe (45), this vulnerable population is at far greater risk of mortality. Finally, the incidence of mortality was found to peak in the ninth decade of life at 14.2% for patients without T2DM and 18.8% for patients with T2DM. This observation also is consistent with the literature showing severity of disease and death to be markedly increased in elderly patients, particularly in those with a comorbid diagnosis of T2DM (46,47).

This study is the first to provide evidence that patients with T2DM treated with GLP-1R agonists, and to a lesser extent pioglitazone and DPP-4 inhibitors, within the 6 months preceding the diagnosis of COVID-19

Table 5—Baseline characteristics of hospitalized patients who continued or discontinued specified medications

Characteristic and cohort	Before propensity matching				After propensity matching*			
	Continued†	Discontinued	P	SMD	Continued†	Discontinued	P	SMD
Age,‡ years, mean (SD)								
No-G/D/P§	64.9 (14.8)	—	—	—	—	—	—	—
GLP-1	58.3 (13.1)	57.5 (13.5)	0.70	0.05	59.2 (13.6)	57.6 (12.8)	0.49	0.11
DPP-4	66.4 (13.0)	68.5 (12.7)	0.03	0.14	67.1 (12.7)	66.4 (12.4)	0.50	0.05
Pioglitazone	65.3 (12.7)	69.5 (11.6)	0.08	0.28	67.2 (12.4)	66.4 (12.7)	0.81	0.05
Any Med‖	64.1 (13.3)	65.3 (13.6)	0.15	0.08	64.3 (13.1)	64.7 (13.4)	0.62	0.03
Male sex, n/N (%)								
No-G/D/P§	3,661/6,742 (54)	—	—		—	—	—	
GLP-1	40/94 (43)	76/173 (44)	0.95		31/67 (46)	29/67 (43)	0.73	
DPP-4	143/264 (54)	212/403 (53)	0.65		133/253 (53)	138/253 (55)	0.66	
Pioglitazone	24/43 (56)	32/65 (49)	0.45		13/30 (43)	16/30 (53)	0.44	
Any Med‖	254/486 (52)	378/773 (49)	0.25		249/482 (52)	237/482 (49)	0.41	
BMI, kg/m², mean (SD)								
No-G/D/P§	30.8 (8.5)	—	—		—	—	—	
GLP-1	30.9 (6.2)	40.2 (11.3)	0.009	1.04	31.4 (6.6)	39.4 (13.6)	0.11	0.90
DPP-4	29.1 (5.9)	30.6 (8.1)	0.14	0.17	29.1 (5.9)	29.2 (7.9)	0.92	0.01
Pioglitazone	33.1 (11.1)	30.0 (6.9)	0.29	0.35	32.3 (12.8)	32.4 (9.2)	0.97	0.01
Any Med‖	31.5 (7.4)	32.8 (9.1)	0.12	0.15	31.5 (7.4)	31.7 (9.7)	0.85	0.02
Comorbidities,¶ n/N (%)								
Essential (primary) hypertension								
No-G/D/P§	3,486/6,741 (52)	—	—		—	—	—	
GLP-1	55/94 (59)	109/173 (63)	0.58		38/67 (57)	44/67 (66)	0.29	
DPP-4	163/264 (62)	250/403 (62)	0.88		156/253 (62)	163/253 (64)	0.52	
Pioglitazone	27/43 (63)	39/65 (60)	0.77		19/30 (63)	18/30 (60)	0.79	
Any Med‖	303/486 (62)	478/773 (62)	0.89		300/482 (62)	304/482 (63)	0.79	
Overweight and obesity								
No-G/D/P§	1,793/6,741 (27)	—	—		—	—	—	
GLP-1	32/94 (34)	86/173 (50)	0.02		26/67 (39)	25/67 (37)	0.86	
DPP-4	73/264 (28)	101/403 (25)	0.46		65/253 (26)	60/253 (24)	0.61	
Pioglitazone	18/43 (42)	24/65 (37)	0.59		12/30 (40)	13/30 (43)	0.79	
Any Med‖	152/486 (31)	264/773 (34)	0.28		151/482 (31)	152/482 (32)	0.95	
Ischemic heart disease								
No-G/D/P§	1,598/6,741 (24)	—	—		—	—	—	
GLP-1	26/94 (28)	38/173 (22)	0.29		16/67 (24)	14/67 (21)	0.68	
DPP-4	75/264 (28)	129/403 (32)	0.31		71/253 (28)	71/253 (28)	>0.99	
Pioglitazone	<10/43 (—)	22/65 (34)	—		<10/30 (—)	<10/30 (—)	—	
Any Med‖	127/486 (26)	226/773 (29)	0.22		127/482 (26)	120/482 (25)	0.56	

Table 5—Continued

Characteristic and cohort	Before propensity matching				After propensity matching*			
	Continued†	Discontinued	P	SMD	Continued†	Discontinued	P	SMD
Heart failure								
No-G/D/P§	1,598/6,741 (19)	—			—	—		
GLP-1	17/94 (18)	31/173 (18)	0.94		12/67 (18)	12/67 (18)	>0.99	
DPP-4	60/264 (23)	111/403 (28)	0.13		59/253 (23)	56/253 (22)	0.75	
Pioglitazone	<10/43 (-)	<10/65 (—)	—		<10/30 (—)	<10/30 (—)	—	
Any Med‖	93/486 (19)	179/773 (23)	0.09		93/482 (19)	94/482 (20)	0.94	
Cerebrovascular disease								
No-G/D/P§	593/6,741 (9)	—			—	—		
GLP-1	<10/94 (—)	<10/173 (—)	—		<10/67 (-)	<10/67 (—)	—	
DPP-4	26/264 (10)	51/403 (13)	0.25		25/253 (10)	30/253 (12)	0.56	
Pioglitazone	<10/43 (—)	<10/65 (—)	—		<10/30 (-)	<10/30 (—)	—	
Any Med‖	45/486 (9)	82/773 (11)	0.48		44/482 (9)	48/482 (10)	0.67	
Chronic kidney disease								
No-G/D/P§	1,598/6,741 (25)	—			—	—		
GLP-1	18/94 (19)	41/173 (24)	0.45		14/67 (21)	18/67 (27)	0.42	
DPP-4	75/264 (28)	154/403 (38)	0.008		78/253 (31)	85/253 (34)	0.51	
Pioglitazone	<10/43 (—)	16/65 (25)	—		<10/30 (—)	<10/30 (—)	—	
Any Med‖	118/486 (24)	244/773 (32)	0.005		119/482 (25)	114/482 (24)	0.72	

P values indicate significance between continued and discontinued and discontinued groups. SMD, standardized mean difference between continued and discontinued groups. *Propensity matching balanced cohorts according to age, sex, race, ethnicity, BMI, and the presence of essential (primary) hypertension, ischemic heart disease, cerebrovascular disease, heart failure, chronic kidney disease, or overweight and obesity in the EMR within 6 months before COVID-19 diagnosis. †Patients with the specified medication listed in the EMR after hospitalization within 28 days of a diagnosis of COVID-19 or positive test results for SARS-CoV-2 were included in the continued group, while those without the specified medications were assigned to the discontinued group. ‡Age is defined as the age of the patient at the time of diagnosis of COVID-19 or positive test results for SARS-CoV-2. §The No-G/D/P cohort consisted of patients with T2DM with a diagnosis of COVID-19 or positive test results for SARS-CoV-2 who did not have any GLP-1R agonists, DPP-4 inhibitors, or pioglitazone in the EMR. Values for the No-G/D/P group represent all hospitalized patients with T2DM with a diagnosis of COVID-19 or positive test results for SARS-CoV-2 who had GLP-1R agonists, DPP-4 inhibitors, and/or pioglitazone in the EMR. ‖The Any Med cohort consisted of patients with T2DM with a diagnosis of COVID-19 or positive test results for SARS-CoV-2. ¶Comorbidities are assessed as presence of a diagnostic code for the six major comorbidities within the EMR within 6 months up to the time of diagnosis of COVID-19 or positive test results for SARS-CoV-2.

Table 6—Risk of adverse outcomes within 28 days after COVID-19 diagnosis or positive SARS-CoV-2 test results among hospitalized patients who continued or discontinued specified medications after hospitalization

Cohort	Exposure	Before propensity matching				After propensity matching*			
		n/N (%)	RR (95% CI)	P	Relative change, %	n/N (%)	RR (95% CI)	P	Relative change, %
Respiratory complications									
GLP-1	Continued†	36/93 (39)	0.87 (0.65–1.18)	0.37	−13	31/67 (46)	0.86 (0.61–1.21)	0.39	−14
	Discontinued	76/171 (44)				36/67 (54)			
DPP-4	Continued†	78/263 (30)	0.69 (0.56–0.85)	<0.001	−31	77/253 (30)	0.67 (0.53–0.84)	<0.001	−33
	Discontinued	173/401 (43)				116/253 (46)			
Pioglitazone	Continued†	15/42 (36)	0.70 (0.44–1.11)	0.11	−30	13/30 (43)	0.93 (0.53–1.63)	0.80	−7
	Discontinued	32/63 (51)				14/30 (47)			
Any Med‡	Continued†	149/487 (31)	0.69 (0.59–0.80)	<0.001	−31	146/482 (30)	0.66 (0.56–0.78)	<0.001	−34
	Discontinued	342/771 (44)				221/482 (46)			
Mortality									
GLP-1	Continued†	<10/93 (—)	—	—	—	<10/67 (—)	—	—	—
	Discontinued	14/167 (8)				<10/67 (—)			
DPP-4	Continued†	23/263 (9)	0.42 (0.27–0.64)	<0.001	−59	22/253 (9)	0.45 (0.28–0.72)	<0.001	−55
	Discontinued	84/401 (21)				49/253 (19)			
Pioglitazone	Continued†	<10/42 (—)	—	—	—	<10/30 (—)	—	—	—
	Discontinued	11/63 (17)				<10/30 (—)			
Any Med‡	Continued†	37/487 (8)	0.48 (0.34–0.69)	<0.001	−52	37/487 (8)	0.51 (0.35–0.73)	<0.001	−49
	Discontinued	120/771 (16)				73/487 (15)			

P values indicate significance between continued and discontinued groups. *Propensity matching balanced cohorts according to age, sex, race, ethnicity, BMI, and the presence of essential (primary) hypertension, ischemic heart disease, cerebrovascular disease, heart failure, chronic kidney disease, or overweight and obesity in the EMR within 6 months before COVID-19 diagnosis. †Patients with the specified medication listed in the EMR after hospitalization within 28 days of a diagnosis of COVID-19 or positive test results for SARS-CoV-2 were included in the continued group, while those without the specified medications were assigned to the discontinued group. ‡The Any Med cohort consisted of patients with T2DM with a diagnosis of COVID-19 or positive test results for SARS-CoV-2 who had GLP-1R agonists, DPP-4 inhibitors, and/or pioglitazone in the EMR.

demonstrated better outcomes than patients not treated with these medications. Matched patients receiving GLP-1R agonists exhibited a relative reduction of 33.0% for hospital admissions, 38.4% for respiratory complications, and 42.1% for mortality within 28 days following the first record of COVID-19. Interestingly, when matched to the GLP-1R agonist–treated cohort, selected patients in the No-G/D/P cohort appeared slightly more resilient than those matched to the DPP-4, pioglitazone, or Any Med cohorts with lower admission rates, fewer respiratory complications, and reduced mortality. Patients on DPP-4 inhibitors had an 18.0% relative reduction in respiratory complications but did not have significant reductions in hospital admissions or mortality. Patients treated with pioglitazone showed a relative reduction of 29.2% for hospital admissions but did not have significant reductions in respiratory complications or mortality. Combined, patients in the Any Med cohort exhibited a relative reduction of 16.2% for hospital admissions, 27.2% for respiratory complications, and 15.1% for risk of mortality within 28 days following the first record of COVID-19.

Among patients in the DPP-4 cohort who were hospitalized, those who continued DPP-4 treatment had reduced mortality compared with those who discontinued DPP-4 treatment during hospitalization (9% vs. 19%, respectively). This is consistent with another recent multicenter retrospective study that showed that treatment with the DPP-4 inhibitor sitagliptin during hospitalization for COVID-19 was associated with decreased mortality and improved clinical outcomes compared with standard-of-care treatment in patients with T2DM (48). In addition to anti-inflammatory effects, DPP-4 inhibitors may reduce the entry of SARS-CoV-2 into cells because ACE2, the binding site for SARS-CoV-2, has high homology with DPP-4 (49).

The mean baseline HbA_{1c} for all patients with T2DM and a diagnosis of COVID-19 or positive SARS-CoV-2 test results was 7.7% (Table 2). This is above the target of 7% and indicates that on average, patients with T2DM and COVID-19 have impaired glycemic control. There was no significant difference in the mean baseline HbA_{1c} between those alive at 28 days compared with those deceased at 28 days (7.7% vs. 7.8%, respectively). This is unexpected as worse glycemic control has been associated with worse clinical outcomes in patients with diabetes who develop COVID-19. Because HbA_{1c} was similar in those deceased at 28 days to those alive at 28 days, this finding suggests that other factors beyond glycemic control contribute to mortality in patients with T2DM and COVID-19.

The mean baseline HbA_{1c} was significantly greater in the GLP-1 cohort compared with the No-G/D/P cohort (8.4% vs. 7.5%) and in the DPP-4 cohort compared with the No-G/D/P cohort (8.0% vs. 7.5%) (Table 3). This may be a limitation of the study as differences in HbA_{1c} may have contributed to differences in hospitalizations, respiratory complications, and mortality between cohorts.

Considering that the mean baseline HbA_{1c} was higher in the GLP-1 cohort compared with the No-G/D/P cohort, the expected effect would have been worse outcomes in the GLP-1 cohort. Despite having worse baseline glycemic control, the GLP-1 cohort had significant reductions in hospitalizations, respiratory complications, and mortality compared with the No-G/D/P cohort. With regard to the DPP-4 cohort, considering that the mean baseline HbA_{1c} was higher in the DPP-4 cohort compared with the No-G/D/P cohort, the expected effect would have been worse outcomes in the DPP-4 cohort. Despite having worse baseline glycemic control in the DPP-4 cohort, there was no significant difference in hospitalizations in the DPP-4 cohort compared with the No-G/D/P cohort. Additionally, the DPP-4 cohort had significant reductions in respiratory complications compared with the No-G/D/P cohort suggesting that factors other than glycemic control may be responsible for the protective effects of GLP-1 analogs and DPP-4 inhibitors in patients with T2DM and COVID-19.

Limitations

The main limitation of this study is its retrospective nature. Causal relationships could not be inferred, and we could not control variables such as the duration of use of medications before hospital admission, dosage, and treatments received after admission. Furthermore, analyses only included patients with a diagnostic code for T2DM in the EMR within the 6 months preceding the first record of COVID-19. Therefore, patients without a visit for T2DM within that time frame or with undiagnosed diabetes or prediabetes were not captured in these analyses. While this limited the sample size, it also increased the certainty that all patients included in the analyses were diagnosed with T2DM, leading to more conservative results. This limitation does, however, prevent analysis of the duration of T2DM. The length of time each patient has had T2DM is an important variable that should be assessed in prospective analyses. Additionally, outside a randomized controlled trial, it is not possible to know whether underlying variables may have influenced the results, such as having an established relationship with a prescribing physician or access to medical care. The design of the current study may have accounted for such factors based on the wide geographical and socioeconomic inclusion of the database and propensity matching; however, a prospective trial is necessary to fully determine whether there are protective effects of GLP-1R agonists, DPP-4 inhibitors, or pioglitazone on adverse outcomes in patients with T2DM and COVID-19. Another limitation of the study is the method of collection and analysis available. To provide real-time electronic health records of patients with COVID-19, the TriNetX COVID-19 Research Network only allows access to aggregated counts and statistical summaries of deidentified information. Furthermore, all analyses are conducted using the browser-based real-time analytics feature of TriNetX as previously

described (42,43), which may limit the flexibility of statistical methods such as the use of propensity matching. Notably, the size of the pioglitazone cohort after propensity matching is much smaller than the other cohorts, making the interpretation of the analyses less reliable than the other cohorts.

Conclusions

The results of this study suggest that treatment with GLP-1R agonists before hospitalization and DPP-4 inhibitors before and/or during hospitalization may be expedient interventions to reduce mortality in patients with COVID-19 and T2DM. This hypothesis warrants further evaluation to determine whether the suggestion of a protective effect bears out in a prospective observational study or adequately powered randomized controlled trial. Subsequent assessment also should consider whether prolonged use is necessary or whether benefit can be derived from acute administration. The DPP-4 data are particularly interesting in this regard. Clinical trials also could be considered in patients without T2DM and across the life span to determine whether these agents possess intrinsic protective properties that could represent a novel therapeutic approach against SARS-CoV-2 infection.

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