Use of Novel Antidiabetic Agents in Patients with Type 2 Diabetes and COVID-19: A Critical Review

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19). The latter is a pandemic that has the potential of developing into a severe illness manifesting as systemic inflammatory response syndrome, acute respiratory distress syndrome, multi-organ involvement and shock. In addition, advanced age and male sex and certain underlying health conditions, like type 2 diabetes mellitus (T2DM), predispose to a higher risk of greater COVID-19 severity and mortality. This calls for an urgent identification of antidiabetic agents associated with more favourable COVID-19 outcomes among patients with T2DM, as well as recognition of their potential underlying mechanisms.

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It is crucial that individuals with T2DM be kept under very stringent glycaemic control in order to avoid developing various cardiovascular, renal and metabolic complications associated with more severe forms of COVID-19 that lead to increased mortality. The use of novel antidiabetic agents dipeptidyl peptidase 4 inhibitors (DPP4i), sodium-glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP-1RAs) in subjects with T2DM may have beneficial effects on COVID-19 outcomes. However, relevant studies either show inconsistent results (DPP4i) or are still too few (SGLT2i and GLP-1RAs). Further research is therefore needed to assess the impact of these agents on COVID-19 outcomes.

Key Summary Points

Advanced age and male gender, as well as certain underlying health conditions, like type 2 diabetes mellitus, obesity and hypertension predispose to a higher risk of greater COVID-19 severity and mortality.

It is crucial that individuals with type 2 diabetes mellitus be kept under very stringent glycaemic control in order to avoid developing various cardiovascular, renal and metabolic complications associated with more severe forms of COVID-19 that lead to increased mortality.

The use of novel antidiabetic agents (dipeptidyl peptidase 4 inhibitors, sodium-glucose co-transporter 2 inhibitors and glucagon-like peptide 1 receptor agonists) in subjects with type 2 diabetes mellitus may have beneficial effects on COVID-19 outcomes.

Relevant studies either show inconsistent results (dipeptidyl peptidase 4 inhibitors) or are still too few (sodium-glucose co-transporter 2 inhibitors and glucagon-like peptide 1 receptor agonists) to make definitive conclusions; still, it seems that some novel antidiabetic agents have a favourable effect during the current pandemic.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19), a new pandemic that is currently ongoing, with a dramatic impact in many countries [1, 2]. In humans, the main route of SARS-CoV-2 transmission is through virus-bearing respiratory droplets [3, 4]. Its main entry receptor in human cells is angiotensin-converting enzyme 2 (ACE2) receptors which are expressed in alveolar lung cells, cardiac myocytes, vascular endothelium and other various types of cells [5, 6].

SARS-CoV-2 induces mild symptoms in the initial stage of infection which usually lasts about 2 weeks. However, it may develop into a more severe illness [7], including systemic inflammatory response syndrome, acute respiratory distress syndrome (ARDS), multi-organ involvement and shock [7]. Certain patient-related characteristics such as advanced age, male sex and underlying health conditions like cardiovascular disease, obesity and diabetes mellitus (DM) predispose to a higher risk of severe forms of COVID-19 and death [8, 9]. The close association between diabetes and COVID-19 hospitalisation and mortality has been reported in multiple cohorts globally [10]. Diabetes is closely correlated with COVID-19 morbidity, including hospitalisation, critical illness and mortality [11].

Several potential mechanisms have been suggested, firstly that hyperglycaemia may promote viral proliferation. Elevated glucose

increases SARS-CoV-2 replication, while glycolysis increases the production of mitochondrial reactive oxygen species (ROS) and activation of hypoxia-inducible factor 1α in human monocytes [12]. Indeed, poor glycaemic control predicts the need for medications and hospitalisation, as well as increased mortality [13, 14]. Secondly, inflammation is the main feature of COVID-19 and increases insulin resistance [15]. Excess inflammation impacts both skeletal muscle and liver function [16]. Inflammation during COVID-19 might increase the risk of micro- and macrovascular complications originating from low-grade vascular inflammation in type 2 DM (T2DM) [17]. The results of a nationwide French study showed that micro- and macrovascular complications of DM were significantly associated with a high risk of mortality in patients with COVID-19 [18]. Thirdly, T2DM is associated with immunological dysregulation, potentially equivalent to accelerated aging, which could explain the poor prognosis in patients with T2DM and COVID-19 [19]. Fourthly, ACE2 is expressed in the endocrine pancreas where coronaviruses might damage the islets, potentially leading to hyperglycaemia [20, 21]. Indeed, high glucose is found to persist up to 3 years after recovery from SARS [21]. Finally, some of the drugs often used in the clinical care of patients with COVID-19 (notably systemic corticosteroids and antiviral agents) may aggravate hyperglycaemia [19, 22].

Hence, it has been suggested that some of antidiabetic agents may be associated with more favourable COVID-19 outcomes and the potential underlying mechanisms [23]. This review summarises the current knowledge regarding the impact of three novel antidiabetic drug classes, namely dipeptidyl peptidase 4 inhibitors (DPP4i), sodium-glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP-1RAs), on clinical outcomes in patients with T2DM and COVID-19.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

SEARCH STRATEGY

We performed an electronic search in PubMed, Google Scholar and SCOPUS databases in order to identify so far published studies using different combinations of the following keywords: COVID-19, coronavirus disease 2019, dipeptidyl peptidase 4 inhibitors, glucagon-like peptide 1 receptor agonists, mortality, outcomes, severity, sodium-glucose co-transporter 2 inhibitors, type 2 diabetes mellitus. Only publications in English language were considered.

USE OF DPP4I IN PATIENTS WITH T2DM AND COVID-19

Although it was speculated that SARS-CoV-2 might enter cells by binding to DPP4, recent studies have demonstrated that SARS-CoV-2 spike protein does not interact with human membrane-bound DPP4 (CD26) [24, 25]. Interestingly, DPP4i may have beneficial effects in patients with T2DM and COVID-19 through other mechanisms. The DPP4 enzyme has been shown to promote cell proliferation, CD86 expression and activation of the nuclear factor kappa-light-chain-enhancer of activated B cells signaling pathway, resulting in excessive inflammatory cytokine production [26, 27]. Additionally, DPP4 degrades endogenous GLP-1, which also harbours anti-inflammatory properties [28, 29]. Finally, DPP4 levels are significantly higher in obesity and metabolic syndrome [30, 31], which are some of the comorbidities associated with poorer outcomes in COVID-19.

Reports on outcomes of DPP4i in patients with T2DM and COVID-19 have not been remarkably consistent.

A multicentre retrospective observational study examined whether sitagliptin added to standard care in patients with T2DM

hospitalised with COVID-19 conferred any benefit [32]. All patients had pneumonia and exhibited oxygen saturation below 95% when breathing ambient air or receiving oxygen support [32]. The primary endpoints were discharge from the hospital/death and improved clinical outcomes (increase of at least 2 points on a 7-point scale) [32]. Add-on sitagliptin was associated with a significant reduction in mortality, enhanced clinical outcomes and a more significant number of hospital discharges [32]. Another work examined the impact of T2DM, different comorbidities, plasma glucose levels and antidiabetic medications on the survival of 90 patients with COVID-19 [33]. DPP4i were significantly and independently associated with a lower risk of mortality [33]. In a nationwide, multicentre observational study among 790 patients with T2DM at least 80 years of age with COVID-19 conducted in Spain, the use of DPP4i was an independent protector against in-hospital mortality [34]. The multinational retrospective cohort study, which included 7769 patients with T2DM and COVID-19 from a COVID-19 Research Network, had mortality as the primary outcome and the incidence of hospitalisation and respiratory complications as secondary outcomes [35]. In DPP4i users significant reductions in mortality (26%) and in hospital admissions (20%) were reported, while hospitalised patients who continued treatment with DPP4i had a 63% relative decrease in the incidence of mortality when compared with those who discontinued treatment with DPP4i [35].

Sainsbury et al. [36] performed a propensity score-matched cohort study to investigate whether SGLT2i prescription may be associated with COVID-19 compared to DPP4i. The primary outcome was confirmed or clinically suspected COVID-19. Ten thousand individuals with prescribed SGLT2i and about 15,000 with prescribed DPP4i were included; the main finding was a similar risk of confirmed or clinically suspected COVID-19 between users of these two classes of antidiabetic drugs [36]. In another multicentre retrospective cohort study

performed in the UK and including about a thousand consecutive inpatients with COVID-19, there was no association between usage of different antidiabetic medications (including DPP4i, insulin, GLP-1RAs, metformin, sulfonylurea and SGLT2i) and the risk of death and/or ICU admission within 30 days of COVID-19 diagnosis [37]. In a retrospective observational study conducted in Italy on 159 patients with diabetes, there was no association between use of some antidiabetic medications (DPP4i, metformin, pioglitazone, insulin, sulfonylurea/ glinides, SGLT2i and GLP-1RAs) and the risk of either COVID-19 or case fatality, with the only exception of metformin, which was associated with the latter [38].

In another retrospective Belgian study of 73 patients with DM and COVID-19, non-survivors were equally often treated with DPP4i, sulfonylurea/glinides, SGLT2i, GLP-1RAs and insulin, but less often treated with metformin prior to admission in comparison to survivors [39]. An update of the results from the nationwide French Coronavirus SARS-CoV-2 and Diabetes Outcomes (CORONADO) study demonstrated that in 2796 patients with DM and COVID-19, routine metformin therapy was one of the predictors of discharge on day 28 and negatively associated with death within 28 days, while routine treatments with DPP4i, sulfonylurea/glinides, GLP-1RAs and insulin were not associated with those outcomes [40].

A large Korean study [41] included patients who had a positive test result for COVID-19, had been diagnosed with T2DM within the preceding 3 years and had at least one antidiabetic prescription within the preceding 180 days. Patients were classified into two groups: users of DPP4i with/without other antidiabetic drugs, and users of other non-insulin antidiabetic drugs, individually or in combination [41]. Unadjusted survival curves demonstrated a significant lower probability of all-cause mortality and severe COVID-19 manifestations among users of DPP4i; yet, DPP4i use was insignificantly associated with all-cause mortality and severe manifestations [41]. A

case–control study by Fadini et al. showed no better outcomes among DPP4i users [42]. Similarly, a study based on medical charts of patients with fatal COVID-19 from different Italian districts reported that geographical differences in DPP4i use did not correlate with DM prevalence among COVID-19 deaths [43]. Consistent with such findings, in the secondary analysis of the CORONADO study, 2449 patients with T2DM hospitalised for COVID-19 in 68 French centres were included [44]. The primary outcome (tracheal intubation for mechanical ventilation and death within 7 days of admission) occurred at similar rates in users vs. non-users of DPP4i [44]. There was no significant association between DPP4i and the primary outcome on days 7 or 28. DPP4i did not reduce the risk of tracheal intubation and death [44].

In a multicentre retrospective analysis including subjects with T2DM who were hospitalised with COVID-19 in 16 Chinese hospitals [45], there was no significant association between in-hospital DPP4i use and 28-day all-cause mortality. In addition, incidences and risks of secondary outcomes, including septic shock, ARDS or acute kidney/liver failure, were comparable between DPP4i users and non-users [45]. Further, in a retrospective, observational cohort study conducted among 717 patients with COVID-19 in Singapore, the fully adjusted model revealed that DPP4i use was associated with higher risk of ICU admission and mechanical ventilation among 76 subjects with T2DM [46]. Another population-based study used data from nationwide registries to examine the impact of DPP4i ($N = 284$) and GLP-1RAs ($N = 370$) compared with SGLT2i ($N = 342$) on the risk of hospital admission and severe outcomes of COVID-19 [47]. GLP-1RAs users had similar 30-day mortality to SGLT2i users (3.3% vs. 3.7%); both were lower vs. DPP4i users (8.6%) [47]. The risks of hospital admission, ICU admission and mechanical ventilation were overall similar in DPP4i and GLP-1RAs users vs. SGLT2i users [47]. In addition, the recently published observational study from the National COVID Cohort Collaborative (N3C), including 12,446 SARS-CoV-2-positive adults, with 60-day mortality as primary outcome, showed that both GLP1-RAs and SGLT2i use were associated with lower 60-day mortality compared to DPP4i use [48].

Finally, two meta-analyses have shown some beneficial effect of DPP4i on mortality among patients with DM and COVID-19, either restricted only to in-hospital use [49] or in general [50]. Ongoing trials should further elucidate the impact of DPP4i on COVID-19 morbidity and mortality among individuals with T2DM (e.g. NCT04542213). The obvious heterogeneity of all the aforementioned studies does not allow one to make firm conclusions, and additional large-scale studies are needed to provide definitive answers. The initial enthusiasm regarding the use of DPP4i, considering a potential role of DPP4 in COVID-19 onset and progression, has dwindled since subsequent studies have shown equivocal results. Overall, the use of DPP4i is considered safe among subjects with T2DM and COVID-19 but probably not the treatment of choice, taking also into account the neutral effect of DPP4i on cardiovascular outcomes [51].

USE OF SGLT2I IN PATIENTS WITH T2DM AND COVID-19

In patients with T2DM, SGLT2i treatment is associated with a favourable decrease in messenger ribonucleic acid (mRNA) levels of some cytokines and chemokines, such as tumour necrosis factor alpha, interleukin-6 and monocyte chemoattractant protein 1 [52]. Additionally, SGLT2i may decrease lactate production due to reduced tissue oxygen demand, thereby potentially reducing viral entry by raising cytosolic pH [53]. On the other hand, SGLT2i could indirectly promote ACE2 activity [54], facilitating viral entry into cells. Undoubtedly, SGLT2i treatment can cause dehydration, ketoacidosis and acute kidney injury, especially among critically ill patients [55]. Either way,

despite their cardiorenal beneficial effects in cardiovascular outcome trials [56], the use of these agents might be complicated and even potentially dangerous in patients requiring critical care.

In a retrospective, observational cohort study performed in Singapore, SGLT2i use was associated with a lower risk of mechanical ventilation among 76 subjects with T2DM [46]. Israelsen et al. demonstrated, using data from nationwide registries, that SGLT2i users had similar 30-day mortality as GLP-1RAs users, while for both it was lower than that of DPP4i users [47]. However, the risks of hospital admission, ICU admission and mechanical ventilation were overall similar for all of three studied drug classes [47]. The previously cited observational study showed that both GLP1-RAs and SGLT2i usage were associated with lower 60-day mortality in comparison to DPP4i usage [48]. Further, a Spanish multicentre observational study enrolling very old patients with T2DM and COVID-19 showed no association between preadmission use of SGLT2i and in-hospital mortality [34].

Sainsbury et al. have shown that the risk of confirmed or clinically suspected COVID-19 between users of SGLT2i and DPP4i was similar [36], while in a multicentre retrospective cohort study conducted in the UK there was no association between use of different antidiabetic medications (including SGLT2i, DPP4i, insulin, GLP-1RAs, metformin and sulfonylurea) with the risk of death and/or ICU admission within 30 days of COVID-19 diagnosis [37]. An Italian retrospective observational study showed no association between usage of different antidiabetic medications (SGLT2i, DPP4i, metformin, pioglitazone, insulin, sulfonylurea/glinides and GLP-1RAs) and the risk of either COVID-19 or case fatality, except of metformin's association with lower rate of case fatality [38]. Finally, in another previously mentioned study from Belgium, enrolling patients with DM and COVID-19, survivors were equally often treated with SGLT2i, DPP4i, sulfonylurea/glinides and

insulin, but more often treated with metformin prior to admission in comparison to non-survivors [39].

Of note, the Dapagliflozin in Respiratory Failure in Patients With COVID-19 (DARE-19) trial that aimed to analyse if cardio- and reno-protective benefits of dapagliflozin can be extrapolated to high-risk patients with COVID-19 (with at least one cardiometabolic risk factor: hypertension, T2DM, atherosclerotic cardiovascular disease, heart failure and chronic kidney disease), but not critically ill [57]. Time to development of new or worsened organ dysfunction, or all-cause mortality, the composite endpoint of change in clinical status through day 30, as well as safety of dapagliflozin, were assessed. However, with some disappointment, trial results did not achieve statistical significance for the primary endpoints of prevention of organ dysfunction, reduction in all-cause mortality and improvement in the clinical status (ranging from early recovery to death) at 30 days [57].

In another randomised, parallel-arm, open-label platform trial (mulTi-Arm Therapeutic Study in Pre-ICU Patients Admitted With Covid-19-Experimental Drugs and Mechanisms (TACTIC-E), patients with COVID-19 without need for ICU admission would be enrolled and randomised to either an experimental drug EDP1815 (preparation of a single strain of *Prevotella histicola*) or dapagliflozin 10 mg daily plus ambrisentan (endothelin receptor antagonist) or standard care alone [58]. The primary outcome includes the composite endpoint of death, mechanical ventilation, extracorporeal membrane oxygenation, cardiovascular organ support or renal failure [58]. This study should scrutinise if the combination of dapagliflozin with ambrisentan may protect the patient against end-organ damage and modulate the pulmonary vascular response [58].

The shortage of dedicated large-scale studies analysing the role of SGLT2i among patients with T2DM and COVID-19 distracts us from any definite conclusions. However, a lot of hope has

been invested in the potential beneficial role of SGLT2i in patients with T2DM and COVID-19, considering their proven metabolic and cardiorenal benefits [56]. Although SGLT2i may prevent or delay the development of cardiovascular and renal events, their practical use might be complicated, especially in patients requiring critical care, since they can cause dehydration, ketoacidosis and acute kidney injury [55].

USE OF GLP-1RAS IN PATIENTS WITH T2DM AND COVID-19

Endogenous GLP-1 harbours anti-inflammatory properties [28, 29, 59]. These may be beneficial in patients with sepsis [60]. Hence, GLP-1RAs might attenuate excess inflammation in COVID-19. Liraglutide was shown to activate ACE2 expression in experimental animals; however, it is still uncertain whether this could lead to the facilitation or prevention of the infection and replication of SARS-CoV-2 in patients with T2DM [61]. On the other hand, since SARS-CoV-2 infection leads to increased ROS production [19], which has multiple negative effects on metabolism, cardiovascular system and the lungs, it has to be recalled that liraglutide has the ability to reduce oxidative stress in T2DM [62]. In addition, GLP-1RAs harbour beneficial cardiorenal properties [63], and could represent an ideal treatment option for patients with T2DM and cardiovascular and/or kidney disease during COVID-19 [64].

In a previously cited multinational retrospective cohort study, using data from a COVID-19 Research Network, GLP-1RAs users were hallmarked by the significant reductions in mortality (47%) and in hospital admissions (40%), including a reduction in respiratory complications (46%) [35]. A previously mentioned observational study from the National COVID Cohort Collaborative (N3C) group demonstrated that both GLP1-RAs and SGLT2i use were associated with lower 60-day mortality compared to DPP4i use [48]. Additionally, a population-based study using data from nationwide registries revealed that GLP-1RAs users had similar 30-day mortality to SGLT2i users, and that users of both of these drug classes had lower 30-day mortality than DPP4i users [47], while the risks of hospital admission, ICU admission and mechanical ventilation were overall similar in GLP-1RAs and DPP4i users in comparison to SGLT2i users [47].

The previously mentioned multicentre observational study encompassing very old patients with T2DM and COVID-19 in Spain revealed no association between preadmission use of GLP-1RAs and in-hospital mortality [34]. Additionally, in a UK multicentre retrospective cohort study there was no association between usage of different antidiabetic medications (including GLP-1RAs, DPP4i, insulin, metformin, sulfonylurea and SGLT2i) and the risk of death and/or ICU admission within 30 days of COVID-19 diagnosis [37]. Finally, in an Italian retrospective observational study, only metformin usage was associated with lower case fatality, while there was no association between usage of various antidiabetic medications (GLP-1RAs, DPP4i, metformin, pioglitazone, insulin, sulfonylurea/glinides and SGLT2i) and the risk of either COVID-19 or case fatality [38].

A recently published meta-analysis analysed the impact of preadmission use of GLP-1RAs on mortality outcomes of COVID-19 among patients with DM [65]. Very interestingly, the authors concluded that preadmission usage of GLP-1RAs was associated with reduction in mortality rate in patients with DM and COVID-19 independently of age, gender, hypertension, cardiovascular disease and the use of metformin and insulin [65]. Further studies investigating the role of GLP-1RAs in COVID-19 are already planned or undergoing [e.g. NCT04615871]. Although lots of hope has been invested in the beneficial role of GLP-1RAs among patients with T2DM and COVID-19 [66], considering the well-established and favourable metabolic and cardiorenal properties [56, 63], their initiation

Table 1 Summary of studies evaluating the use of novel antidiabetic agents in patients with T2DM and COVID-19

Authors	Study design	Primary outcome	N of patients	Main results
DPP4i				
Solerte [32]	Multicentre, case–control, retrospective, observational study; adding sitagliptin to standard of care	Discharge from hospital, improvement of clinical outcomes and mortality	338	*Positive* Reduced mortality, improvement in clinical outcomes, greater number of hospital discharges with sitagliptin
Mirani [33]	Single-centre, case series; evaluating the use of DPP4i	Mortality	90	*Positive* Lower risk of mortality with DPP4i
Ramos-Rincón [34]	Nationwide, multicentre observational study; evaluating use of several antidiabetic drugs, including DPP4i, GLP-1RAs and SGLT2i	Mortality	790	*Positive* DPP4i were independent protectors for mortality; metformin, insulin, GLP-1RAs and SGLT2i had a neutral effect on mortality
Nyland [35]	Multinational retrospective cohort study; evaluating use of pioglitazone, GLP-1RAs and DPP4i in comparison to no use of such therapies	Mortality	7769	*Positive* Significant reductions in mortality among users of pioglitazone, GLP-1RAs and DPP4i in comparison to non-users of pioglitazone, GLP-1RAs or DPP4i
Sainsbury [36]	Propensity score-matched cohort study, evaluating SGLT2i use in comparison to DPP4i	Confirmed or clinically suspected COVID-19	24,865	*Neutral* Similar risk of confirmed or clinically suspected COVID-19
Izzi-Engbeaya [37]	Multicentre retrospective cohort study; evaluating use of insulin, GLP-1RAs, metformin, sulfonylurea, SGLT2i and DPP4i	Death and/or ICU admission within 30 days of COVID-19 diagnosis	278	*Neutral* No association between insulin, GLP-1RAs, metformin, sulfonylurea, SGLT2i and DPP4i use and the risk of death and/or ICU admission within 30 days of COVID-19
Silverii [38]	Retrospective observational study; evaluating use of metformin, pioglitazone, insulin, sulfonylurea/glinides, DPP4i, SGLT2i and GLP-1RAs	COVID-19 prevalence and case fatality	159	*Neutral* No association with COVID-19 prevalence; metformin use associated with a lower case fatality

Table 1 continued

Authors	Study design	Primary outcome	N of patients	Main results
Orioli [39]	Retrospective single-centre cohort study; evaluating use of different antidiabetic medications	In-hospital mortality	73	*Neutral* Non-survivors were less often treated with metformin prior to admission in comparison to survivors
Wargny [40]	Update on the results of nationwide CORONADO study; evaluating use of metformin, sulfonylurea/glinides, DPP4i, GLP-1RAs and insulin	Hospital discharge and death within 28 days	2796	*Neutral* Routine metformin therapy was one of the predictors of discharge on day 28 and negatively associated with death within 28 days; routine insulin therapy was associated with greater risk of death within 28 days
Noh [41]	Nationwide cohort study; evaluating use of DPP4i	All-cause mortality	586	*Negative* DPP4i had no effect on all-cause mortality
Fadini [42]	Case–control study; evaluating use of DPP4i	Risk of hospitalisation	85	*Negative* DPP4i had no effect on the risk of hospitalisation
Strollo [43]	Review of medical charts; evaluating geographical differences in DPP4i use	Prevalence of diabetes among COVID-19 deaths	3351	*Negative* Geographical differences did not correlate with diabetes prevalence among COVID-19 deaths
Roussel [44]	Secondary analysis of the nationwide CORONADO study; evaluating DPP4i use	Tracheal intubation for mechanical ventilation and death within 7 days of admission	2449	*Negative* DPP4i had no effect on tracheal intubation for mechanical ventilation and death within 7 days of admission occurred at similar rates
Zhou [45]	Multicentre retrospective analysis; evaluating DPP4i use	28-day all-cause mortality	1257	*Negative* DPP4i had no effect on all-cause mortality
Dalan [46]	Retrospective, observational cohort study; evaluating use of DPP4i, SGLT2i and sulfonylureas	Hypoxia, ICU admission, mechanical ventilation or death	76	*Negative* DPP4i associated with higher risk of ICU admission and mechanical ventilation, SGLT2i associated with lower risk of mechanical ventilation

Table 1 continued

Authors	Study design	Primary outcome	N of patients	Main results
Israelsen [47]	Population-based cohort study; evaluating use of SGLT2i in comparison to DPP4i and GLP-1RAs	Death within 30 days after a positive SARS CoV-2 test	996	*Negative* Higher 30-day mortality compared to SGLT2i
Kahkoska [48]	National observational study, evaluating use of GLP-1RAs, SGLT2i and DPP4i	60-day mortality	12,446	*Negative* GLP1-RAs and SGLT2i use both associated with lower 60-day mortality in comparison to DPP4i use
SGLT2i				
Dalan [46]	Retrospective, observational cohort study; evaluating use of DPP4i, SGLT2i and sulfonylureas	Hypoxia, ICU admission, mechanical ventilation or death	76	*Positive* SGLT2i associated with lower risk of mechanical ventilation; DPP4i associated with higher risk of ICU admission and mechanical ventilation
Israelsen [47]	Population-based cohort study; evaluating use of SGLT2i in comparison to DPP4i and GLP-1RAs	Death within 30 days after a positive SARS CoV-2 test	996	*Positive vs. DPP4i* *Neutral vs. GLP-1RAs* Similar 30-day mortality compared to GLP-1RAs users and lower 30-day mortality compared to DPP4i
Kahkoska [48]	National observational study, evaluating use of GLP-1RAs, SGLT2i and DPP4i	60-day mortality	12,446	*Positive* GLP1-RAs and SGLT2i use both associated with lower 60-day mortality in comparison to DPP4i use
Ramos-Rincón [34]	Nationwide, multicentre observational study; evaluating use of several antidiabetic drugs, including DPP4i, GLP-1RAs and SGLT2i	Mortality	790	*Neutral* DPP4i were independent protectors for mortality; metformin, insulin, GLP-1RAs and SGLT2i had a neutral effect on mortality
Sainsbury [36]	Propensity score-matched cohort study, evaluating SGLT2i use in comparison to DPP4i	Confirmed or clinically suspected COVID-19	24,865	*Neutral* Similar risk of confirmed or clinically suspected COVID-19

Table 1 continued

Authors	Study design	Primary outcome	N of patients	Main results
Izzi-Engbeaya [37]	Multicentre retrospective cohort study; evaluating use of insulin, GLP-1RAs, metformin, sulfonylurea, SGLT2i and DPP4i	Death and/or ICU admission within 30 days of COVID-19 diagnosis	278	*Neutral* No association between insulin, GLP-1RAs, metformin, sulfonylurea, SGLT2i and DPP4i use and the risk of death and/or ICU admission within 30 days of COVID-19
Silverii [38]	Retrospective observational study; evaluating use of metformin, pioglitazone, insulin, sulfonylurea/glinides, DPP4i, SGLT2i and GLP-1RAs	COVID-19 prevalence and case fatality	159	*Neutral* No association with COVID-19 prevalence; metformin use associated with a lower case fatality
Orioli [39]	Retrospective single-centre cohort study; evaluating use of different antidiabetic medications	In-hospital mortality	73	*Neutral* Non-survivors were less often treated with metformin prior to admission in comparison to survivors
Kosiborod [57]	Randomised, double-blind, placebo-controlled trial; evaluating use of dapagliflozin in comparison to placebo among high-risk but not critically ill patients with COVID-19	The outcome of prevention (time to new or worsened organ dysfunction or death) and the hierarchial composite outcome of recovery (change in clinical status by day 30)	1250	*Negative* No significant impact on prevention of organ dysfunction, reduction in all-cause mortality and improvement in the clinical status (ranging from early recovery to death) at 30 days
GLP1-RAs				
Nyland [35]	Multinational retrospective cohort study; evaluating use of pioglitazone, GLP-1RAs and DPP4i in comparison to no use of such therapies	Mortality	7769	*Positive* Significant reductions in mortality among users of pioglitazone, GLP-1RAs and DPP4i in comparison to non-users of pioglitazone, GLP-1RAs or DPP4i
Kahkoska [48]	National observational study, evaluating use of GLP-1RAs, SGLT2i and DPP4i	60-day mortality	12,446	*Positive* GLP1-RAs and SGLT2i use both associated with lower 60-day mortality in comparison to DPP4i use

Table 1 continued

Authors	Study design	Primary outcome	N of patients	Main results
Israelsen [47]	Population-based cohort study; evaluating use of SGLT2i in comparison to DPP4i and GLP-1RAs	Death within 30 days after a positive SARS CoV-2 test	996	*Positive vs. DPP4i* *Neutral vs. SGLT2i* GLP-1RAs had similar 30-day mortality compared to SGLT2i users and lower 30-day mortality compared to DPP4i
Ramos-Rincón [34]	Nationwide, multicentre observational study; evaluating use of several antidiabetic drugs, including DPP4i, GLP-1RAs and SGLT2i	Mortality	790	*Neutral* DPP4i were independent protectors for mortality; metformin, insulin, GLP-1RAs and SGLT2i had a neutral effect on mortality
Izzi-Engbeaya [37]	Multicentre retrospective cohort study; evaluating use of insulin, GLP-1RAs, metformin, sulfonylurea, SGLT2i and DPP4i	Death and/or ICU admission within 30 days of COVID-19 diagnosis	278	*Neutral* No association between insulin, GLP-1RAs, metformin, sulfonylurea, SGLT2i and DPP4i use and the risk of death and/or ICU admission within 30 days of COVID-19
Silverii [38]	Retrospective observational study; evaluating use of metformin, pioglitazone, insulin, sulfonylurea/ glinides, DPP4i, SGLT2i and GLP-1RAs	COVID-19 prevalence and case fatality	159	*Neutral* No association with COVID-19 prevalence; metformin use associated with a lower case fatality

COVID-19 coronavirus disease 2019, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *DPP4i* dipeptidyl peptidase 4 inhibitors, *GLP-1RAs* glucagon-like peptide 1 receptor agonists, *SGLT2i* sodium-glucose co-transporter 2 inhibitors, *CORONADO* coronavirus SARS-CoV-2 and diabetes outcomes, *ICU* intensive care unit

and maintenance in critically ill patients were not fully recommended, since they require slow dose uptitration, need time to become effective and are often associated with transient gastrointestinal side effects such as nausea and vomiting [19]. Yet, GLP-1RAs seem to represent appropriate treatment for non-critically ill patients with T2DM, and a molecular mechanism by which GLP1-RAs seem to interact with SARS-CoV-2 activity has been recently discussed [67]; in addition, GLP1-RAs are able to reduce inflammatory cytokines, which have a critical role in both diabetes and cardiovascular diseases [68], therefore reducing the cytokine storm produced by SARS-CoV-2 [69].
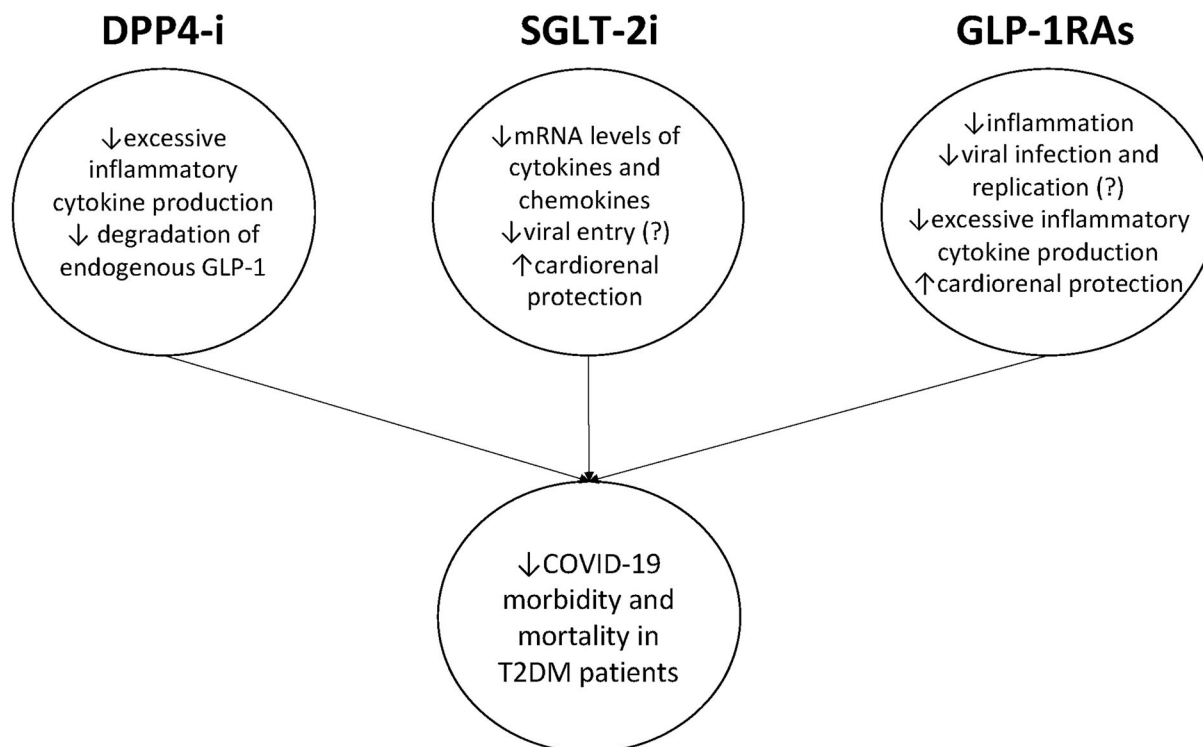
Fig. 1 Potential mechanisms of beneficial effects of novel antidiabetic agents on COVID-19 morbidity and mortality among patients with T2DM

CONCLUSIONS

Appropriate treatment of people with T2DM and COVID-19 is a top priority considering the unfavourable outcomes in this vulnerable population. In this regard, the use of novel antidiabetic agents has generated considerable interest. However, studies conducted thus far either show inconsistent results (DPP4i) or are sparse in number (SGLT2i and GLP-1RAs) (Table 1). Potential mechanisms of beneficial effects of novel antidiabetic agents on COVID-19 outcome are shown in Fig. 1. Interestingly, recent meta-analysis performed to clarify effects of antidiabetic agents on COVID-19 in patients with DM showed that metformin use was associated with lower mortality and poor composite outcomes [70]. Sulfonylurea/glinides use was associated with lower mortality, while there was no significant association for DPP4i, SGLT2i and GLP-1RAs [70].

On top of that, a nationwide observational cohort study from England, analysing 13,479

COVID-19 related deaths in patients with T2DM, showed that adjusted hazard ratios associated with different antidiabetic drugs were 0.75 for meglitinides, 0.77 for metformin, 0.82 for SGLT2i, 0.94 for thiazolidinediones, 0.94 for sulfonylureas, 0.94 for GLP-1RAs, 1.07 for DPP4i, 1.26 for α-glucosidase inhibitors and 1.42 for insulin [71]. This data suggests that some of the traditional antidiabetic drugs, such as metformin, might have beneficial effects on COVID-19 outcomes among patients with T2DM [72], although there are also totally opposite data [73].

In conclusion, the use of novel antidiabetic agents DPP4i, SGLT2i and GLP-1RAs in subjects with T2DM and COVID-19 have shown overall some beneficial effects but with different results for different studies. This may be linked to the large discrepancy in many critical aspects among the different studies, such as the inclusion and exclusion criteria, the type of outcome evaluated as well as the presence of concomitant comorbidities. Relevant studies either show

inconsistent results (as for DPP4i) or are still too few (as for SGLT2i and GLP-1RAs) to be able to make definitive conclusions. Nevertheless, it is hoped that future trials will be helpful in clarifying the risk–benefit ratio of specific antidiabetic agents on COVID-19 outcomes.

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