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COVID-19 and Diabetes Outcomes: Rationale for and Updates from the CORONADO Study

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Abstract

Purpose of Review In France, in order to describe the phenotypic characteristics of patients with diabetes hospitalized for coronavirus disease-2019 (COVID-19) and to identify the prognostic factors in this specific population, the CORONADO (CORONAvirus and Diabetes Outcomes) study was launched. This review will summarize the key findings from the CORONADO study and put them in perspectives with others studies published on the subject.

Recent Findings For almost 2 years, the new SARS-CoV-2 (Severe Acute Respiratory Syndrome-CoronaVirus-2), which causes COVID-19, has spread all around the world leading to a pandemic. From the first epidemiological reports, diabetes mellitus has rapidly emerged as a major risk factor associated with severe forms of COVID-19 but few data were available about diabetes characteristics in hospitalized people with COVID-19.

Summary Between March 10 and April 10, 2020, 2951 patients were included in 68 centers throughout the national territory, including overseas territories. In the CORONADO study, the primary outcome was a composite endpoint combining invasive mechanical ventilation (IMV) and/or death within day 7 (D7). Secondary outcomes included death, IMV, intensive care unit (ICU) admission, and hospital discharge, all considered within D7 and day 28 (D28). The primary outcome occurred in 29.0% participants within D7 following hospital admission. Within D28, the end of the follow-up period, the mortality rate was 20.6%, while 50.2% of patients were discharged. In multivariable analysis, advanced age, microvascular complications, treatment with insulin or statin prior to admission, dyspnea on admission, as well as biological markers reflecting the severity of the infection (high levels of transaminases, leukocytes and CRP, and low platelet levels) were associated with an increased risk of death. Several exploratory analyses were performed to clarify the influence of some parameters such as weight status, sex, type of diabetes, and some routine drugs, including metformin or statins.

Keywords COVID-19 · Diabetes · Outcomes · Prognosis · Risk factors · CORONADO study

Introduction

Facing with the new SARS-CoV-2 (severe acute respiratory syndrome-coronavirus-2), which causes coronavirus disease-2019 (COVID-19) since almost 2 years, significant progress has been made to better understand this new threat that spread all around the world. Beyond knowledge on the virus itself, a better understanding of the people most likely to develop severe forms of the disease has rapidly emerged as an important challenge. From the first epidemiological reports from China, some prognostic factors for COVID-19 have been identified such as older age, male sex or comorbidities such as hypertension or diabetes [1]. Of note, some of these risk factors have been previously identified during the epidemic outbreaks owing to the H1N1 influenza in 2009 or MERS-CoV in

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2012 [2, 3]. Numerous studies identified diabetes as one of the major prognostic factors associated with severe forms of COVID-19 [4, 5, 6••]. For instance, in France, a recent cohort study from the National Health Data System (SNDS) which includes almost the entire French population (66,050,090 people) analyzed the influence of chronic diseases on COVID-19 related hospitalizations and deaths between February 15 and June 15, 2020 [7]. Diabetes was associated with a higher risk of COVID-19-related hospitalization and death (respectively, adjusted hazard ratio (aHR) = 1.64 [1.61–1.67] and 1.75 [1.68–1.81]) compared to the general population. At the beginning of the pandemic, if diabetes rapidly appeared as a major risk factor for severe forms of COVID-19, few data were available about diabetes characteristics in hospitalized people with COVID-19, making it difficult to optimize the management of patients with diabetes. In this context, the CORONAvirus Diabetes Outcomes (CORONADO) study has been designed to describe phenotypic traits of people with diabetes hospitalized in French hospitals during the first wave of the pandemic and also to identify prognostic factors in this specific population (Table 1).

In this review, we will turn back on the results from the CORONADO study, a French collaborative initiative that has contributed to increase our knowledge on the relationship between diabetes and COVID-19. We will put them in perspectives with others studies published on the subject.

Methodology of the CORONADO Study

The French multicenter nationwide CORONADO study (ClinicalTrials.gov NCT04324736) is a retrospective and prospective observational study conducted during the first wave of the COVID-19 pandemic. Sixty-eight centers spread across France, including French overseas territories, participated (Fig. 1). The aim of the CORONADO study was to describe the phenotypic characteristics and prognosis of individuals with diabetes admitted to hospital for COVID-19 between 10 March and 10 April, 2020.

Full study details have been reported previously [8•]. Inclusion criteria were (1) hospitalization in a dedicated COVID-19 unit with COVID-19 diagnosis confirmed biologically (by SARS-CoV-2 PCR test) and/or clinically and/or radiologically (i.e., as ground-glass opacity and/or crazy paving on chest computed tomography (CT) scan); (2) personal history of diabetes or newly diagnosed diabetes on admission (i.e., $HbA_{1c} \geq 6.5\%$ [48 mmol/mol] during hospitalization).

Data collection was performed by clinical research associates and physicians in participating centers. Collected data included clinical data (age, sex, ethnicity, body mass index (BMI)), classification of diabetes as noticed in the medical file by the physician in charge of the patient, duration of diabetes, recent glycemic control (i.e., two most recent HbA_{1c} dosages before admission), microvascular and macrovascular complications and comorbidities. HbA_{1c} considered in the analysis was determined locally in the 7 days following admission or, if not available, was the

Table 1 Summary of main analyses performed from the CORONADO database

Type of analysis	Aim of the study	Reference
Intermediate	To identify poor early prognosis factors (IMV and/or death within D7)	Cariou et al., Diabetologia 2020 [8•]
Principal	To identify prognosis factors for IMV, death or discharge within D28	Wargny et al., Diabetologia 2021 [10••]
Exploratory	To analyze the influence of sex on prognosis within D7 and D28 and to identify specific prognosis factors according to the sex	Tramunt et al., Eur J Endocrinol 2021 [20]
	To describe early prognosis (on D7) among patients with T1D vs patients with T2D	Wargny et al., Diabetes Care 2020 [28]
	To describe phenotypic traits and prognosis of newly diagnosed diabetes during hospitalization for COVID-19	Cariou et al., Diabetes Res & Clin Pract 2021 [37]
	Influence of weight status according to the age on early prognosis (D7) among people with T2D	Smati et al., Diab Obes Metab 2020 [25]
	Influence of bariatric surgery on prognosis (within D7 and D28) among people with T2D	Blanchard et al., Obesity 2021 [27]
	Influence of metformin prior to admission on prognosis (within D7 and D28) among people with T2D	Lalau et al., Diabetes & Metab 2020 [48]
	Influence of DPP-4 inhibitors prior to admission on prognosis (within D7 and D28) among people with T2D	Roussel et al., Diab Obes Metab 2020 [56]
	Influence of statins prior to admission on prognosis (within D7 and D28) among people with T2D	Cariou et al., Diabetes & Metab 2021 [62]

D7 day 7, *D28* day 28; *IMV* intubation for mechanical ventilation, *T1D* type 1 diabetes, *T2D*: type 2 diabetes

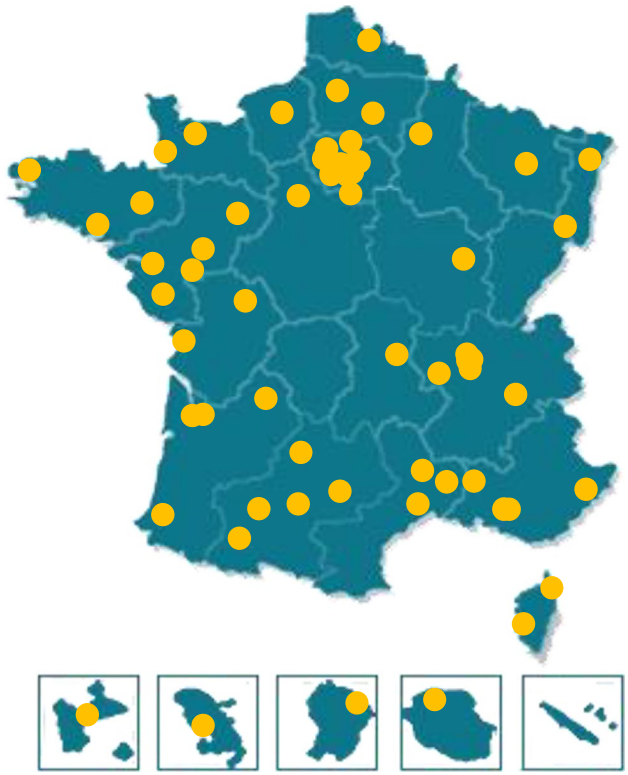

Fig. 1 Location of the 68 centers participating to the CORONADO study throughout France, including overseas territories

result of a routine determination in the previous 6 months. Moreover, COVID-19-related clinical, radiological and biological characteristics were collected at admission as well as clinical evolution during hospital stay.

The composite primary endpoint combined intubation for mechanical ventilation (IMV) and death within day 7 (D7) of admission. Secondary outcomes included death, IMV, admission to intensive care unit (ICU) and discharge observed separately both within D7 and day 28 (D28). Each participant was followed until hospital discharge, death or day 28 after admission, whichever came first, with a minimum follow-up of 7 days for patients discharged earlier.

All statistical analyses were performed on available data, without imputation excepting for the analysis on dipeptidyl peptidase-4 inhibitors (iDPP-4). Besides the descriptive analyses on prevalence of the events of interest, we analyzed associated factors for severe forms of COVID-19 using multivariable logistic regression models. Variables included in the final model were selected according to their clinical relevance (background knowledge) or by stepwise backward/forward selection process.

The study was conducted in accordance with the declaration of Helsinki and French legislation, and obtained approvals from the local ethics committee (IRB/IEC—GNEDS; Ref. CORONADOV2), the CEREES (n° INDS:1544730), and the CNIL (DR-2020–155/920129).

The first objective of CORONADO was to describe phenotypic characteristics of hospitalized diabetic patients for COVID-19. The second objective was to identify prognostic factors in this specific population. Following a remarkable collective effort, almost 3,000 patients hospitalized for COVID-19 were quickly recruited in the CORONADO study between 10 March and 10 April, 2020.

Phenotypic Traits of the CORONADO Population

According to the first objective of the study, phenotypic description of the CORONADO population indicated a large male predominance (63.7%) with a mean age of 69.7 years. Only 13.1% of the population was under 55 years old while 38.2% were more than 75. The median BMI was 28.4 kg/m^2 with 39.0% of people with obesity (BMI $\geq$ 30 kg/m^2) and 24.8% with a BMI < 25 kg/m^2. The median HbA_{1c} was 7.7% (60.7 mmol/mol) a value higher than the 7.1% (56.0 mmol/mol) observed in the French ENTRED study (Representative national sample of people with diabetes in France) [9]. Type 2 diabetes (T2D) represented the first etiology of diabetes, concerning 88.2% of patients. Median duration of diabetes was 11 years. Micro and macrovascular complications were present respectively in 44.2 and 38.6% of the CORONADO population. In addition, comorbidities were frequently present in the participants, such as hypertension (76.8%), dyslipidemia (46.8%), heart failure (11.4%), treated obstructive sleep apnea (OSA) (10.5%) and chronic obstructive pulmonary disease (COPD) (9.6%). As expected, metformin was the most common antidiabetic drug (55.6%), following by insulin therapy (37.2%), while sulfonylurea/glinides (28.0%), iDPP-4 (22.0%) and glucagon-like peptide-1 receptor agonist [GLP-1 RA] (9.1%) were less frequently reported. Renin–angiotensin–aldosterone system (RAAS) blockers and statins were respectively reported in 56.2 and 45.9% of people. On admission, 94.2% of patients had a positive SARS-CoV-2 PCR and 96.8% had abnormal chest CT scan. Median time from symptom onset to hospital admission was 5 days. As expected, the most common clinical presentation was fever (75.4%) and dyspnea (64.3%). Digestive disorders were reported in just over a third of cases. Biological data on admission indicated the following median values: glycemia 9.5 mmol/L (172 mg/dL), CRP 86 mg/L, LDH 351 UI/L and lymphocyte count 990 10^3/mm^3.

Main Results of the CORONADO Study: COVID-19 Outcomes and Risk Factors

In a first intermediate analysis, focusing on 1317 subjects hospitalized between 10 and 31 March, 2020 (a prespecified premature database lock), outcomes were studied within D7 following admission [8•]. The primary composite outcome (IMV and/or death) within D7 was met in 29.0% of participants. The mortality rate was significant since 10.6% of participants died within D7 while 18.0% were discharged. The second analysis was performed on the whole analyzable CORONADO population (i.e., 2796 participants), including the previous 1317 subjects, hospitalized between 10 March and 10 April, 2020 [10••]. Within D28, 35.0% of participants met the primary composite outcome (IMV and/or death) and 20.6% died, confirming the severity of the COVID-19 infection in inpatients with diabetes. In contrast, 50.2% were discharged. Of note, at D28, 12.2% were still hospitalized highlighting how long the need of hospital care can be [10••]. Table 2 summarizes these findings.

Beyond the first objective to describe phenotypic traits of people with diabetes hospitalized for COVID-19, a second objective was to determine prognostic factors in this specific population. In the first intermediate analysis on 1317 people, only BMI, among characteristics before admission, was still significantly and positively associated with the primary composite outcome (odds ratio for 1 SD [OR_{1SD}] = 1.28 [95%confidence interval [CI]: 1.10–1.47]) after multivariable adjustment while age (OR_{1SD} = 2.48 [95%CI: 1.74–3.53]), treated OSA (OR = 2.80 [95%CI: 1.46–5.38]), microvascular (OR = 2.14 [95%CI: 1.16–3.94]) and macrovascular (OR = 2.54 [95%CI: 1.44–4.50]) complications were associated with death within D7 [8•]. Concerning characteristics on admission, dyspnea (OR = 2.10 [95%CI: 1.31–3.35]), lymphocytes count (OR_{1SD} = 0.67 [95%CI: 0.50–0.88]), CRP (OR_{1SD} = 1.93 [95%CI: 1.43–2.59]), and aspartate aminotransferases (AST) (OR_{1SD} = 2.23 [95%CI: 1.70–2.93]) were significant predictors of early severity within D7. On the analysis of the entire cohort, prognostic factors for death within D28 were determined. After multivariable adjustment, older age (OR_{1SD} = 1.84 [95%CI: 1.49–2.27]), microvascular complications (OR = 2.11 [95CI: 1.35–3.27]), insulin therapy (OR = 1.44 [1.01–2.06]) or statin treatment (OR = 1.42 [1.00–2.02]) prior to admission, dyspnea (OR = 1.89 [95%CI:1.31–2.73]), increased AST (OR_{1SD} = 1.47 [95%CI: 1.25–1.74]), decreased platelet count (OR_{1SD} = 0.71 [95%CI: 0.84–1.00]), and increased leucocyte count (OR_{1SD} = 1.30 [95%CI: 1.10–1.54]) and CRP (OR_{1SD} = 1.48 [95%CI: 1.21–1.80]) were predictors of death within D28. In contrast, metformin prior to admission (OR = 0.65 [95%CI: 0.45–0.93]) and longer time between onset of COVID-19 symptoms and hospitalization (OR = 0.72 [95%CI: 0.57–0.90]) were two factors associated with better survival [10••].

Focus on Specific Subgroups

Age

Many studies have shown that advanced age was the most important risk factor for COVID-19-related mortality. An English study, carried out on more than 17 million individuals in the OpenSAFELY platform, showed a risk of mortality multiplied by 20 in people over 80 years old compared to

Table 2 Incidence of clinical outcomes within day 7 (D7) and day 28 (D28) after hospitalization for COVID-19 according to Wargny et al. [10••]

Type of events	Number of events (% [95%CI])	
	D7	D28
Primary composite outcome*	800 (28.6% [26.9–30.3])	979 (35.0% [33.2–36.8])
Death	312 (11.2% [10.0–12.4])	577 (20.6% [19.2–22.2])
IMV	532 (19.0% [17.6–20.5])	556 (19.9% [18.4–21.4])
ICU admission	798 (28.5% [26.9–30.3])	823 (29.4% [27.7–31.2])
Any discharge	704 (25.2% [23.6–26.8])	1877 (67.1% [65.3–68.9])
Home discharge	574 (20.5% [19.0–22.1])	1404 (50.2% [48.3–52.1])
Transfer to other hospital and/or rehabilitation care	130 (4.6% [3.9–5.5])	473 (16.9% [15.5–18.4])

Results based on the analysis of 2796 people with diabetes hospitalized for COVID-19 between 10 March and 10 April, 2020. Results within D7 were updated with the entire population data

CI confidence interval, *D7* day 7, *D28* day 28, *IMV* intubation for mechanical ventilation, *ICU* intensive care unit

*Primary composite outcome combines IMV and/or death (patients that required IMV before death were counted only once)

the population aged 50 to 59 years [6••]. Due to an increase in the prevalence of diabetes with age, patients infected with SARS-CoV-2 with diabetes were, as expected, older than those without diabetes. In the CORONADO study, the mean age was 69.7 years. Within D28, the deceased subjects were on average 76.8 years old compared to 67.9 years in the patients still alive. In multivariable analysis, older age remains significantly associated with higher mortality [10••]. These results were consistent with data obtained from a Turkish cohort of 21,180 patients with T2D in Istanbul, in which COVID-19-related mortality within D28 was associated with advanced age (OR = 1.10 [95%CI: 1.07–1.14]) [11]. Moreover, in the nationwide study from Scotland, the severity of COVID-19 increased with age. Whereas only 2.8% of the 1082 participants with fatal or ICU-treated COVID-19 were under 50 years old, 89.9% were aged 60 years or more [12].

Sex

In addition to older age, data from the general population show a large predominance of the male sex among patients hospitalized, admitted to intensive care or deceased as a result of COVID-19, while the proportion of patients infected with SARS-CoV-2 is the same in both sexes [13–15]. The underlying biological mechanisms responsible for the gender differences in the prognosis of COVID-19 are not clearly established. A sex-specific modulation in the expression of genes encoding the angiotensin-converting enzyme receptor 2 and TMPRSS2, two receptors allowing cellular entry of SARS-CoV-2, has been suggested [15, 16]. Furthermore, the link between biological sex and immune responses to viral infections has long been identified [17, 18]. Few studies have specifically analyzed the sex differences in the diabetic population. Recently, an English registry study (UK Biobank) showed that men and women with diabetes were at similar risk of COVID-19 mortality, in contrast to what is observed in the general population [19]. This finding suggests that diabetes can mitigate the deleterious effect of male sex on COVID-19, even while the mortality was globally increased in people with diabetes. In contrast, in an analysis including 319,349 people with diabetes in Scotland, male sex remained associated with higher risk of fatal or critical care unit-treated COVID-19 [12]. A sex-stratified analysis of the patients included in the CORONADO study provided characterization of the differences between men and women concerning outcomes and prognostic factors during hospitalization for COVID-19 [20]. As previously noted, male preponderance also concerned CORONADO, with men representing 63.7% of the whole study population. After multiple adjustment, female sex was negatively associated with the primary outcome (IMV and/or death), (OR = 0.66 [95%CI: 0.49–0.88]), ICU admissions (OR = 0.57 [95%CI: 0.43–0.77]), and death (OR = 0.49 [95%CI: 0.30–0.79]) within D7, whereas this only concerned ICU admissions within D28 (OR = 0.58 [95%CI: 0.43–0.77]). Regarding prognostic factors, advanced age and presence of microvascular complications were associated with the risk of death within D28 in both sexes. In contrast, COPD was associated with these fatal outcomes only in women. On admission, plasma CRP and AST levels as well as estimated glomerular filtration rate (eGFR) were associated with the risk of death within D28 in both sexes. While lymphopenia was an independent factor of death within D28 only in women, thrombocytopenia and hyperglycemia on admission were associated with death only in men [20]. Altogether, our data show that female sex could be protective against early (within D7) severe outcomes related to COVID-19 but does not significantly influence mortality within D28. These results suggest that diabetes could mitigate female protection against severe forms of COVID-19.

Weight Status

From the first reports, obesity has appeared as a pejorative prognostic factor in patients with COVID-19 in terms of admission to ICU, use of mechanical ventilation, or death [21–23]. In people with diabetes, Holman et al. [24••] found a U-shaped association between mortality and BMI, with an increased risk in patients with a BMI < 20 kg/m^2 or ≥ 40 kg/m^2 compared to overweight population (BMI between 25 and 29.9 kg/m^2), both in people with type 1 diabetes (T1D) or T2D. In the interim analysis of the CORONADO study, BMI was positively associated with the occurrence of the primary outcome (IMV and/or death) within D7 (OR = 1.28 [95%CI: 1.10–1.47]), even after multivariable adjustment [8•]. In a specific analysis focusing on 1,965 patients with T2D, we evaluated the association between BMI and COVID-19 severity [25]. The occurrence of the primary outcome within D7 was significantly associated with overweight (BMI between 25.0 and 29.9 kg/m^2), grade 1 obesity (BMI between 30.0 and 34.9 kg/m^2) and grades 2–3 obesity (BMI ≥ 35.0 kg/m^2) with ORs at 1.65 [95%CI: 1.05–2.59], 1.93 [95%CI: 1.19–3.14] and 1.98 [95%CI: 1.11–3.52], respectively. Obesity was also associated with the risk of IMV, but not with the risk of death within D7. This absence of association between BMI and mortality was confirmed in the analysis of the entire CORONADO study population within D28 [10••]. Interestingly, in the analysis performed specifically in patients with T2D, the association between obesity and the primary outcome on D7 was no longer found in participants over 75 years [25]. Therefore, it is advisable to be careful with public health messages regarding the management of obesity in older patients (> 75 years). In agreement with these results, Gao et al. showed that obesity was positively associated with COVID-19 mortality in

a population of subjects with or without diabetes, particularly in people younger than 40 years. This association was no longer found in people older than 80 years [26]. Data on patients with bariatric surgery were analyzed and suggested that the body weight obtained after surgery was more closely related to the patient prognosis that their weight before bariatric surgery [27].

Type of Diabetes

People with diabetes have been classified as at increased risk for severe forms of COVID-19 without any distinction between the types of diabetes. Nevertheless, due to pathophysiological differences, the COVID-19 prognostic trajectory according to the type of diabetes is a legitimate issue. In France, the first information based on CORONADO study was reassuring for the population of people with T1D. Indeed, in an exploratory analysis from 2,608 CORONADO participants [28], the prevalence of T1D was lower than that observed in the ENTRED study (2.1% versus 5.6% respectively) [9]. Among participants with T1D, the primary composite outcome occurred in 23.2% of patients, IMV on 19.6%, and death in 5.4% within D7. In parallel, in patients with T2D, these outcomes occurred in 27.7%, 18.4%, and 10.6%, respectively. In a large part, the age mainly influenced the early COVID-19 prognosis in people with T1D. The risk of death among people with T1D was equivalent to that with T2D from the age of 75 years. Moreover, no death occurred on people with T1D before 55 years old [28]. Our findings are consistent with data from a Belgian study that reported a lower risk of hospitalization among people with T1D, a risk that was similar to people without diabetes [29]. In the same line, in a UK nationwide study involving 196 adults with T1D hospitalized for COVID-19, 35.0% of the population died or was admitted in ICU. Among patients who died, only 7.0% were < 55 years old whereas 38.0% were between 55–74 years and 38.0% were ≥ 75 years. Thus, as observed in the CORONADO study, the risk of severe COVID-19 seems to be very low in people with T1D who are under 55 years of age [30]. Nevertheless, in the two larger cohorts from England or Scotland, the authors consistently reported an increased risk of mortality for both T2D and T1D compared to the general population [12, 31••]. For instance, in the 263,830 patients with T1D (0.4%) from 61,474,470 individuals registered with a general practice in England, the ORs for in-hospital COVID-19-related death was 3.51 (95%CI: 3.16–3.90) [31••]. In contrast to CORONADO, participants included in these nationwide studies were not restricted to those admitted to hospital. In a meta-analysis, including fifteen studies with data of both adult and pediatric patients, Nassar et al. found a prevalence of T1D ranging from 0.15 to 28.98% in COVID-19 patients and suggested that COVID-19 outcomes varied widely among studied populations. Due to the heterogeneity of these studies, they claimed for more data to conclude on these specific populations of people with T1D [32]. Moreover, as illustrated by an observational study in the USA, acute complications of T1D as diabetic ketoacidosis or severe hypoglycemia represent a major driver for hospitalization, found in more than 50% of cases in people with T1D [33]. Thus, despite the reassuring data from CORONADO, it is essential not to trivialize the risks of infection for people with T1D and we have to encourage this population to be vaccinated and to maintain barrier gestures.

Beyond preexisting diabetes, newly diagnosed diabetes (NDD) was pointed as an entity experiencing poor prognosis for COVID-19 by several studies [34, 35]. Actually, under the term "NDD", various subgroups can be distinguished as undiagnosed diabetes before hospitalization for COVID-19, transient hyperglycemia at the beginning of hospitalization or newly diabetes due to a possible direct effect of the virus on β-cell [36]. In the CORONADO study, NDD, defined as people without history of diabetes and who presented with $HbA_{1c} \geq 6.5\%$ (48 mmol/mol) during the first days of hospitalization, represented only 2.8% of the population [37]. Their mean age was 60.2 years and their mean HbA_{1c} was 9.0% (75.1 mmol/mol). Patients with NDD were younger and more frequently from African or Caribbean origin than patients with T2D whereas they presented less comorbidities, as hypertension or dyslipidemia, than patients with T2D. In a center-, age-, and sex-matched patient analysis, our results did not show any association between NDD and severe COVID-19 prognosis within D7 or D28. Only the rate of hospital discharge was significantly lower in the NDD group within D7 although no longer significant within D28 [37]. Our results were in contrast with the previous reports above cited. First, the lower occurrence of NDD in our population than in some other studies [38] could explain such differences. Then, we did not take into account the lower prevalence of associated comorbidities in our NDD population, conducting to possible difference between analyses. Nevertheless, to definitively conclude on the question of poorer prognosis for NDD in COVID-19, prospective studies with better phenotyping are needed to limit confusion biases.

Glycemic Parameters

As mentioned above, the median HbA_{1c} of 7.7% (60.7 mmol/mol) on admission in CORONADO was higher than that reported in the ENTRED study (7.1% or 56.0 mmol/mol), a cohort representative of the French diabetic population [9]. This finding might suggest that COVID-19 might impact glycemic control. However, HbA_{1c} was not associated with COVID-19-related outcomes in CORONADO [10••]. This absence of association between glycemic control before admission and COVID-19 prognosis was in line with other

reports, including an American study carried out in 1126 patients with diabetes and hospitalized for COVID-19 infection [39]. In contrast, high blood glucose levels on admission was associated with more severe forms of COVID-19 [10••, 40]. Nevertheless, in the CORONADO study, hyperglycemia was no longer significantly associated with the severity of COVID-19 after adjustment for other biological parameters on admission (CRP, leukocytosis, thrombocytopenia). These data do not make possible to distinguish if hyperglycemia on admission is an independent risk factor or rather an indirect marker of inflammatory reaction associated to COVID-19. This hypothesis is also supported by several Chinese studies in which, in individuals without diabetes, hyperglycemia was still associated with higher COVID-19-related mortality [41–43]. To date, no interventional study has yet evaluated the benefit of tight blood glucose control during COVID-19 infection.

Few studies questioned the place of continuous glucose monitoring (CGM) during COVID-19 infection, but none evaluated its efficacy to improve blood glucose control compared to point-of-care glucose testing. Preliminary studies with a little number of patients suggested that CGM could be a good alternative to reduce point-of-care glucose testing, especially in critically ill patients [39, 44, 45]. However, the authors remained cautious about the complete replacement of point-of-care glucose testing due to potential errors in detecting hypo or hyperglycemia and the risk associated with interfering treatments [39]. A Danish randomized trial of 64 individuals with diabetes and hospitalized for COVID-19 infection showed that CGM did not improve glycemic control compared to point-of-care glucose testing but facilitated the work of the healthcare personnel [46]. Thus, the use of CGM in patients with COVID-19 requires further investigations to evaluate its efficacy on blood glucose control and ultimately its impact on the prognosis of the infection.

Treatment Prior to Admission

Several observational studies analyzed the impact of drugs commonly used to treat patients with diabetes. However, the interpretation of these results must remain cautious while only statistical associations can be highlighted. To date, only very few interventional studies with anti-diabetic drugs have been performed in patients with COVID-19 [47].

In the CORONADO analysis, metformin, the first-line treatment for T2D, was associated with lower mortality within D28. In order to reduce the possible role of confounding factors, an analysis using a propensity score between individuals treated or not with metformin was carried out. This study confirmed the significant reduced mortality within D28 in patients with T2D treated with metformin (OR = 0.71 [95%CI: 0.54–0.94]) [48]. These results are consistent with a recently published observational nationwide study in England [49] that also indicated a lower risk of mortality in patients under metformin (HR = 0.77 [95%CI: 0.73–0.81]). Of note, treatment with metformin can be used with caution in patients with T2D and COVID-19 infection, based on their clinical course, in order to avoid any occurrence of lactic acidosis [50]. While there were few data regarding the continuation of treatment during the hospitalization, a recent proof of concept study suggests that the beneficial association between COVID-19 related outcomes and metformin might be related to the drug's continuation during hospitalization rather than previous exposure [51]. In the sex-stratified analysis of CORONADO population [20], the reduced risk of death associated with metformin use was only observed in men. This result contrasts with a retrospective study that suggests that metformin was associated with lower mortality only in women [52].

Association between prognosis of COVID-19 and iDPP-4, another drug widely used in people with diabetes, was also evaluated. Indeed, fundamental studies indicated that DPP-4 could act as a SARS-CoV-2 co-receptor [53]. Due to the potential involvement of DPP-4 in the entry of the virus, a protective role of DPP-4 inhibitor has been suggested. Results from observational analyses were discordant concerning the association between COVID-19 mortality and DPP-4 inhibitor treatment [54, 55]. In a secondary analysis of CORONADO using a propensity score approach, treatment with DPP-4 inhibitor did not influence the prognosis of COVID-19 [56]. Consistent with CORONADO observations, an analysis of 2666 patients with T2D from the Spanish Society of Internal Medicine COVID-19 registry did not report association between glucose-lowering therapies and COVID-19 issues [57]. In addition, current use of DPP-4 inhibitors was associated with an increased risk of COVID-19-related death in the largest study so far (HR = 1.07 [95%CI: 1.01–1.13]) [49]. Altogether, observational studies seem to indicate this DPP-4 inhibitor treatment is at best neutral, with no argument for a protective effect in COVID-19.

Performed on 1250 patients hospitalized for COVID-19 with one cardiometabolic risk factor (i.e., hypertension, T2D, atherosclerotic cardiovascular disease, heart failure or chronic kidney disease), the DARE-19 study, is one of the rare double randomized, placebo-controlled, clinical trial, evaluating the effect of dapagliflozin on COVID-19 outcomes. Dapagliflozin treatment did not significantly reduce mortality nor improve clinical recovery [47]. Because they were not available in France until April 2020, SGLT2 inhibitors had not been studied in CORONADO.

Concerning insulin therapy prior to admission in the CORONADO study, we found that insulin was significantly associated with a lower rate of discharge within D28 in an age-adjusted model (OR = 0.78 [95%CI: 0.67–0.92]) but this was no longer the case after multivariable adjustment.

Insulin was also significantly associated with increased mortality within D28 in multivariable model (OR = 1.44 [95%CI: 1.01–2.06]) [10••]. These findings were in accordance with other reports in the literature. Notably, in the large nationwide ABCD cohort study in England, insulin therapy was associated with an increased risk of COVID-19-related death (HR = 1.42 [95%CI: 1.35–1.49]) [49]. In a meta-analysis, Yang et al. also found an association between insulin treatment, increased risks of mortality (OR = 2.10 [95%CI: 1.51–2.93]) and incidence of severe/critical COVID-19 complications (OR = 2.56 [95%CI: 1.18–5.55]) [58]. Nevertheless, these findings were only obtained from observational studies and almost exclusively from T2D cohorts. Thus, it is difficult, as previously highlighted, to draw conclusion on which is the culprit of poor prognosis in patients with COVID-19 and diabetes between insulin use or hyperglycemia [59]. Even with the use of propensity scores, it cannot be excluded that insulin therapy remains a marker of frailty in patients with T2D. Therefore, dedicated prospective studies are needed to clarify this link.

Beyond anti-diabetic treatments, observational studies have shown a favorable association between the use of statins and COVID-19 prognosis [60, 61]. Conversely, in the CORONADO study, routine use of statins before admission was associated with an increased risk of mortality (OR = 1.46 [95%CI: 1.08–1.95]) after a propensity score-weighting approach [62]. Since the beginning of the COVID-19 pandemic, there were more than 300 articles (studies, meta-analyses or review) on the impact of statins on COVID-19 prognosis [63–65]. Observational studies have produced very heterogeneous results [61], highlighting the limitations of these approaches and limiting the strengths of their conclusions. Once again, only controlled interventional studies will help to clarify these associations.

Limits and Perspectives

Although the CORONADO study provided a large amount of data, some limitations need to be highlighted. Because we focused on patients with diabetes hospitalized for COVID-19, our results cannot be extended to all the people with diabetes, especially those with a less severe form of the disease. Moreover, due to the retrospective nature of the study, missing data led to exclude some patients from the different analyses we performed. Conducted between 10 March and 10 April, 2020, i.e., during the first wave of the pandemic, the CORONADO study cannot take into account the impact of new SARS-CoV-2 variants that appeared in the last months and currently replaced the native strain of the virus. In the same line, the effect of vaccines cannot be evaluated. New specific studies are needed to address these issues. As previously discussed, the exploratory nature of some analyses limits the possibility to conclude on causal relationship between comorbidities, biomarkers, routine treatments and COVID-19 outcomes. Only associations can be evocated. Finally, in the absence of a non-diabetic control group, we are unable, to date, to conclude on the weight of diabetes per se (i.e., beyond associated comorbidities) in our observations. Thus, the question about the impact of diabetes on prognosis compared to other comorbidities frequently associated with diabetes is still debated. First epidemiological reports described diabetes as a comorbidity frequently associated with poor prognosis and severe forms of COVID-19 [4, 5]. In the OpenSafely database, diabetes was described as an independent risk factor [6••]. Moreover, in Scotland and British nationwide databases, patients with diabetes were more prone to severe forms of COVID-19 than people without diabetes [12]. These data were observational leading to possible confusion bias and few studies reported a comparison between people with diabetes versus people without diabetes. In a systematic review and meta-analysis, Corona et al. found that diabetes was the best predictor of mortality rate compared to other comorbidities. Furthermore, a significant increase in mortality risk was observed in people with diabetes compared to people without diabetes, even if this increased risk was reduced in studies with a higher proportion of patients with hypertension or chronic kidney disease [66]. Nevertheless, Sutter et al. claimed for opposite conclusions using a propensity score matching approach to take in account different comorbidities [67]. Based on retrospective data of critical COVID-19 France, an observational and multicenter study conducted during the first wave of the pandemic, found that patients with diabetes ($n = 603$) and without diabetes ($n = 603$) experienced the same prognosis. Primary outcomes were found respectively in 35.5% of people with diabetes and 31.8% of people without diabetes ($p = 0.20$) [67]. Moreover, Diedisheim et al. reported that diabetes was an independent risk factor for severe forms of COVID-19 in young adults more than in older adults [68]. In order to answer the question of the impact of diabetes on prognosis in our CORONADO population, we are currently performing a case–control study, pairing each CORONADO participant with a non-diabetic control matched on age and sex.

Conclusion

Thanks to the collaborative work of French actors in the field of diabetes, CORONADO study provided a large amount of data to better understand the profile of people with diabetes exposed to severe forms of COVID-19. If we must acknowledge some limits, part of our pioneer results has already been replicated in further studies, thereby validating most of our

conclusions. Waiting for new results in the next future, we are glad that CORONADO is still going on.

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Declarations

Conflict of Interest SH reports grants, non-financial support or personal fees from Air Liquid, Allergan, Astra Zeneca, Bayer, Boehringer Ingelheim, Dinno Santé, Eli Lilly, Elivie, Fortil, Lifescan, LVL, Merck Sharpe Dome, NHC, Novartis, Pierre Fabre Santé, Sanofi, Servier, and Valbiotis. PG reports grants or personal fees from Abbott, Air Liquid, Allergan, Amgen, Astra-Zeneca, Boehringer Ingelheim, Eli Lilly, Elivie, Fortil, Lifescan, Merck Sharp and Dohme, Mundipharma, NHC, Novo Nordisk, Sanofi, and Servier. BC reports grants, non-financial support or personal fees from Abbott, Allergan, Amgen, Akcea AstraZeneca, Pierre Fabre, Genfit, Gilead, Eli Lilly, Elivie, Fortil, Lifescan, Merck Sharpe Dome, NHC, Novo Nordisk, Regeneron and Sanofi. MW reports personal fees from Novo Nordisk. Other authors report no conflict of interest.

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•• Of major importance

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