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Short running title: Dipeptidyl Peptidase-4 inhibitors and COVID-19 in type 2 diabetes

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¶ A complete list of the CORONADO trial investigators is provided in the appendix.

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ABSTRACT

Aims

Dipeptidyl Peptidase-4 (DPP-4), the target of oral antidiabetic drugs DDP-4 inhibitors, has been suggested to be involved in the pathogenesis of coronavirus infections, including COVID-19. It is unclear whether the routine use of DPP-4 inhibitors increases the severity of COVID-19 in people with type 2 diabetes (T2D). Our purpose was to investigate the association between routine use of DPP-4 inhibitors and the severity of COVID-19 infection in a large multicentric study.

Material and Methods

This study was a secondary analysis of the CORONADO study on 2449 patients with T2D hospitalized for COVID-19 in 68 French centres. The composite primary endpoint combined tracheal intubation for mechanical ventilation and death within 7 days of admission. Stabilized weights were computed for patients based on propensity score (DPP-4 inhibitors users vs non-users) and were used into multivariable logistic regression models to estimate Average Treatment effect in the Treated as Inverse Probability of Treatment Weighting (IPTW).

Results

596 participants were under DPP-4 inhibitors before admission to hospital (24.3%). The primary outcome occurred at similar rates in users and non-users of DPP-4 inhibitors (27.7% vs 28.6%, P=0.68). In propensity analysis, the IPTW-adjusted models showed no significant association between use of DPP-4 inhibitors and the primary outcome within day 7 (OR [95%CI]: 0.95 [0.77-1.17]) or day 28 (OR [95%CI]: 0.96 [0.78-1.17]). Similar neutral findings were found between use of DPP-4 inhibitors and the risk of tracheal intubation and death.

Conclusions

These data support the safety of DPP-4 inhibitors for diabetes management during the COVID-19 pandemic and they should not be discontinued.

INTRODUCTION

Diabetes has been evidenced as one of the main clinical factors associated with severity of coronavirus disease 2019 (COVID-19). Dipeptidyl Peptidase-4 (DPP-4, or CD26), a transmembrane glycoprotein, expressed in endocrine cells, immune cells, endothelial cells, and pneumocytes, among many tissues, is now recognized as a coronavirus receptor protein (1). Its functions, which are incompletely unveiled, include degradation of incretins such as glucagon like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide, but also immune regulation by activation of T cells, up-regulation of CD86 expression and NF-kappaB pathway, and cleavage of a number of cytokines, chemokines, and growth factors (2). During the former coronavirus epidemics, it was suggested that higher severity of MERS-CoV infection in type 2 diabetes (T2D) could be associated with a DPP-4-mediated dysregulated immune response. The hypothesis was supported by an experimental work, using human-DPP-4-expressing obese mice (3), and also by a genetic association study in patients (4), and has been recently reviewed (5-7). On the other hand, administration of recombinant soluble DPP-4 attenuated lung histopathology in another pre-clinical study (8). This was consistent with the observation of lower circulating levels of soluble DPP-4 in human subjects with MERS-CoV, relative to healthy controls (9).

People with T2D, whether they are obese or not, are commonly treated with DPP-4 inhibitors. There is no evidence for a higher risk of respiratory tract infections associated with the use of this class of antidiabetic drugs according to randomized controlled trials (RCTs) (10) or observational studies (11-12), although a 2011 report of the WHO adverse drug reactions database had shown a higher prevalence of upper respiratory tract infections among users of DPP-4 inhibitors compared with users of other antidiabetic drugs (13). Therefore, the effects of DPP4 inhibition on the immune response in patients with T2D remain unclear, and the critical role of regulation of cytokines during the course of COVID-19 with the burst of apparently uncontrolled immune activation a few days after the onset of the symptoms in many severely affected patients has led to a call for caution in the use of DPP-4 inhibitors on one side and the launch of a small clinical randomized trial to assess whether a DPP-4 inhibitor could reduce the severity of COVID-19 on the other side (NCT04341935).

Thus, discrepant messages have been received by health-care providers and people with diabetes. To our knowledge, the clinical evidence they need to guide their decisions regarding their use of DPP-4 inhibitors is still limited to a small neutral case-control study (14).

Our purpose was to investigate the association between the use of DPP-4 inhibitors and the early severity of illness and mortality in patients with T2D hospitalized for COVID-19 infection, by using propensity score matching in the CORONADO (CORONAvirus and Diabetes Outcomes) study.

MATERIALS AND METHODS

Study design and participants

The current study was a secondary analysis of the CORONADO study (ClinicalTrials.gov NCT04324736), which aimed at describing the phenotype and prognosis of people with diabetes admitted to hospital for COVID-19 and diabetes between 10 March and 10 April 2020. The study was sponsored by CHU Nantes, designed in accordance with the declaration of Helsinki and conducted in accordance with French legislation with approval obtained from the local ethics committee (Institutional Review Board/Institutional Ethics Committee – GNEDS [groupe nantais d'éthique dans le domaine de la santé]), the CEREES (comité d'expertise pour les recherches, les études et les évaluations dans le domaine de la santé; n° INDS [institut national des données de santé]: 1544730) and the CNIL (commission nationale de l'informatique et des libertés; DR-2020-155/920129). A 'non-opposition to participate' was orally collected after informed consent if feasible, according to the recommendation of the ethical committee for this observational study.

Inclusion criteria and design of the CORONADO study have been detailed elsewhere (15). For the purpose of the current sub-analysis, information on routine use of DPP-4 inhibitors (*i.e.* sitagliptin, vildagliptin and saxagliptin which are commercially available in France) prior to the admission was mandatory for inclusion.

Clinical and biological data have been described previously (15). In the current analysis, HbA_{1c} and estimated Glomerular Filtration Rate (eGFR) values correspond to the more recent routine biological determinations in the 6- and 12-months preceding admission, respectively.

Study outcomes

The composite primary endpoint combined tracheal intubation for mechanical ventilation and death within 7 days of admission. Secondary outcomes included death on day 7, tracheal intubation on day 7, admission to ICUs and discharge on day 7. In the population still hospitalized on day 7, these outcomes were reassessed until day 28.

Statistical analyses - Propensity score analysis

Quantitative data were given as mean ± SD or median [25^{th}–75^{th} percentile]. Categorical variables were given as number (percentage) of participants. Patients were classified in two groups according to the use of DPP-4 inhibitors prior to admission. For between group comparisons, unpaired t-tests or Wilcoxon rank-sum tests were used for quantitative variables, while Fisher's exact tests were used for categorical variables. For missing values, a multiple imputation by chained equation using R package mice (7 replicates with

"predictive mean matching" and "logistic regression" methods for respectively continuous and binary variables) was performed (16). After a careful study of the performance of imputation, replicates were pooled to get the complete dataset to conduct multivariable analyses.

In order to balance the distributions of baseline covariates between groups and then limit confounding bias in analyses, we estimated a propensity score (PS) with a logistic regression model on sex, age, body mass index (BMI), arterial hypertension, history of ischemic heart disease, history of heart failure, active cancer, treated obstructive sleep apnea (OSA), and use of metformin, sulfonylurea, glucagon-like peptide 1 receptor agonists (GLP-1 RAs), insulin, corticosteroids, renin-angiotensin system blockers, statins, thiazide diuretics, and anti-platelet therapy. In sensitivity analysis, the following complementary variables were added: eGFR using the CKD-EPI formula, diabetes duration, and the latest HbA_{1c} (< 6 months prior to admission). For each model, these variables were selected based on their relevance in clinical practice and statistically ($p<0.15$ in univariable association with outcome). We did not include in PS calculation variables that are associated with exposition status but not with the primary endpoint because it might have a counterproductive effect by increasing bias and variance in the estimate of treatment effect (17). Comparability was assessed by analyzing reduction in Standardized Mean Differences (SMD) after PS utilization. Stabilized weights (18) were computed for patients based on overlap weighting method and were used into multivariable logistic regression models to estimate Average Treatment effect in the Treated (ATT) as Inverse Probability of Treatment Weighting (IPTW) (19). In addition, PS was used in Cox models to estimate IPTW-Hazard Ratios, presented in supplemental materials. Proportional hazards assumption has been carefully studied. Analyses were performed using R version 3.6.2, in particular packages PSW (19), hrIPW (20) and ggplot2 (21) to estimate the treatment effect in logistic regression models, in survival models and for figures, respectively.

RESULTS

Baseline characteristics

The study population consisted of 2449 patients with T2D declaring the use of at least one antidiabetic drug prior to hospital admission for COVID-19, and available information on the primary outcome at day 7 after admission (see flow chart, **Figure 1**). Among them, 596 were under DPP-4 inhibitors (24.3%), mainly under sitagliptin (n=424, 17.2%). The baseline characteristics of the patients according to the use of DPP-4 inhibitors are shown in **Table 1**. Patients using DPP-4 inhibitors were less frequently women (32.6 vs 37.1% in non-users, P=0.0455), had a lower median BMI, had less frequently a history of severe diabetic retinopathy, peripheral artery disease or non-alcoholic fatty liver disease. As expected, treatment patterns were strikingly different for antidiabetic but also cardiovascular therapies. DPP-4 inhibitors users were more frequently under metformin and less frequently under GLP-1 RAs or insulin therapy. In addition, they were more frequently under renin-angiotensin-aldosterone system (RAAs) blockers and less frequently under beta blockers. On admission, patients under DPP-4 inhibitors appeared to have a slightly more severe form of infection at admission, with higher plasma glucose and CRP concentrations, two biological markers which have been associated to poorer COVID-19 prognosis (15) (**Table 2**). The information on how the DPP-4 inhibitors were handled during the hospitalization could be recorded in 455 patients: 358 (81%) remained on treatment, including those who have had a transitory suspension (n=147 [33%]) or a change in dosage (n=14 [3%]); while 84 (19%) have stopped the treatment.

Clinical outcomes according to the use of DPP-4 inhibitors

The primary outcome (tracheal intubation for assisted mechanical ventilation or death on day 7 after admission) occurred at similar rates in users and non-users of DPP-4 inhibitors (27.7% vs 28.6%, P=0.6765). The same was true for each component of the primary outcome taken individually (see **supplemental Table 1**). The pattern was similar when outcomes were reassessed at day 28, except a trend for a non-significant reduction of mortality in DPP-4 inhibitors users (18.1% vs 21.8%, P=0.0561) (**supplemental Table 1**).

Propensity score analysis

Because the use of DPP-4 inhibitors and outcomes were significantly associated with some baseline characteristics that can alter the severity of COVID-19, we conducted a ~~complete-case~~ PS analysis to balance

baseline distributions of age, sex, body mass index, history of heart failure, arterial hypertension or ischemic heart disease, active cancer and also regarding treatments for obstructive apnea, anti-platelet therapy and the use of metformin, insulin, sulfonylurea, renin-angiotensin system blockers, statins, corticosteroids and thiazide diuretics. ~~Supplemental Tables 2, 3 and 5 allow comparisons of baseline characteristics and outcomes between patients not included in multivariable analyses and the complete-case sample with reference to the previously mentioned variable~~s. We performed a multiple imputation for the missing values. As shown in the **Figure 2,** the reduction in SMD after using IPTW in models illustrated the gain in comparability between groups on baseline covariates. The IPT-Weighted models at day 7 showed no association between use of DPP-4 inhibitors and the primary outcome or its individual component, even after further adjustment on kidney function (*i.e.* GFR values), diabetes duration and HbA_{1c} (**Table 3**).

DISCUSSION

In the present study, we reported evidence supporting safety of the use of DPP-4 inhibitors prior to hospitalization for COVID-19 in people with T2D. These results, based on the largest cohort analyzed so far to test the safety of this class of drugs during the course of the SARS-Cov-2 pandemics, thus provide reassurance in that regard.

The prevalence of the use of DPP-4 inhibitors in patients with T2D requiring hospitalization for COVID-19 from the CORONADO cohort was slightly lower than what was reported in previous observational studies in France (24.3% vs 32% in Roussel et al., mostly sitagliptin (22), and 27% in Overbeek et al. (23)). This is not suggestive of an increased risk of severe form of COVID-19 due to the use of DPP-4 inhibitors in the community, prior to the admission to the hospital. This finding was also consistent with a recent observational study from Italy (14). In this work, similar rates of treatment with DPP-4 inhibitors were reported in people hospitalized for COVID-19 and in several control groups of people with diabetes in the community and requiring hospitalization for other causes of pneumonia.

In people with diabetes, prior studies suggested the lack of association between the use of DPP-4 inhibitors and the occurrence of community-acquired pneumopathy from any cause (12, 24) but also specifically due to SARS-CoV-2 (14). Furthermore, recent observations reported either a reduced mortality rate (25, 26) or a neutral effect (27, 28) associated with the use of DPP-4 inhibitors prior or during hospitalization for COVID-19, in patients with T2D. The literature already includes papers questioning a wide use of the class for preventing COVID and its complications (29). As thoroughly discussed in a commentary paper (30), all these studies have strong limitations (some of which were shared by our current work, first of all their observational nature). These limitations were likely balanced with the potential importance of their messages during the editorial process, due to the emergency of the still raging pandemics. Calls for randomized trials have been made, but they will take time to be delivered, and the community is in urgent need of more evidence meanwhile.

In the CORONADO study, participants on routine DPP-4 inhibitors showed a few traits at admission presumed to be associated with a severe illness, as higher prevalence of fatigue, lower lymphocyte count, higher plasma D-dimer, glucose and CRP concentrations. These features underline the imperative need of statistical methods to control for different characteristics in participants according to the use of DPP-4 inhibitors with the aim of limiting residual confounding factors. Here, we used multivariable logistic regression models to

estimate Average Treatment effect in the Treated as Inverse Probability of Treatment Weighting, elsewhere described to be less biased and associated with a lowest variance than other PS based methods (31, 32). With this approach, we observed similar rates of the primary outcome (combined tracheal intubation and/or death) as well as its individual components (*i.e.* tracheal intubation and death) both within 7- and 28-days after admission. ~~We also observed a significant 47% reduction of all-cause death on day 28 after admission (OR: 0.53 [0.31-0.89]) but not on day 7 (OR: 0.56 [0.28-1.12]) (**Table 3**). Nonetheless, we definitively would not draw any definitive conclusion due to the observational design, the secondary nature of these analyses and their borderline significance. Complete-case analyses also reduce the scope for inference of results with respect to the target population.~~

The possibility of a reduction in the severity of COVID associated with in-hospital treatment with DPP-4 inhibitors have raised an important issue, although again challenged due to limitations of the study design (6, 25, 26). Indeed, COVID-19 is a multi-organ disease, and beside respiratory failure, which could lead eventually to tracheal intubation and supportive ventilation, other processes may cause death like thrombotic disease. Therefore, we could speculate that DPP-4 inhibitors could limit the damages triggered by the SARS-CoV-2 at the systemic level, beyond the lung. Unfortunately, the challenges of clinical care in hospitals at the peak of the epidemics in France have made less accurate than usually the exploration in critical settings, and eventually the death reports. Therefore, they were not collected in the current study. However, experimental and further confirmatory epidemiological data are strongly required to validate the hypothesis raised here.

As highlighted before, our study presents some limitations that should be reminded. CORONADO is an observational study which collected data from people with diabetes and COVID-19 at admission in a large number of hospitals in France. As such, it cannot provide insight on the outcomes of COVID-19 in the community. Moreover, it was not feasible to reliably collect extensive data on the use of antidiabetic drugs during the hospital stay and after hospital discharge, if any. Therefore, we cannot study the relationship between in-hospital exposure to any specific drug, including DPP-4 inhibitors, and outcomes. Even while the data is not exhaustive, it seems that a large majority (>80%) of patients remained on DPP-4 inhibitors after admission to hospital. In addition, our experience showed that most of the patients with diabetes were switched to insulin therapy soon after their admission. Ultimately, routine prescription of drugs does not mean that they were duly taken by patients. Drug compliance was not evaluated in this study.

Consistently with recently published evidence, the current findings did not identify any deleterious association between treatment with DPP-4 inhibitors and severe outcomes of COVID-19 in patients with T2D admitted to the hospital. These data support safe use of this class of drugs for treating diabetes during the COVID-19 pandemic and they should not be discontinued. ~~Actually, taken together, these observational studies suggest that DPP4 inhibition could carry health benefits in the treatment of COVID-19. Thus, basic and clinical research resources should be dedicated to test this hypothesis.~~

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AUTHORS CONTRIBUTION

Drs B. Cariou and R. Roussel had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Concept and design*: B. Cariou, P. Darmon, P.

Gourdy, S. Hadjadj, M. Pichelin, R. Roussel, M. Wargny. *Acquisition, analysis, or interpretation of data:* on behalf of the scientific committee of the study (the list of scientific comittee is available on ESM). *Drafting of the manuscript:* B. Cariou, P. Darmon, P. Gourdy, S. Hadjadj, M. Pichelin, R. Roussel, M. Wargny. *Critical revision of the manuscript for important intellectual content:* all co-authors. *Statistical analysis*: M. Wargny, T Goronflot. *Patient recruitment*: Y. Abouleka, Leila Ait Bachir, I. Allix, D. Ancelle, S. Barraud, L. Bordier, A. Carlier, N. Chevalier, C. Coffin Boutreux, E. Cosson, A. Dorange, O. Dupuy, P. Fontaine, B. Fremy, F. Galtier, N. Germain, A.M. Guedj, E. Larger, S. Laugier-Robiolle, B. Laviolle, L Ludwig, A. Monier, N. Montanier, P. Moulin, I. Moura, G. Prevost, Y. Reznik, N. Sabbah, P.J. Saulnier, P. Serusclat, C. Vatier, S. Hadjadj, P. Gourdy, B. Cariou. *Fundraising*: B. Cariou, P. Gourdy, S. Hadjadj, M. Pichelin and B. Bauduceau.

CONFLICT OF INTEREST

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LEGENDS TO FIGURES

FIGURE 1. Study Flowchart

FIGURE 2. Baseline characteristics balance between DPP4-inhibitors users and non-users after propensity score use in models as inverse probability of treatment weighting.

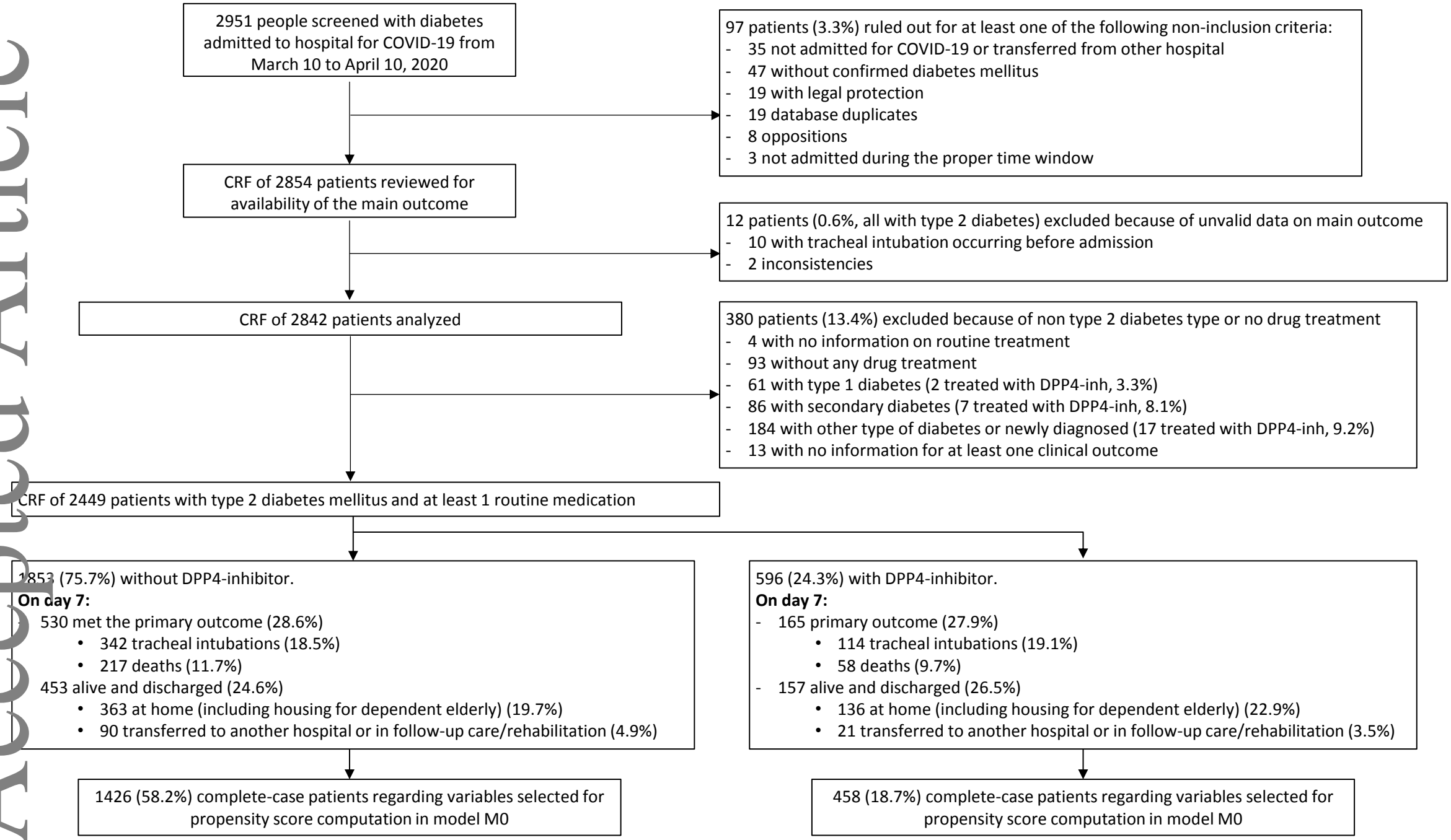

Figure 1: Study Flowchart.

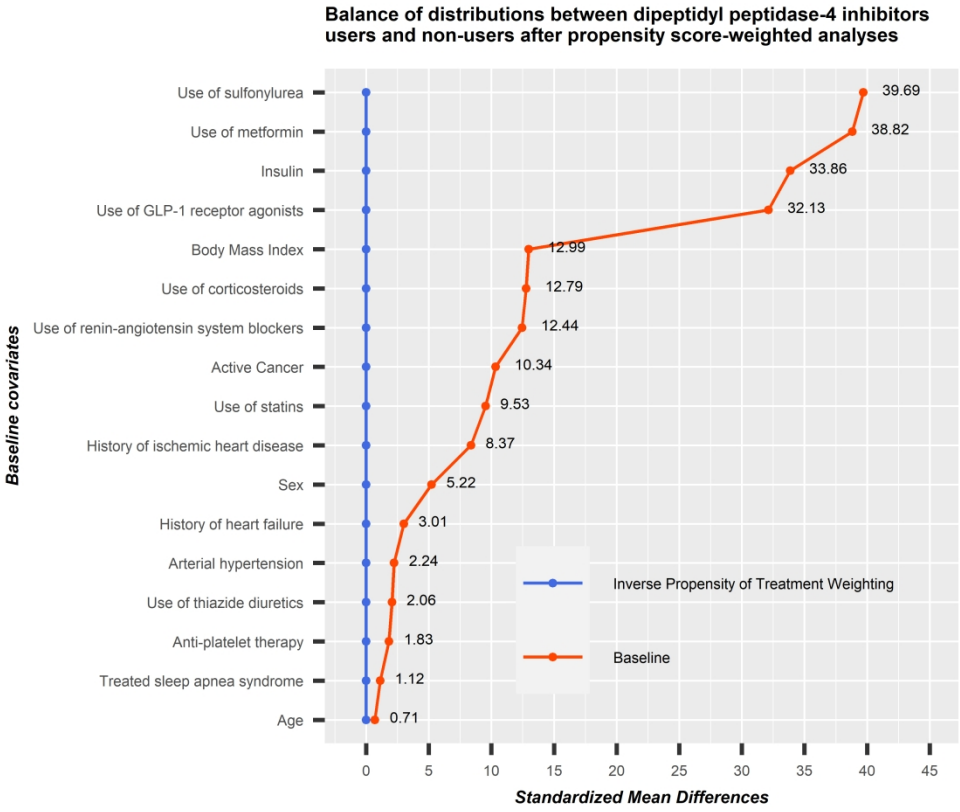

Figure 2: Balance of distributions between Dipeptyl Peptidase-4 inhibitors users and non-users after propensity score-weighted analyses

Table 1. Clinical characteristics prior to admission of CORONADO participants according to the use of DPP-4 inhibitors

			DPP4-inhibitor before admission			
Clinical features	**Available data**	**All**	No (n = 1853)	Yes (n = 596)	*P value*	*SMD*
Sex (female)	2449	881/2449 (36%)	687/1853 (37.1%)	194/596 (32.6%)	0.0455	9.5
Age (years)	2449	70.9+/-12.5	71.1+/-12.8	70.3+/-11.5	0.2339	6.3
Ethnicity	2095				0.2478	4.1
EU		1229/2095 (58.7%)	933/1587 (58.8%)	296/508 (58.3%)		
MENA		446/2095 (21.3%)	345/1587 (21.7%)	101/508 (19.9%)	0.5405	
AC		339/2095 (16.2%)	244/1587 (15.4%)	95/508 (18.7%)	0.1382	
AS		81/2095 (3.9%)	65/1587 (4.1%)	16/508 (3.1%)	0.3765	
BMI (kg/m²)	2150	28.7 [25.3; 32.7]	28.9 [25.5; 33.1]	28.0 [24.9; 31.6]	0.0045	15.9
Diabetes duration (years)	1483	13.9+/-9.6	14.1+/-9.9	13.2+/-8.3	0.1274	9.9
HbA_{1c} (mmol/mol)	1552	64.8+/-20.1	64.3+/-19.8	66.5+/-21.1	0.0808	11
HbA_{1c} (%)	1552	8.1+/-1.8	8+/-1.8	8.2+/-1.9	0.0808	11
eGFR (CKD-EPI), mL/min.1.73m²	1606	68.0+/-29.4	67.7+/-29.7	69.1+/-28.3	0.8628	4.8
Hypertension	2429	1947/2429 (80.2%)	1472/1836 (80.2%)	475/593 (80.1%)	0.969	0.2
Dyslipidemia	2375	1173/2375 (49.4%)	892/1796 (49.7%)	281/579 (48.5%)	0.6351	2.3
Tobacco use	2005	113/2005 (5.6%)	86/1532 (5.6%)	27/473 (5.7%)	0.9378	0.4
Microvascular complications†	1724	782/1724 (45.4%)	606/1319 (45.9%)	176/405 (43.5%)	0.3793	5
Macrovascular complications‡	2308	923/2308 (40.0%)	719/1748 (41.1%)	204/560 (36.4%)	0.0482	9.7
Comorbidities						
Heart failure	2329	280/2329 (12.0%)	217/1760 (12.3%)	63/569 (11.1%)	0.4229	3.9
NAFLD	2078	158/2078 (7.6%)	132/1577 (8.4%)	26/501 (5.2%)	0.0205	12.7
Liver cirrhosis	2301	62/2301 (2.7%)	49/1743 (2.8%)	13/558 (2.3%)	0.5416	3
Active cancer	2405	233/2405 (9.7%)	188/1819 (10.3%)	45/586 (7.7%)	0.0596	9.3
COPD	2394	233/2394 (9.7%)	185/1809 (10.2%)	48/585 (8.2%)	0.1524	7
Treated OSA	2268	255/2268 (11.2%)	194/1713 (11.3%)	61/555 (11%)	0.8285	1.1
Routine treatment before admission						
Sulfonylurea/glinide	2449	754/2449 (30.8%)	493/1853 (26.6%)	261/596 (43.8%)	< 0.0001	36.6
Metformin	2449	1496/2449 (61.1%)	1048/1853 (56.6%)	448/596 (75.2%)	< 0.0001	40
GLP-1 RA	2449	242/2449 (9.9%)	222/1853 (12.0%)	20/596 (3.4%)	< 0.0001	32.8
Insulin therapy	2449	902/2449 (36.8%)	749/1853 (40.4%)	153/596 (25.7%)	< 0.0001	31.7
Acarbose	2449	31/2449 (1.3%)	16/1853 (0.9%)	15/596 (2.5%)	0.0048	12.9
Thiazide diuretic§	2449	494/2449 (20.2%)	366/1853 (19.8%)	128/596 (21.5%)	0.3615	4.3
Loop diuretic	2449	495/2449 (20.2%)	388/1853 (20.9%)	107/596 (18.0%)	0.1147	7.5
MRA	2449	113/2449 (4.6%)	84/4853 (4.5%)	29/596 (4.9%)	0.7366	1.6
ARB and/or ACE inhibitor	2449	1422/2449 (58.1%)	1052/1853 (56.8%)	370/596 (62.1%)	0.0225	10.8
Beta blocker	2449	919/2449 (37.5%)	726/1853 (39.2%)	193/596 (32.4%)	0.0029	14.2
Calcium Channel Blocker	2449	855/2449 (34.9%)	645/1853 (34.8%)	210/596 (35.2%)	0.8822	0.9
Statin	2449	1192/2449 (48.7%)	882/1853 (47.6%)	310/596 (52.0%)	0.0608	8.8

Anti-platelet agent	2449	1039/2449 (42.4%)	780/1853 (42.1%)	259/596 (43.5%)	0.5583	2.8
Vitamin K antagonist	2449	135/2449 (5.5%)	108/1853 (5.8%)	27/596 (4.5%)	0.2567	2.8
Oral direct factor Xa inhibitor	2449	230/2449 (9.4%)	181/1853 (9.8%)	49/596 (8.2%)	0.2940	5.4
Corticosteroid	2449	129/2449 (5.3%)	109/1853 (5.9%)	20/596 (3.4%)	0.0178	12.1
COPD and/or treatment of asthma	2449	269/2449 (11%)	207/1853 (11.2%)	62/596 (10.4%)	0.6019	2.5

Data are presented as No. (%) and mean ± SD, or median (IQR) if not normally distributed. P values are calculated using Wald test. Abbreviations: N/A: not applicable; EU (Europid); MENA (Middle East North Africa); AC (African or Caribbean); AS (Asian); Glycated A1c corresponds to the glycated hemoglobin determined in the 6 months prior to or in the first 7 days following hospital admission; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea; NAFLD, non-alcoholic fatty liver disease; DPP4-inhibitors, Dipeptidyl peptidase 4-inhibitors; GLP-1RA, Glucagon-Like Peptide 1-Receptor Agonist; MRA, Mineralocorticoid Receptor Agonist; ARB, angiotensin-2 receptor blocker; ACE-Inhibitors, angiotensin converting enzyme-inhibitors; SMD, Standardized Mean Difference

† Microvascular complication was defined as history of one or more of the following: diabetic kidney disease and/or severe diabetic retinopathy and/or diabetic foot ulcer

‡ Macrovascular complication was defined as history of one or more of the following comorbidities: acute coronary syndrome, coronary artery disease revascularization, transient ischemic attack and/or lower limber artery revascularization

§Thiazide diuretics, and potassium-sparing diuretics.

Table 2. COVID-19-related clinical, radiological and biological characteristics on admission of CORONADO participants according to the use of DPP-4 inhibitors.

Clinical features	**People with available data**	All	**DPP4-inhibitor before admission**		*P value*	*SMD*
			No (n = 1853)	Yes (n = 596)		
Positive SARS-CoV-2 PCR	2374	2245/2374 (94.6%)	1704/1802 (94.6%)	541/572 (94.6%)	0.9862	0.1
COVID-19 symptoms	2448	2317/2448 (94.6%)	1753/1852 (94.7%)	564/596 (94.6%)	0.9823	0.1
Time between symptom onset and hospital admission (days)	2399	5 [2; 8]	5 [2; 8]	6 [2; 9]	0.0162	11.5
Clinical presentation						
Fever	2414	1807/2414 (74.9%)	1366/1827 (74.8%)	441/587 (75.1%)	0.861	0.8
Fatigue	2337	1456/2337 (62.3%)	1075/1770 (60.7%)	381/567 (67.2%)	0.0058	13.5
Cough	2383	1606/2383 (67.4%)	1213/1799 (67.4%)	393/584 (67.3%)	0.9529	0.3
Cephalalgia	2263	283/2263 (12.5%)	216/1714 (12.6%)	67/549 (12.2%)	0.8061	1.2
Dyspneoa	2416	1562/2416 (64.7%)	1183/1834 (64.5%)	379/582 (65.1%)	0.7864	1.3
Rhinitis and/or pharyngeal signs	2227	181/2227 (8.1%)	143/1686 (8.5%)	38/541 (7.0%)	0.2811	5.5
Agueusia and/or Anosmia	2129	298/2129 (14.0%)	226/1602 (14.1%)	72/527 (13.7%)	0.7984	1.3
Digestive disorders	2336	775/2336 (33.2%)	584/1770 (33.0%)	191/566 (33.7%)	0.7411	1.6
Chest CT imaging						
Abnormal chest CT	1735	1675/1735 (96.5%)	1245/1290 (96.5%)	430/445 (96.6%)	0.9068	0.6
Ground-glass opacity/crazy paving	1712	1548/1712 (90.4%)	1145/1270 (90.2%)	403/442 (91.2%)	0.5309	3.5
Biological findings						
Admission plasma glucose (mg/dL)	1834	170 [127; 236]	167 [125; 229]	185 [131; 256]	0.0063	12.7

eGFR (CKD-EPI) (mL/min/1.73 m²)	2287	67.2 [41.0; 88.5]	67.1 [40.5; 88.3]	67.8 [42.5; 89.3]	0.12 67	4.5
ALT (%ULN)	2056	0.61 [0.42; 0.98]	0.61 [0.42; 0.98]	0.62 [0.42; 1.00]	0.98 31	5.3
AST (%ULN)	2023	1.06 [0.75; 1.59]	1.06 [0.75; 1.60]	1.06 [0.75; 1.55]	0.41 04	6.3
GGT (%ULN)	1915	0.93 [0.55; 1.73]	0.94 [0.55; 1.75]	0.92 [0.58; 1.68]	0.92 34	0.5
Hemoglobin (g/dL)	2387	12.7 [11.4; 14.2]	12.7 [11.4; 14.2]	12.7 [11.4; 14.1]	0.81 44	0.3
White cell count (10^3/mm3)	2384	6600 [5000; 8820]	6530 [5000; 8890]	6685 [4985; 8718]	0.56 08	3.1
Lymphocyte count (10^3/mm^3)	2313	990 [690; 1400]	1000 [690; 1422]	920 [690; 1300]	0.13 22	1.7
Platelet count (10^3/mm3)	2383	201 [155; 258]	201 [155; 258]	201 [156; 260]	0.14 25	4.8
D-dimers (µg/L)	957	880 [328; 1730]	820 [300; 1670]	1000 [430; 1894]	0.24 84	7.8
CRP (mg/L)	2286	86 [40.8; 146.9]	83.6 [38.2; 144]	92.8 [47.5; 149.2]	0.00 3	5.3
LDH (UI/L)	1253	350 [262; 494]	349 [256; 485]	351 [273; 500]	0.91 1	0.4
CPK (UI/L)	1207	132 [66; 302]	134 [65; 326]	118 [67; 252]	0.33 42	8.0
Fibrinogen (g/L)	1227	6.2 [5.0; 7.4]	6.2 [5.0; 7.4]	6.2 [5.0; 7.2]	0.68 84	5.5

Data are presented as No. (%) and mean ± SD, or median (IQR) if not normally distributed. P values are calculated using Wald test. Quantitative variables were natural log transformed and associated OR correspond to an increase of 1 SD after standardization, except for time between symptoms onset and hospital admission (1-day increase).

Abbreviations: CT, computed tomography; eGFR, estimated glomerular filtration rate, according to the CKD-EPI formula; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; CRP, C-reactive protein; LDH, lactate dehydrogenase; CPK, creatine phosphokinase; ULN, Upper limit of normal; SMD, Standardized Mean Difference

Table 3: Association between the use vs no use of DPP-4 inhibitor and outcomes estimated in logistic regression models weighted by patients' inverse probability of treatment (n = 2 449, imputed sample).

	Day 7			**Day 28**		
	Model M0 Baseline parameters	**Model M1 M0 + eGFR using CKD-EPI**	**Model M2 M1 + diabetes duration + HbA_{1c}**	**Model M0 Baseline parameters**	**Model M1 M0 + eGFR using CKD-EPI**	**Model M2 M1 + diabetes duration + HbA_{1c}**
DPP4-inh user/pop. size	**596/2449 (24%)**					
Primary outcome	0.95 [0.77-1.17]	0.94 [0.76-1.16]	0.93 [0.75-1.15]	0.96 [0.78-1.17]	0.94 [0.77-1.15]	0.93 [0.76-1.14]
Tracheal intubation	0.93 [0.73-1.18]	0.94 [0.74-1.19]	0.93 [0.73-1.18]	0.97 [0.77-1.22]	0.97 [0.77-1.23]	0.97 [0.77-1.23]
Death	0.99 [0.73-1.34]	0.96 [0.71-1.30]	0.95 [0.70-1.29]	0.94 [0.74-1.18]	0.90 [0.71-1.14]	0.89 [0.70-1.12]

OR [95%CI] for primary outcome (tracheal intubation for assisted mechanical ventilation and death), tracheal intubation and death.