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PROTOCOL

Impact of use of newer glucose lowering drugs on outcomes in patients with COVID-19

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Background

The coronavirus disease 2019 (COVID-19) pandemic poses great health care challenges worldwide. In Denmark, authority regulated social distancing has been the key to limit rapid spread of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) keeping the diseased population below the tolerable threshold. However, the COVID-19 epidemic is expected to return in one or more waves which emphasizes the need for identifying modifiable risk factors in vulnerable patients.

Studies from China, UK, Denmark and the US report that risk of severe or fatal COVID-19 disease increase with age, male sex and certain comorbid disease including cardiovascular disease and diabetes mellitus[1–5]. Diabetes is a well-established risk factor for both SARS and Middle East Respiratory Syndrome (MERS)[6–8] and has recently been associated with rapid progression of disease and poor outcomes in patients with COVID-19[9]. In a recent Danish population-based cohort study of 9,519 nationwide COVID-19 cases in Denmark, diabetes was associated with a 1.9-fold (95% CI 1.6-2.2) increased risk of inpatient admission and a 1.6-fold (1.3-2.1) increased 30-day mortality. The associations were mainly driven by the subgroup of insulin-treated diabetes patients, and disappeared when adjusting for related multimorbidity[4]. The OpenSAFELY Collaborative in the UK reported similar findings for patients with diabetes and COVID-19, with a worse prognosis in poorly glycaemic controlled individuals (OR for death 2.4 (2.2-2.6)) than in persons with good glycaemic control (OR for death 1.5 (1.4-1.6))[5]. The mechanism of action for these associations is suggested to include an aberrant (innate) immune response to infection, decreased viral clearance, and increased susceptibility to hyperinflammation and cytokine storm[10]. Additionally, poor glycaemic control has been associated with increased morbidity and mortality in SARS[11] and in pneumonia in general[12–14].

Newer glucose lowering drugs (GLD), , have potential for affecting the disease course by suppressing the inflammatory state[15] or by upregulation of the angiotensin-converting enzyme 2 (ACE2)[16,17].

Glucagon Like Peptid-1 (GLP-1) receptor agonists have been shown to reduce pulmonary inflammation in rodent models of experimental lung injury[18] and have exerted broad anti-inflammatory actions in both animals and human studies[15]. Dipeptidyl Peptidase-4 (DPP-4) was identified as a functional MERS-CoV receptor[19], but has not yet been associated with SARS-CoV-2 viral entry like ACE2. The effect on the human immune system by DPP-4 inhibitors is not well established, and a meta-analysis of 74 randomised controlled trials did not show increased risk of upper respiratory tract infections in this group of diabetes patients[20].

However, it is suggested that DPP-4 inhibitors could reduce the risk of respiratory complications in COVID-19 patients with diabetes[21].

As response to the observed link between diabetes and poor COVID-19 outcomes, several international diabetic associations have provided guidance on management of patients with diabetes in the COVID-19 epidemic. Based on current evidence, both metformin and Sodium-Glucose Transport Protein-2 (SGLT2) inhibitors have been recommended to be discontinued in patients with severe COVID-19 due to increased risk of lactic acidosis and ketoacidosis, respectively, while outpatients without symptoms should continue their treatment[22]. However, the existing evidence is still sparse and thus uncertainty prevails about which treatments are safe and which should be revised.

Objectives

This study will examine the association between ongoing use of newer glucose-lowering drugs (DPP4i, SGLT2i, and GLP-1 receptor agonists) and other glucose lowering drugs and risk of severe outcomes in COVID-19 patients. Severe outcomes include hospital admission, intensive care unit (ICU) admission, mechanical ventilation and death within 30 days from positive SARS-CoV-2 test.

Methods

Study design

The study is a national cohort study on patients tested positive for SARS-CoV-2 in Denmark.

Study period

The study will include patients tested positive for SARS-CoV-2 from 27 February 2020 to 30 April 2020 or up to 30 days before final data extraction and analysis.

Data sources

Data will be retrieved from the Danish Microbiology Database and Danish national registries including the Danish National Patient Registry, the Danish Civil Person Registry, and the Danish National Prescription Registry. COVID-19 cases are identified by real-time polymerase chain reaction (RT-PCR) for SARS-CoV-2 on oro- or nasopharyngeal swabs or lower respiratory tract aspirates. See Table 1 for an overview of available variables and their sources.

Table 1: Data sources

Type of information	**Variables**	**Source**
COVID-19 test	Sampling date Test result Test type Sample material	The Danish Microbiology Database
COVID-19 outcomes	Date of hospital admission Date of hospital discharge Intensive care unit admission Intensive care unit discharge Mechanical ventilation	The Danish National Patient Registry
Vital status	Date of death	The Danish Registry of Causes of Death
Demographic data	Sex	The Danish Civil Person Registry

	Date of birth Dates of immigration/emigration	
Medical conditions and procedures	Diagnosis code (ICD-10) Date of diagnosis Procedures Date of procedure	The Danish National Patient Registry
Drug use	Date of prescription fill Drug dispensed (ATC codes) Pack size Number of packs Strength of tables Drug administration and formulation	The Danish National Prescription Registry

ICD-10: International Classification of Diseases version 10, ATC: Anatomical Therapeutic Chemical Classification System

Study population

The study population consists of all patients tested positive for SARS-CoV-2 in Denmark who have had permanent residence in Denmark for at least the past year. As of 30 April 2020, the number of tested persons in Denmark was 193,165 while the number of positive was 9,158. Patients currently or formerly hospitalised numbered 1,989, whereof 298 included ICU admission. Deaths were reported in 452 patients[23].

Follow-up

Patients with confirmed COVID-19 are followed from and including date of positive SARS-CoV-2 test until ICU admission, mechanical ventilation, date of death, or for up to 30 days.

Exposure

The exposure of interest is current use of GLP-1 receptor agonists and DPP-4 inhibitors, which is defined as having redeemed prescriptions of GLP-1 receptor agonists (ATC code A10BJ) or DPP-4 inhibitors (ATC code A10BH) within 90 days prior to positive SARS-CoV-2 test. Patients in the exposed group will be compared to patients with current use of SGLT2 inhibitors (ATC code A10BK). Redeemed prescriptions are retrieved from the Danish National Prescription Registry according to ATC codes, see table 2.

The choice of 90 days is based on GLP-1 receptor agonists and SGLT2 inhibitors expected renewal patterns. A sensitivity analysis of patients with an extended window of redeemed prescriptions up to the prior 120 days will be performed to account for irregular prescription renewal.

We will use comparison with an active comparator to assess if any observed association with outcomes is specific to GLP-1 receptor agonists and DPP4i exposure. SGLT2 inhibitors are chosen as comparator because they are used for the similar medical indication, i.e. second or third choice of treatment of diabetes mellitus type 2, or first choice in case of metformin intolerability.

Both GLP-1 receptor agonists and SGLT2 inhibitors can induce a weight loss and are especially recommended to patients with concurrent cardiovascular disease. Patients initiating GLP-1 receptor agonists or SGLT2 inhibitors in Denmark are previously shown to be similar regarding age, duration of GLD therapy and diabetes, cardiovascular and other comorbidities, and prevalence of diabetic complications[24]. However, initiators of GLP-1 receptor agonists are likely to have a higher body max index (BMI) corresponding to a higher prevalence of recorded medical obesity[24] due to a more pronounced expected weight loss, and are more often treated in combination with insulin than users of SGLT2 inhibitors[24].

Additionally, we will examine patients initiating DPP-4 inhibitors as a secondary exposure of interest due to the similarity with GLP-1 receptor agonists, both being incretin mimetic drugs. Patients initiating SGLT2 inhibitors will be used as active comparator as described above. Patients in these two groups are expected to differ more, as users of DPP-4 inhibitors are shown to be older and have a shorter duration of GLD therapy and diabetes than users of both GLP-1 receptor agonists and SGLT2 inhibitors[24]. These differences will be adjusted for in the analysis by propensity score matching.

Table 2. Glucose lowering medications and corresponding ATC codes

Medication	**ATC codes**	**Source**
GLP-1 receptor agonists	A10BJ	The Danish National Prescription Registry
Exenatide	A10BJ01, A10BX04	-
Liraglutide	A10BJ02, A10BX07	-
Lixisenatide	A10BJ03, A10BX10	-
Albiglutide	A10BJ04, A10BX13	
Dulaglutide	A10BJ05, A10BX14	-
Semaglutide	A10BJ06	-
SGLT2 inhibitors	A10BK	-
Dapaglifozin	A10BK01, A10BX09, A10BD15,	-

Canaglifozin	A10BK02, A10BX11, A10BD16	-
Empaglifozin	A10BK03, A10BX12, A10BD20	-
Ertuglifozin	A10BK04	-
DPP-4 inhibitors	A10BH	-
Sitagliptin	A10BH01, A10BD07, A10BD12	-
Vildagliptin	A10BH02, A10BD08	-
Saxagliptin	A10BH03, A10BD10,	-
Alogliptin	A10BH04, A10BD09, A10BD13	-
Linagliptin	A10BH05, A10BD11	-
Gemigliptin	A10BH06, A10BD18	-
SGLT2 and DPP4 combinations (excluded)	A10BD19, A10BD21, A10BD24-25	-

Outcomes

The primary outcome is death within 30 days after positive SARS-CoV-2 test. The secondary outcomes include hospital admission, ICU admission and mechanical ventilation within 30 days after positive SARS-CoV-2 test.

Patients are registered as hospital admitted if they are admitted to hospital within 30 days after positive test for SARS-CoV-2 or if they have a positive test for SARS-CoV-2 within 48 hours of hospital admission if already admitted before the date of the test.

Confounding

Confounding by indication will be reduced by using an active comparator design as users of the active comparator are expected to have the same indication for treatment including disease severity. To account for differences between the groups, we will include duration of diabetes (i.e. years since first redeemed GLD prescription or diabetes diagnosis), concomitant use of metformin and insulin, diagnoses of microvascular and macrovascular diabetic complications, other cardiovascular diseases including hypertension, any atherosclerotic cardiovascular disease, and heart failure, medical obesity, smoking-related diseases or inhalation drug use as a marker of tobacco smoking, alcoholism, socioeconomic and frailty markers (marital status, region of residence, total number of inpatient admission days the last 2 years), and the total burden

of comorbidity based on Charlson's Comorbidity Index, in the matching model described below. Although we include a range of comorbidities and drug therapies, we cannot exclude the impact of residual confounding by imperfectly measured, unmeasured, or unknown factors, e.g. lifestyle factors, socioeconomic status, or frailty/low functional level before COVID-19 onset.

Selection bias

The risk of selection bias is present as the Danish authorities have restricted SARS-CoV-2 testing of the Danish population based on certain criteria, partly due to limited testing capacity. However, these criteria have been eased during the study period. The in-hospital capacity for COVID-19 patients have likewise been increased during the study period. These changing conditions are handled by including calendar time in the matching model, as described in the statistics section below. In addition, patients suffering from diabetes mellitus have been considered a risk group throughout the study period.

Statistical analysis

We will estimate odds ratios for hospital admission, ICU admission, mechanical ventilation and death in patients tested positive for SARS-CoV-2 for the exposed group (current use of GLP-1 receptor agonists) vs. the active comparator group (current use of SGLT2 inhibitors) by logistic regression.

In both analyses, we will apply propensity score matching to adjust for pre-existing differences in significant risk factors between the exposed and active comparator group. Patients will be matched 1:1, unless other matching sets are possible. All covariates included in the matching model are listed in table 3.

In secondary analyses, we will study patients with current use of DPP-4 inhibitors compared to the active comparator group (i.e. patients with current use of SGLT2 inhibitors).

Logistic regression is preferred to Cox regression in this study as time-to-event analysis will be greatly influenced by the difference in delay from testing to outcome as patients are tested on different indications and on different time points in the disease course during the study period. In a sensitivity analysis, inverse probability weight will be used to account for competing risk of death in the analyses of the secondary outcomes (ICU admission and mechanical ventilation).

Sample size considerations

As of 30 April 2020, there were 9,158 cases of COVID-19 in Denmark, with 452 deaths. The number of patients using GLP-1 receptor agonists in the study population is expected to be between 50-100, primarily based on data from the Danish Health Data Authority from 2018 (medstat.dk). Assuming a 30-day mortality of 5% in active comparator/unexposed, we will have a power of 80% for detecting an odds ratio (OR) of 2.6, at a significance level of 5%.

Table 3. Covariates

Type of information	Variables	Diagnosis codes / ATC codes
Demographics	Sex Age Marital status Region of residence	-
Total number of inpatient admission days the last 2 years		-
Calendar week	Weeks 9-22, 2020	
CCI group	0 1-2 3+	See table 4
Diabetes		E10-E14
Duration of diabetes	GLP-1 receptor agonists SGLT2 inhibitors DPP-4 inhibitors	See table 2
Concomitant use of other glucose lowering drugs	Metformin Insulin	A10BA02, A10BD03, A10BD05, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13, A10BD14, A10BD15, A10BD16, A10BD17, A10BD18, A10A
Diabetic microvascular complications	Retinopathy Neuropathy Nephropathy	E103, E113, E143, H340, H341, H342, H334, H450, H360, H540, H541, H544, H430, H431, H438C, H439, H334A, H330, H335, H470, KCKC10, KCKC15, KCKD65 E104, E114, E144, G590, G632, G598, G603, G628, G629, G632, G638, G990 E102, E112, E142, I120, N083, N06, N17, N18, N19, R809, BJFD2
Diabetic macrovascular complications	Ischemic heart disease Cerebrovascular disease Peripheral vascular disease	I20, I21, I22, I23, I24, I25 I60, I61, I62, I63, I64, I65, I66, I67, I68, I69, G45, G46 I70, I71, I72, I73, I74, I77 E105, E115, E145
Cardiovascular comorbidities	Hypertension Chronic heart failure	I10, I11, I12, I13, I15 I50, I110, I130, I132

	Any atherosclerotic cardiovascular disease (excluding ischemic heart disease and cerebrovascular disease)	T822A, T823, KFNA, KFNB, KFNC, KFND, KFNE, KFNF, KFNG, KFNH, KFNW, KFLF, KAAL10, KAAL11, KPAE, KPAF, KPAH, KPAN, KPAP, KPAQ, KPAW99, KPAU74, KPBE, KPBF, KPBH, KPBN, KPBP, KPBQ, KPBW, KPGH10, KPCE, KPCF, KPCH, KPCN, KPCP, KPCQ, KPCW99, KPCW20, KPCU74, KPCU82, KPCU83, KPCU84, KPGE, KPGF, KPGH, KPGN, KPGP, KPGQ, KPGW99, KPGW20, KPEE, KPEF, KPEH, KPEN, KPEP, KPEQ, KPEW, KPFE, KPFH, KPFN, KPFP, KPFQ, KPFW, KPGH20, KPGH21, KPGH22, KPGH23, KPGH30, KPGH31, KPGH40, KPGH99, KPDU74, KPDU82, KPDU83, KPDU84, KPEU74, KPEU82, KPEU83, KPEU84, KPFU74, KPFU82, KPFU83, KPFU84, KPGU74, KPGU83, KPGU84, KPGU99, KPGW, KPWG
Co-medications	Blood pressure lowering drugs	C02, C03A, C03B, C03D, C03E, C07, C08, C09A, C09B, C09C, C09D, C09X
	Lipid lowering drugs (Statins)	C10AA, C10BA C10BX
	Antiplatelets drugs	B01AC06, N02BA01, B01AC30, B01AC07, B01AC22, B01AC04, B01AC24
LIFESTYLE AND SOCIAL FACTORS		
Diagnoses for COPD or smoking	COPD	J41, J42, J43, J44,
	Smoking	DF17, DZ716, DZ720
Medications for COPD or smoking	Inhaled corticosteroids (in combinations or alone)	R03BA
	Inhaled beta-2-agonists	R03A
	Inhaled anti-cholinergics	R03BB
	Anti-smoking	N07BA
Medical obesity	Diagnoses	E65, E66, E67, E68
	Anti-obesity drug use	A08
Alcoholism	Alcoholism-related diagnoses	E244, F10 (except F100), G312, G621, G721, I426, K292, K70, K852, K860, Q860, R780, T51, Z502, Z714, Z721

Medications for alcohol deterrent	V03AA, N07BB

CCI: Charlson's Comorbidity Index ICD-10 version (since 1994), ICD-10: International Classification of Diseases version 10, COPD: Chronic Obstructive Pulmonary Disease

Table 4. ICD-10 Coding Algorithms for Charlson Comorbidities

Comorbidities	**ICD-10**
Myocardial infarction	I21.x, I22.x, I25.2
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0
Peripheral vascular disease	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Cerebrovascular disease	G45.x, G46.x, H34.0, I60.x-I69.x
Dementia	F00.x-F03.x, F05.1, G30.x, G31.1
Chronic pulmonary disease	I27.8, I27.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3
Rheumatic disease	M05.x, M06.x, M31.5, M32.x-M34.x, M35.1, M35.3, M36.0
Peptic ulcer disease	K25.x-K28.x
Mild liver disease	B18.x, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73.x, K74.x, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4
Diabetes without chronic complications	E10.0, E10.l, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Diabetes with chronic complication	E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2-E13.5, E13.7, E14.2-E14.5, E14.7
Hemiplegia or paraplegia	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0-G83.4, G83.9
Renal disease	I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18.x, N19.x, N25.0, Z49.0-Z49.2, Z94.0, Z99.2
Any malignancy, including lymphoma and leukaemia, except malignant neoplasm of skin	C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x-C76.x, C81.x-C85.x, C88.x, C90.x-C97.x
Moderate or severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Metastatic solid tumour	C77.x-C80.x
AIDS/HIV	B20.x-B22.x, B24.x

Ethical/data protection issues

The Danish COVID-19 cohort data are kept at the Danish Health Data Authority (record no. 00004874) and approved by the Data Protection Office at University of Southern Denmark (record no 10.960). Data are pseudonymised centrally at the Danish Health Data Authority. According to Danish law, ethical permission is not required for registry-based research. Individual-level data will not be made publicly available in accordance with Danish law.

Publication of study results

The study protocol will be registered in the EU PAS registry prior to data analysis and publication. Results of the study will be published in international peer-reviewed journals and made available via the Danish Medicines Agency.

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