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PROTOCOL

Impact of use of proton pump inhibitors on susceptibility to infection and risk of hospitalisation in patients with COVID-19

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Study group

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1. Background

Since the coronavirus disease 2019 (COVID-19) epidemic was introduced in Denmark, measures have been taken to contain the spread and fight the disease. Studies from China and Italy describe that risk of severe or fatal COVID-19 disease increase with age, male sex and certain comorbid disease[1,2]. The observed risk varied in the populations implying that the results are not necessarily transferable to other countries. This poses a great need to confirm known risk factors and identify unknown risk factors in a Danish population.

Concern has been raised regarding antihypertensives and non-steroidal anti-inflammatory drugs (NSAIDs) via their suspected upregulation of ACE-2 receptors, but international recommendations have not yet been modified due to limited scientific evidence[3,4]. Other medication possibly related to the host's susceptibility to infection include proton pump inhibitors (PPIs) that reduce the protective stomach acid production.

Proton pump inhibitors have previously been associated with increased risk of infection in a meta-analysis from 2015 which showed that the risk of acquiring pneumonia and being admitted to hospital due to pneumonia was increased in persons receiving PPI[5].

Objectives

This study will examine the association between concomitant use of PPI and risk of SARS-CoV-2 infection in patients tested for SARS-CoV-2 and risk of hospitalisation, intensive care unit (ICU) admission, mechanical ventilation and death among patients with confirmed COVID-19, respectively.

2. Methods

2.1 Study design

The study is a national register-based study on patients tested for SARS-CoV-2 in Denmark. The risk of SARS-CoV-2 infection will be examined using a case control design with test-positive patients as cases and test-negative patients as controls. The risk of hospital admission and severe outcomes will be restricted to a cohort of test-positive patients only.

2.2 Study period

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

2.3 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	The Danish National Patient Registry
Demographic data	Sex Date of birth Dates of immigration/emigration	The Danish Civil Person Registry
Medical conditions	Diagnosis code (ICD-10) Date of diagnosis	The Danish National Patient Registry
Drug use	Date of prescription fill Drug dispensed (ATC codes) Pack size Number of packs Strength of tablets Drug administration and formulation	The Danish National Prescription Registry

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

2.4 Study population

The study population consists of all patients tested for SARS-CoV-2 in the case-control design investigating the risk of infection. In the cohort design, the study population comprises patients with a positive test for SARS-CoV-2 examining the risk of hospitalisation and severe outcomes.

As of 30 April 2020, the number of patients tested for SARS-CoV-2 in Denmark was 193,165 while the number of patients tested positive was 9,158. The number of patients currently or earlier admitted to hospital was 1,989[6].

2.5 Follow-up

Patients in the cohort design with confirmed COVID-19 are followed from date of positive SARS-CoV-2 test until hospital admission, date of death, or for up to 90 days.

2.6 Exposure

Patients are considered exposed to PPIs if they have redeemed a prescription for PPI within 90 days prior to their positive SARS-CoV-2 test, or in case of negative test result 90 days prior to the first SARS-CoV-2 test performed. Redeemed prescriptions for PPI are defined by ATC code A02BC and are retrieved from the Danish National Prescription Registry, see table 2. Patients are classified as past users if they have redeemed a prescription more than 90 days prior to their positive or first SARS-CoV-2 test. The choice of 90 days is based on experience from a Danish population-based case-control study on PPI use and the risk of community-acquired pneumonia, in which the authors analysed PPI prescription renewal patterns[7].

Table 2. Medications and corresponding ATC codes

Medication	**ATC codes**	**Source**
Proton pump inhibitors	A02BC	The Danish National Prescription Registry
Omeprazol	A02BC01	-
Pantoprazol	A02BC02	-
Lansoprazol	A02BC03	-
Rabeprazol	A02BC04	-
Esomeprazol	A02BC05	-

3. Outcomes

The primary outcome is hospital admission within 30 days after positive test for SARS-CoV-2 or a positive test for SARS-CoV-2 within 48 hours of hospital admission in patients already admitted before the date of the test. Secondary outcomes comprise ICU admission, mechanical ventilation and death within 30 and 90 days after positive SARS-CoV-2 test.

In the risk of infection analysis, the outcome is a positive SARS-CoV-2 test among all patients tested during the study period, and where the negative tests are included as potential controls.

4. Bias

4.1 Confounding

Confounding by indication will be reduced by including the most common diseases indicating PPI use in the matching model, see below. Additionally, the analyses will be repeated after excluding patients with gastric or duodenal ulcers which are the most severe indications for PPI use. To account for differences between the groups, we will include diagnoses of peptic ulcer, chronic respiratory diseases (including asthma and chronic obstructive pulmonary disease (COPD)), ischemic heart disease, stroke, heart failure, diabetes mellitus, renal failure, liver cirrhosis, major psychiatric disorders, smoking-related diagnoses and alcohol-related diagnoses or drug use, frailty markers based on health care utilisation, co-medications including inhaled drug use, corticosteroid treatment, immunomodulating treatment, antibiotics, blood pressure lowering drugs, lipid lowering drugs, glucose lowering drugs, antiplatelets, anticoagulants, treatment of alcohol dependence and antipsychotic agents, and finally the total burden of comorbidity based on Charlson's Comorbidity Index. Although we include a wide 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.

4.2 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, as described in the statistics section below.

5. Statistical analysis

We will estimate odds ratios for hospital admission and severe outcomes in patients with positive SARS-CoV-2 test for the exposed group (current PPI use) relative to the unexposed group by using logistic regression.

In the case-control design, we sample controls by a risk set strategy, i.e., subjects who are eligible to be sampled as control for a given case will be those that are present in the source population and who have not yet developed the outcome of interest. Controls will be matched on sex and birth year to the case and will be assigned an index date identical to the matching case. We will perform conditional logistic regression to examine a possible association between current PPI use and COVID-19 susceptibility, and results will be presented as odds ratios with 95% confidence intervals. In the nested case-control study, confounding by age, sex and calendar time will be handled by virtue of the risk set sampling and the matched analysis. Other potential confounders will be handled by multivariable modelling (conditional logistic regression).

In the cohort analysis, we will apply matching to adjust for pre-existing differences in significant risk factors between the exposed and unexposed groups. Patients will be matched 1:1, unless other matching sets are possible. Matching will be performed by use of propensity scores, which will include all variables listed in table 3. Covariate balance will be ascertained by use of standardised differences of the mean (SDM). SDM values below 0.1 will be considered as representing acceptable balance.

Sensitivity analysis will be performed on patients with current PPI use vs. past PPI use vs. never PPI use.

5.1 Sample size considerations

As of 30 April 2020, there were 9,158 cases of COVID-19 in Denmark, with 1,989 hospital admissions. The proportion of patients using PPI is expected to be approximately 10% based on data from a previous Danish population-based study on PPI use[7]. Assuming a 30-day hospital admission rate of 20% in unexposed, we will have a power of 80% for detecting an odds ratio (OR) of 1.26, at a significance level of 5%.

Table 3. Covariates

Type of information	Variables	Time frame / Diagnosis codes
Demographics	Sex	
	Date of birth	
Calendar week	Weeks 9-22, 2020	
Health care utilisation	Number of hospital admissions	Within 3 years prior to positive test
Comorbidities (CCI group)	0	Since 1994 (ICD-10)
	1-2	
	3+	
Comorbidities	Peptic ulcer	K25, K26, K27
	Asthma	J45
	COPD	J44
	Liver cirrhosis	K703, K717A, K717B, K743, K744, K745, K746, K746B, K746C, K746D, K746E, K746F, K746G, K746H, DP788A
	Ischemic heart disease	I20, I21, I22, I23, I24, I25, N02BA, C01DA, B01AC24
	Diabetes mellitus	E10, E11, E13, E14
	Renal failure	I12, I13, N00-N05, N07, N08, N11, N14, N18, N19, E102, E112, E142
	Heart failure	I099A, I110, I130, I132, I50
	Stroke	I60, I61, I62, I63, I64, I69
	Alcohol-related diagnosis or drug use	F10, E244, G312, G621, G721, I426, K292, K70, K852, K860, Q860, Z502, Z714, Z721
	Smoking-related diagnosis	DF17, DZ716, DZ720
	Psychiatric disorder	F20, F25, F30, F31
Co-medications	Systemic corticosteroids	H02AB
	Inhaled corticosteroids	R03AK, R03AL, R03BA
	Bronchodilators	R03AA, R03AC
	H2RAs	A02BA
	NSAIDs	M01A (excluding M01AX)
	Anticholinergic agents	R03BB
	Immunomodulating drugs	L04AA, L04AB, L04AC, L04AD, L04AX, L01XC02
	Antipsychotic agents	N05AA, N05AB, N05AC, N05AD, N05AE, N05AF, N05AG, N05AH, N05AL, N05AN, N05AX
	Antibiotics	J01

	Treatment to support alcohol abstinence	N07BB
	Treatment to support smoking cessation	N07BA
	Blood pressure lowering drugs	C03A, C07, C08, C09
	Lipid lowering drugs	C10
	Glucose lowering drugs	A10A, A10B
	Antiplatelets	B01AC
	Anticoagulants	B01AA, B01AE07, B01AF

CCI: Charlson's Comorbidity Index ICD-10 version, ICD-10: International Classification of Diseases version 10, COPD: Chronic obstructive pulmonary disease, H2Ras: H2-receptor antagonists, NSAIDs: Non-steroidal anti-inflammatory drugs

6. Ethical considerations/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.

7. 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.

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

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