Renin-angiotensin-aldosterone system inhibitors and adverse outcomes of COVID-19: a Danish nationwide cohort study (ACE-I/ARB and COVID-19)

First published: 27/04/2020
Last updated: 10/12/2020

Study | Finalised

Administrative details

PURI
https://redirect.ema.europa.eu/resource/38561

EU PAS number
EUPAS34887

Study ID
38561

DARWIN EU® study
No

Study countries
Denmark

Study description
Speculations suggest that use of ACE-I/ARB may increase the risk of developing severe or fatal COVID-19 by upregulating expression of the ACE2 enzyme. The European Medicines Agency, and other major institutions and societies, have called for research and issued warnings against ACE-I/ARB discontinuation in patients with COVID-19, as drug discontinuation may worsen underlying cardiometabolic conditions. As ACE-I/ARB are widely used drugs, any association with risk and prognosis may have public health impact. Thus, there is an urgent need to clarify the hypothesis of any increased risk for COVID-19

or worsened prognosis for adverse outcomes of COVID-19. The primary aim of the study is to examine the association between ACE-I/ARB use and risk of death in patients with COVID-19. The secondary aim is to examine the association of ACE-I/ARB use with risk of hospital admission, ICU admission, mechanical ventilation, and renal replacement therapy. The third aim is to examine the risk of being diagnosed with COVID-19 among all patients referred to SARS-CoV-2 testing. This nationwide study will include all patients tested for SARS-CoV-2 in Denmark. By individual-level linkage of Danish registries, the impact of ACE-I/ARB on risk of COVID-19 will be examined using a test-negative case-control design, while the prognosis with regard to mortality and intensive care admission will be examined in a cohort design of test-positive COVID-19 patients.

Study status
Finalised

Research institution and networks

Institutions

Aarhus University & Aarhus University Hospital DEPARTMENT OF CLINICAL EPIDEMIOLOGY

Denmark
First published: 20/07/2021
Last updated
02/04/2024

Institution | Educational Institution | ENCePP partner

Pharmacoepi center, University of Southern Denmark

Denmark
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27/07/2023

Institution | Educational Institution | ENCePP partner

Contact details

Study institution contact

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Primary lead investigator

Study timelines

Date when funding contract was signed
Planned:
22/04/2020
Actual:
22/04/2020

Study start date
Planned:
27/02/2020
Actual:
27/02/2020

Data analysis start date
Planned:
27/04/2020

Date of final study report
Planned:
01/06/2020
Actual:
09/12/2020

Sources of funding

- Other

More details on funding

Aarhus University

Study protocol

Protocol ACEi-ARB COVID-19 EU PAS.pdf(773.31 KB)

Regulatory

Was the study required by a regulatory body?
Yes

Is the study required by a Risk Management Plan (RMP)?
Not applicable

Methodological aspects

Study type

Study type list

Study topic:
Human medicinal product
Disease /health condition

Study type:
Non-interventional study

Scope of the study:
Assessment of risk minimisation measure implementation or effectiveness

Data collection methods:
Secondary data collection

Main study objective:
To examine the association between ACE-I/ARB use and adverse outcomse of COVID-19.

Study Design

Non-interventional study design
Cohort
Case-control

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code
(C09A) ACE INHIBITORS, PLAIN
(C09B) ACE INHIBITORS, COMBINATIONS
(C09C) ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs), PLAIN
(C09D) ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs), COMBINATIONS

Medical condition to be studied
COVID-19

Population studied

Short description of the study population
The source population is all Danish citizens (popuation~5.8 million). The study population for risk analysis (the test-negative case-control analysis) will be all patients tested for SARS-CoV-2, while the prognosis analysis (cohort analysis) will only include patients tested positive SARS-CoV-2, i.e., patients with COVID-19.

Age groups
Preterm newborn infants (0 – 27 days)
Term newborn infants (0 – 27 days)
Infants and toddlers (28 days – 23 months)
Children (2 to < 12 years)
Adolescents (12 to < 18 years)
Adults (18 to < 46 years)
Adults (46 to < 65 years)
Adults (65 to < 75 years)
Adults (75 to < 85 years)
Adults (85 years and over)

Special population of interest
Renal impaired
Hepatic impaired
Immunocompromised
Pregnant women

Estimated number of subjects
7515

Study design details

Outcomes
Death within 30 days after positive test for SARS-CoV-2. Hospital admission at day of or within 30 days after a positive test for SARS-CoV-2.Intensive care unit admission, mechanical ventilation, and renal replacement therapy at dayof or within 30 days after positive test for SARS-CoV-2.Positive tests among all patients tested for SARS-CoV-2.

Data analysis plan
Propensity-score weighted risk, risk difference and risk ratio for the outcomes.Adjusted odds ratio for positive test among all tested.

Documents

Study publications
Christiansen CF, Pottegård A, Heide-Jørgensen U, Bodilsen J, Søgaard OS, Maeng …

Data management

Data sources

Data source(s)
Danish registries (access/analysis)

Data sources (types)
Administrative data (e.g. claims)
Other

Data sources (types), other
The Danish Microbiology Database

Use of a Common Data Model (CDM)

CDM mapping
No

Data quality specifications

Check conformance
Unknown

Check completeness
Unknown

Check stability
Unknown

Check logical consistency
Unknown

Data characterisation

Data characterisation conducted
No