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

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 institutions and networks

Institutions

Aarhus University & Aarhus University Hospital CLINICAL EPIDEMIOLOGY AND DATA SCIENCE, DEPARTMENT OF CLINICAL MEDICINE

Denmark

First published: 20/07/2021

Last updated: 20/10/2026

Institution | Educational Institution

Pharmacoepi center, University of Southern Denmark

Denmark

First published: 22/04/2010

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Institution | Educational Institution | ENCePP partner

Contact details

Study institution contact

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Study contact

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Primary lead investigator

Henrik Toft Sørensen

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 use of data

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

ACE INHIBITORS, PLAIN

(C09B) ACE INHIBITORS, COMBINATIONS

ACE INHIBITORS, COMBINATIONS

(C09C) ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs), PLAIN

ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs), PLAIN

(C09D) ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs), COMBINATIONS

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

7.515

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

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s)

Danish registries (access/analysis)

Data sources (types)

Administrative healthcare records (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