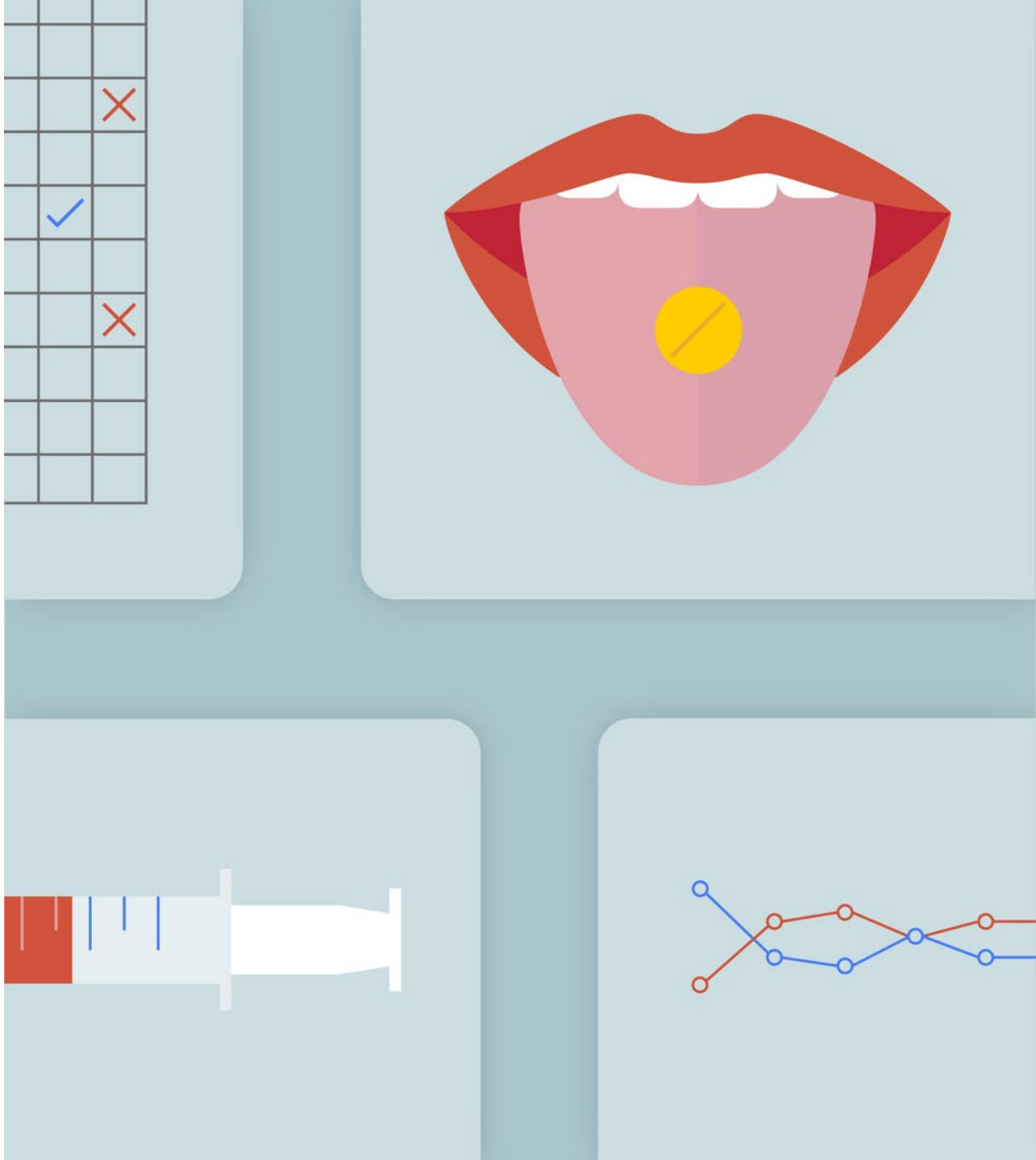
Prof. Dr. Olaf Klungel

# *Key considerations for observational studies on COVID-19*



Utrecht University

Pharmacoepidemiology
and Clinical Pharmacology

# *Medicines and impact on risk and prognosis of COVID-19*

# Many hypotheses/rumours on specific medicines

…. and risk of infection
….. and prognosis.

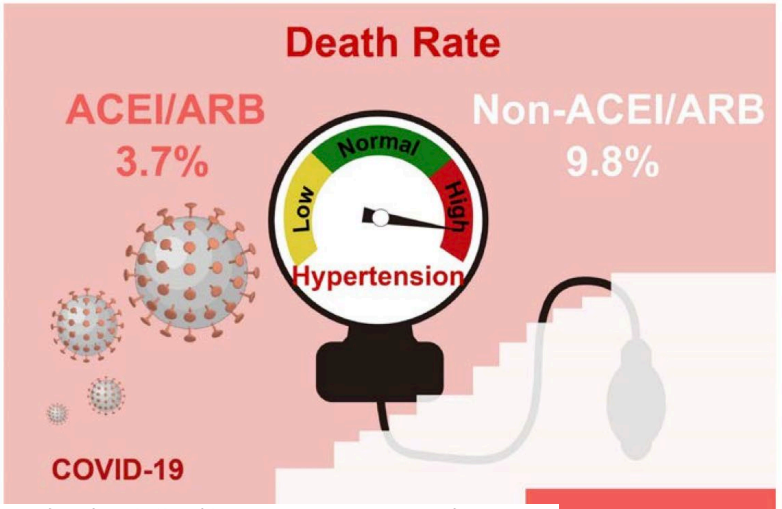
Ibuprofen, hydroxychloroquine, ACE inhibitors,
Angiotensin II type 1 receptor antagonists, statins….

Need for urgent and reliable evidence

# Association of Inpatient Use of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers with Mortality Among Patients With Hypertension Hospitalized With COVID-19

Peng Zhang, LiHua Zhu, Jingjing Cai, I
Ye-Mao Liu, Yan-Ci Zhao, Xuewei Huar
Ming-Ming Chen, Xu Cheng, Xiao Zhan

**Originally published** 17 Apr 2020 |
https://doi.org/10.1161/CIRCRESAHA.120.31




to February 20, 2020. Unadjusted mortality rate was lower in the ACEI/ARB group versus the non-ACEI/ARB group (3.7% vs. 9.8%; $P = 0.01$). In mixed-effect Cox model treating site as a random effect, after adjusting for age, gender, comorbidities, and in-hospital medications, the detected risk for all-cause mortality was lower in the ACEI/ARB group versus the non-ACEI/ARB group (adjusted HR, 0.42; 95% CI, 0.19-0.92; $P$ =0.03). In a propensity score-matched analysis followed by adjusting imbalanced variables

# Use ACE inhibitors/ARBs to treat COVID-19?

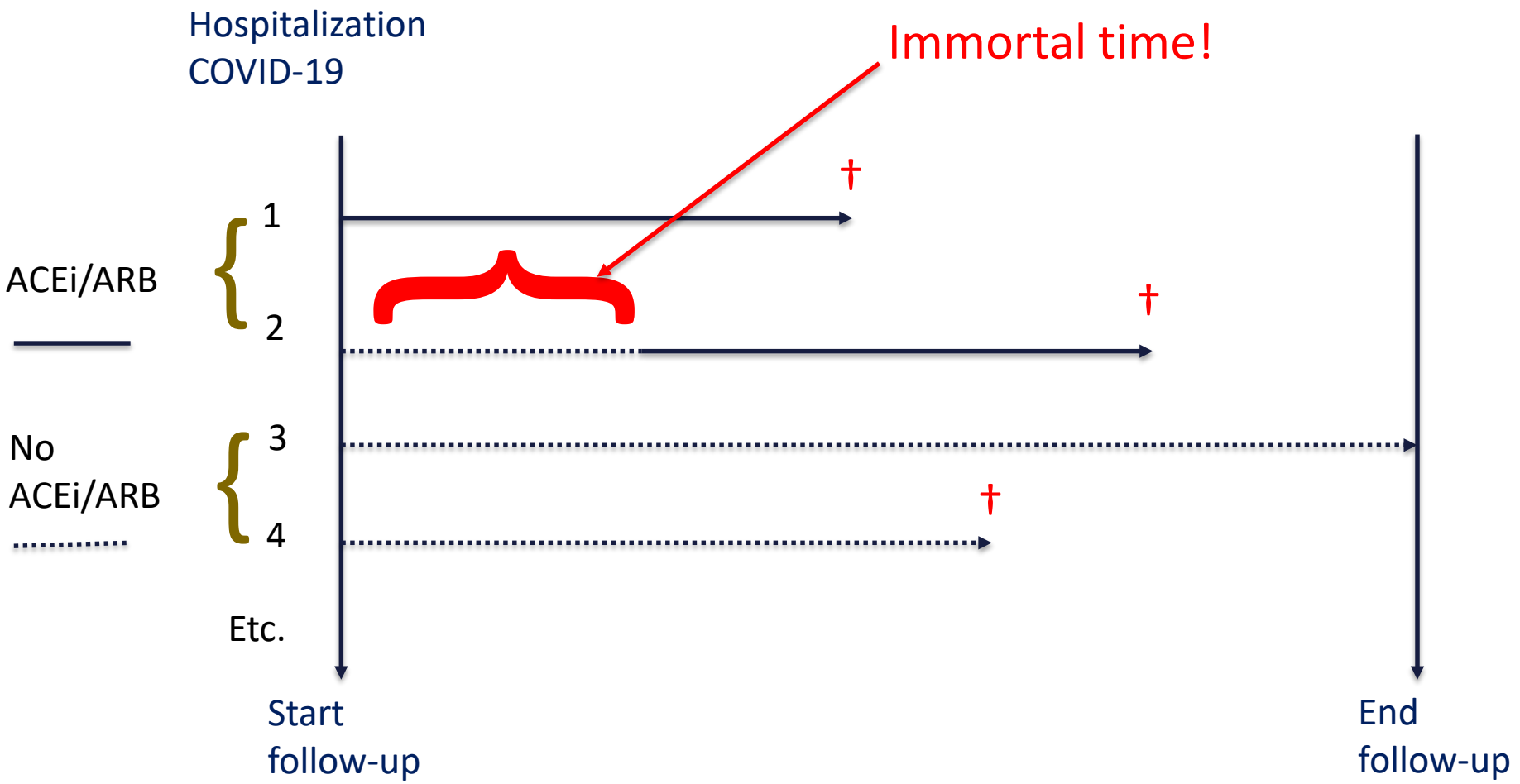
# OR

# Too good to be true?

# Misclassification of exposure

The onset of COVID-19 was defined as the time point when the symptoms were first noticed. Patients with hypertension who received ACEI/ARB during hospitalization were classified as ACEI/ARB group. Patients with hypertension who did not receive ACEI/ARB during hospitalization were classified as non-ACEI/ARB group. In the subgroup propensity score-matched cohort analysis among patients taking antihypertensive

# Immortal time bias



Annals of Internal Medicine REVIEW

# Risks and Impact of Angiotensin-Converting Enzyme Inhibitors or Angiotensin-Receptor Blockers on SARS-CoV-2 Infection in Adults

## A Living Systematic Review

**Katherine Mackey, MD, MPP; Valerie J. King, MD, MPH; Susan Gurley, MD, PhD; Michael Kiefer, MD; Erik Liederbauer, MD; Kathryn Vela, MLIS, AHIP; Payten Sonnen, BS; and Devan Kansagara, MD, MCR**

*Ann Intern Med.* doi:10.7326/M20-1515



***Table 2*–Continued**

| Study (Reference)* | Period; Population; Setting | Patient Characteristics | Disease Severity Definition | Patients Receiving ACEI or ARB With Severe Illness, *n/n (%)*; With Nonsevere Illness, *n/n (%)* | Unadjusted OR for Severe Illness With ACEI or ARB (95% CI) | aOR for Severe Illness With ACEI or ARB (95% CI) | Other Outcomes |
|---|---|---|---|---|---|---|---|
| Yang et al (39) | 1/5/20–2/22/20; adults with preexisting HTN at 1 hospital; Hubei, China | *n* = 126<br>Median age: 66 y<br>Male: 49%<br>HTN: 100%<br>Diabetes: 30%<br>Heart disease: 18% | Per National Health Commission of China§; mortality | 15/50 (30.0); 28/76 (36.8) | 0.74 (0.34–1.58) | NR | Unadjusted OR for death, 0.32 (0.07–1.51) |
| Peng et al (40) | 1/20/20–2/15/20; adults with COVID-19 and preexisting CVD at 1 hospital; China | *n* = 112<br>Patients with preexisting CVD<br>Mean age: 62 y<br>Male: 47%<br>HTN: 82%<br>Diabetes: 21% | Per National Health Commission of China§; mortality | 3/16 (18.6); 19/96 (19.8) | 0.94 (0.24–3.61) | NR | – |
| Zeng et al (41) | 1/5/20-3/8/20; adults with COVID-19 admitted to 1 hospital; China | *n* = 75<br>Patients with COVID pneumonia and HTN<br>Mean age: 67 y<br>Male: 55%<br>HTN: 100%<br>Diabetes: 31% | Pneumonia severity | 15/30 (50); 13/45 (29) | 2.46 (0.94–6.45) | NR | Unadjusted OR for death, 0.65 (0.12–3.58) |
| Zhang et al (42) | 12/31/19–2/20/20; adults aged 18–74 y with COVID-19 admitted to 9 hospitals; China | *n* = 1128<br>Mean age: 64 y<br>Male: 53%<br>HTN: 100% | Death, septic shock, ARDS | NR | HR for septic shock, 0.38 (0.17–0.87)<br>HR for ARDS, 0.70 (0.47–1.02) | HR for septic shock, 0.36 (0.16–0.84)<br>HR for ARDS, 0.69 (0.47–1.02)*** | Adjusted HR for death, 0.42 (0.19–0.92)*** |

# Use of renin–angiotensin–aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study

*Francisco J de Abajo, Sara Rodríguez-Martín, Victoria Lerma, Gina Mejía-Abril, Mónica Aguilar, Amelia García-Luque, Leonor Laredo, Olga Laosa, Gustavo A Centeno-Soto, Maria Ángeles Gálvez, Miguel Puerro, Esperanza González-Rojano, Laura Pedraza, Itziar de Pablo, Francisco Abad-Santos, Leocadio Rodríguez-Mañas, Miguel Gil, Aurelio Tobías, Antonio Rodríguez-Miguel, Diego Rodríguez-Puyol, on behalf of the MED-ACE2-COVID19 study group**

*Lancet* 2020; 395: 1705–14

Published Online
May 14, 2020
https://doi.org/10.1016/

## Summary

**Background** Concerns have been raised about the possibility that inhibitors of the renin–angiotensin–aldosterone system (RAAS) could predispose individuals to severe COVID-19; however, epidemiological evidence is lacking. We report the results of a case-population study done in Madrid, Spain, since the outbreak of COVID-19.

**Interpretation** RAAS inhibitors do not increase the risk of COVID-19 requiring admission to hospital, including fatal cases and those admitted to intensive care units, and should not be discontinued to prevent a severe case of COVID-19.

Utrecht University
Pharmacoepidemiology
and Clinical Pharmacology

JAMA | Original Investigation

# Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With COVID-19 Diagnosis and Mortality

Emil L. Fosbøl, MD, PhD; Jawad H. Butt, MD; Lauge Østergaard, MD; Charlotte Andersson, MD, PhD; Christian Selmer, MD, PhD; Kristian Kragholm, MD, PhD; Morten Schou, MD, PhD; Matthew Phelps, MSc; Gunnar H. Gislason, MD, PhD; Thomas A. Gerds, Dr rer nat; Christian Torp-Pedersen, MD, DMSc; Lars Køber, MD, DMSc

**IMPORTANCE** It has been hypothesized that angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) may make patients more susceptible to coronavirus disease 2019 (COVID-19) and to worse outcomes through upregulation of the functional receptor of the virus, angiotensin-converting enzyme 2.

Editor's Note page 177

Audio and Supplemental content

*JAMA*. 2020;324(2):168-177. doi:10.1001/jama.2020.11301
Published online June 19, 2020.

**CONCLUSIONS AND RELEVANCE** Prior use of ACEI/ARBs was not significantly associated with COVID-19 diagnosis among patients with hypertension or with mortality or severe disease among patients diagnosed as having COVID-19. These findings do not support discontinuation of ACEI/ARB medications that are clinically indicated in the context of the COVID-19 pandemic.

Received: 14 April 2020 | Revised: 28 April 2020 | Accepted: 2 May 2020

DOI: 10.1002/pds.5029

REVIEW

WILEY

# Considerations for pharmacoepidemiological analyses in the SARS-CoV-2 pandemic

Anton Pottegård[1] | Xavier Kurz[2] | Nicholas Moore[3] | Christian F. Christiansen[4] | Olaf Klungel[1,5]

This commentary received endorsement from the International Society for Pharmacoepidemiology (ISPE).

*Pharmacoepidemiol Drug Saf.* 2020;1–7.

## Key Points

- Consideration #1: Study questions needing urgent answers in the acute phase of the pandemic should be prioritised over those better answered at a later stage where our understanding of SARS-CoV-2 has improved and/or when increased sample size may allow more precise answers.
- Consideration #2: Observational studies to assess efficacy are, in the context of an ongoing pandemic, unlikely to add significant value in the short term. If performed, their hypothesis generating nature should be made clear.
- Consideration #3: The conduct of real-time epidemiology comes with specific challenges related to for example, lag in data availability and delay in coding of in-hospital outcomes, requiring close collaboration with both registry holders and clinicians to ensure valid analyses.
- Consideration #4: A core challenge is the identification of the underlying source population from which study subjects are identified given the considerable potential for bias, for example, related to changing thresholds for testing and admittance. Care must be taken to ensure that study subjects are all "at risk" of the outcome being studied.
- Consideration #5: Ascertainment of exposure generally follows standard pharmacoepidemiological principles. Rapid changes to prescribing practices during the pandemic and the analysis of in-hospital drug use comprise specific challenges.
- Consideration #6: Selecting useful covariates for risk studies are challenging as these are largely unknown or unmeasured (eg, adherence to quarantine regulations). For studies of COVID-19 prognosis, measures of frailty are particularly valuable. However, particular care must be taken as to not adjust for intermediates, for example, lab values obtained upon hospital admission or treatments after study inclusion.
- Consideration #7: The temporal and geographical variation in testing strategies and thresholds for hospitalisation and intensive care admission, as well as the delay from infection to admission and death, must be taken into account when ascertaining outcomes in COVID-19 patients
- Consideration #8: In the face of an ongoing pandemic, rapid assessment of evidence is important. This can be greatly facilitated by transparent reporting, including the use of checklist and design diagrams, as well as public registration of study protocols.



*Pharmacoepidemiol Drug Saf.* 2020;1–7.

Hydroxychlo

YOU ARE READING
BREAKING: Sur
Covid-19
TECH STA

HOME » FEATURE

BREAK
falsifyir
hydrox
to halt

Nickie Louise

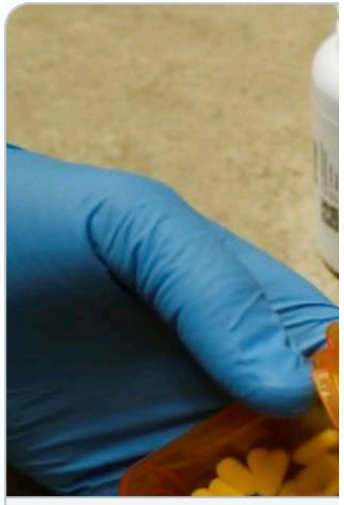
James Todaro, MD
@JamesTodaroMD

So Surgisphere Corp was caught falsifying data for the Lancet study on hydroxychlor

Hospitals deny ever sl
database

When asked to reveal
Surgisphere refused

Is this real life?thegua



CrossMark

Articles

ych
Revi

## Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

*Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel*

**Summary**

**Background** Hydroxychloroquine or chloroquine, often in combination with a second-generation m…lide, are b… widely used for treatment of COVID-19, despite no conclusive evidence of their benefit. Althoug… generally … whe… used for approved indications such as autoimmune disease or malaria, the safety and bene… of th… treatment regimens are poorly evaluated in COVID-19.

**Methods** We did a multinational registry analysis of the use of hydroxychloroquine … oquine with… thout a macrolide for treatment of COVID-19. The registry comprised data from 671 hosp…s in s… ntinents. We included patients hospitalised between Dec 20, 2019, and April 14, 2020, with a positive laboratory … g for SARS-CoV-2. Patients who received one of the treatments of interest within 48 h of diagn… included in … of four treatment groups (chloroquine alone, chloroquine with a macrolide, hydroxychlor…ine alone, or hydroxychloroquine with a macrolide), and patients who received none of these treatments formed … control gr… Patients for whom one of the treatments of interest was initiated more than 48 h after diagnosis o…ile they w… on mechanical ventilation, as well as patients who received remdesivir, were excluded. The main outc… of int…st were in-hospital mortality and the occurrence of de-novo ventricular arrhythmias (… tained o… ed ventricular tachycardia or ventricular fibrillation).

**Findings** 96 032 patients (mean age 53·8 years, 46·3% women) … COVID-19 were hospitalised during the study period and met the inclusion criteria. Of the… patie… were in the treatment groups (1868 received chloroquine, 3783 received chloroquine with… macro…e, 3016 …eived hydroxychloroquine, and 6221 received hydroxychloroquine with a macrolide) and … pati… in the control group. 10 698 (11·1%) patients died in hospital. After controlling for multiple … fou… ctors (… sex, race or ethnicity, body-mass index, underlying cardiovascular disease and its risk fac… diabetes, …derlying lung disease, smoking, immunosuppressed condition, and baseline disease severity), wh… mpared wi… ortality in the control group (9·3%), hydroxychloroquine (18·0%; hazard ratio 1·335, 95% … 457), hydro…ychloroquine with a macrolide (23·8%; 1·447, 1·368–1·531), chloroquine (16·4%; 1·365, …318–1·531), …chloroquine with a macrolide (22·2%; 1·368, 1·273–1·469) were each independently associated … an increased … of in-hospital mortality. Compared with the control group (0·3%), hydroxychloroquine (6… ; 2·36… ·935–2·906), hydroxychloroquine with a macrolide (8·1%; 5·106, 4·106–5·983), chloroquine (4·3%; …1, 2… …–4·596), and chloroquine with a macrolide (6·5%; 4·011, 3·344–4·812) were independently associate… an incr…ed risk of de-novo ventricular arrhythmia during hospitalisation.

**Interpretation** We w… unabl… nfirm a benefit of hydroxychloroquine or chloroquine, when used alone or with a macr… on in…spital outc…mes for COVID-19. Each of these drug regimens was associated with decreased in-hospita… …eased frequency of ventricular arrhythmias when used for treatment of COVID-19.

**Funding** William… …wey Distinguished Chair in Advanced Cardiovascular Medicine at Brigham and Women's Hospital.



Published Online
…22, 2020
https://doi.org/10.1016/
S0140-6736(20)31180-6

**This online publication has been corrected. The corrected version first appeared at thelancet.com on May 29, 2020**

See Online/Comment
https://doi.org/10.1016/
S0140-6736(20)31174-0

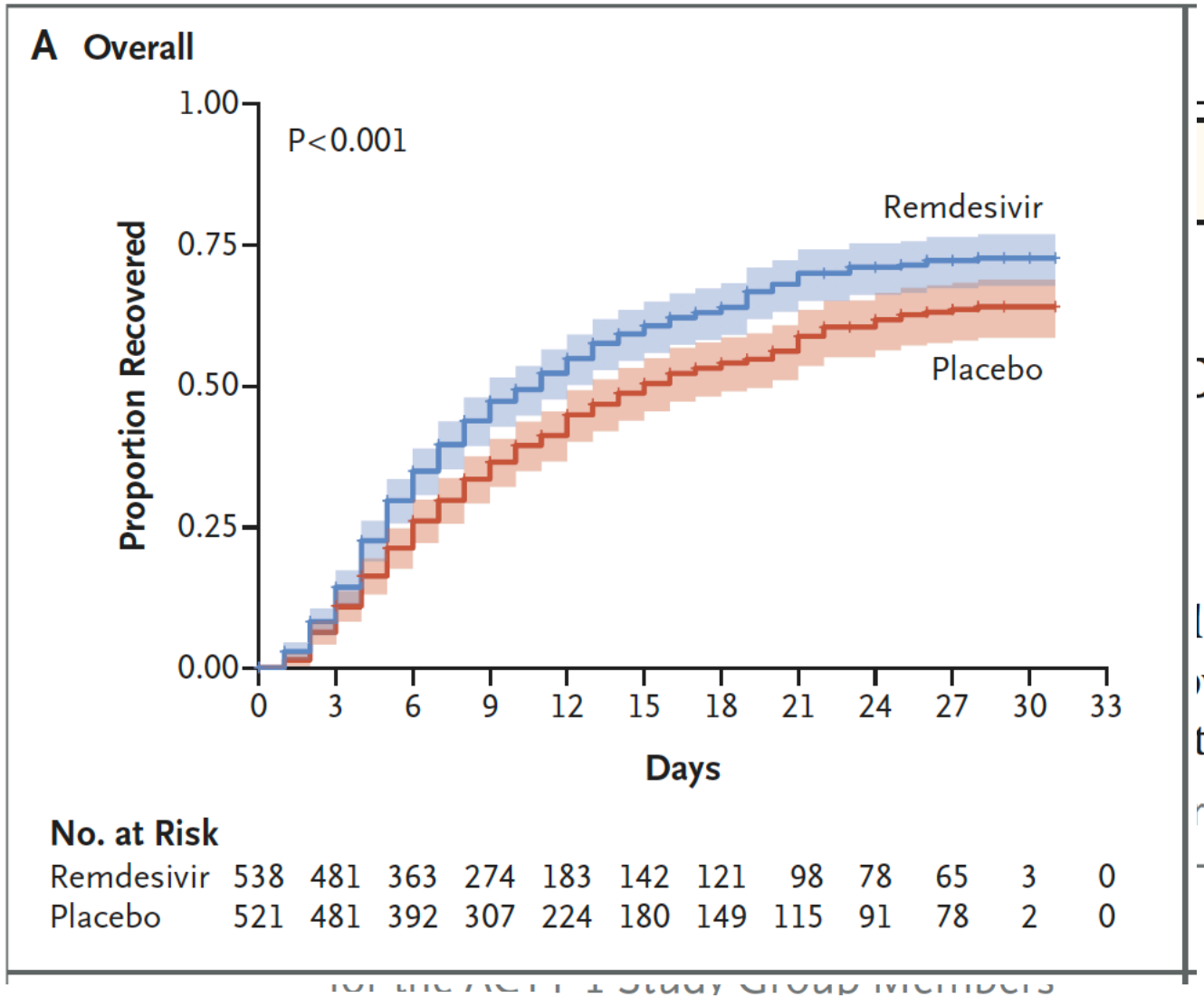
**Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston, MA, USA** (Prof M R Mehra MD); **Surgisphere Corporation, Chicago, IL, USA** (S S Desai MD); **University Heart Center, University Hospital Zurich, Zurich, Switzerland** (Prof F Ruschitzka MD); **Department of Biomedical Engineering, University of Utah, Salt Lake City, UT, USA** (A N Patel MD); **and HCA Research Institute, Nashville, TN, USA** (A N Patel)

Correspondence to:
Prof Mandeep R Mehra, Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston, MA 02115, USA
**mmehra@bwh.harvard.edu**

RETRACTED

**Interpretation** We were unable to confirm a ben… a macrolide, on in-hospital outcomes for COV… in-hospital survival and an increased frequency

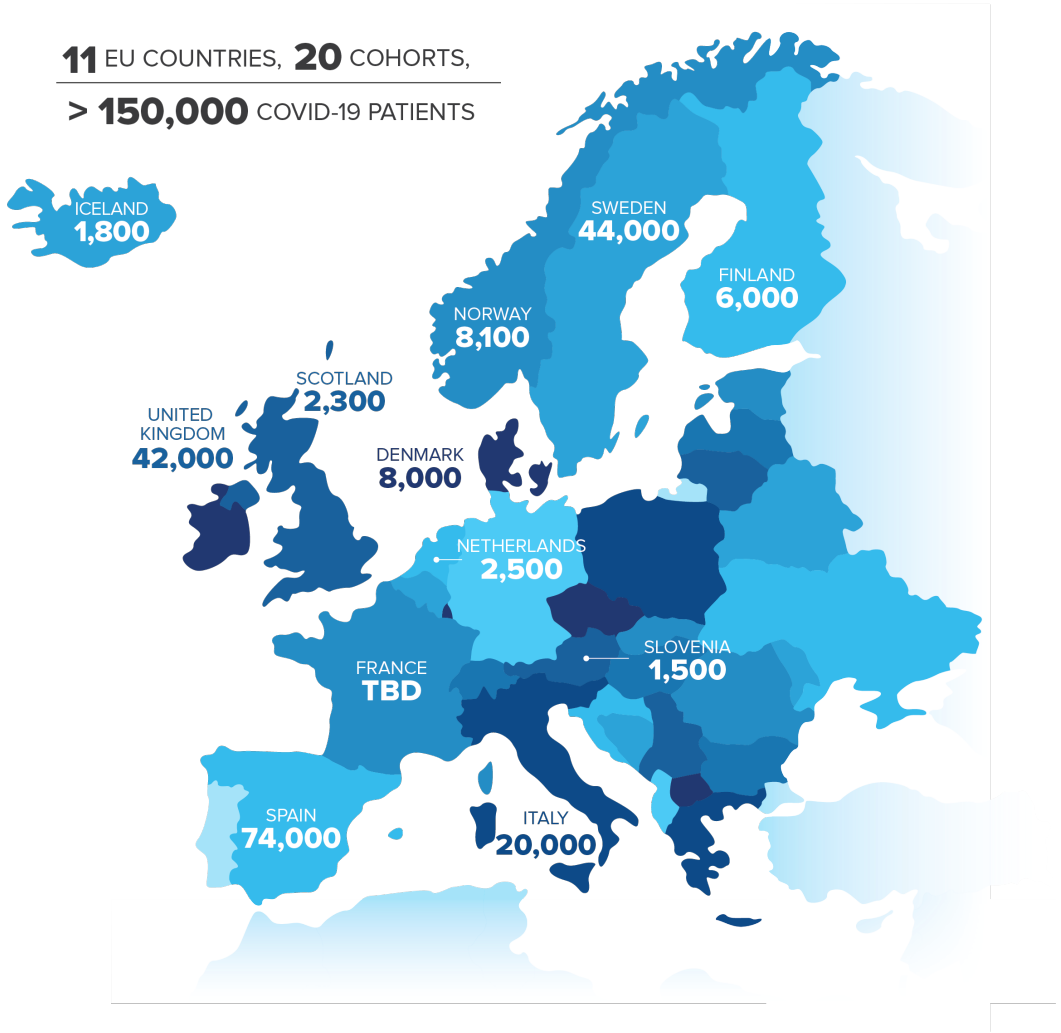
Utrecht University




## CONCLUSIONS

Remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with Covid-19 and evidence of lower respiratory tract infection.

# Estimated numbers of COVID-19 patients in EU cohorts during 1st wave



# The European Union electronic Register of Post-Authorisation Studies (EU PAS Register)

On this page you can register (or resume a draft application for) a new study, update existing study records or search the EU PAS Register.

To **register a new study** please click on 'Add Study' below:
(If this is a study related to the coronavirus pandemic, please include the text **COVID-19** in the study title)

Add Study

To **resume a draft application** saved previously (but not submitted yet) or to amend and re-submit a previously rejected application, please follow the link:
Resume Draft/Rejected application.

To **update** an existing study record please click on 'Edit Study' below:

# EMA inventory of observational studies related to COVID-19

| Highlights | Studies including at least one European country | Studies outside Europe | Total |
|---|---|---|---|
| Numbers | **131** | **85** | **216** |
| Finalised | **53** | **79** | **132** |
| Ongoing | **61** | **5** | **66** |
| Planned (or under discussion) | **17** | **1** | **18** |
| Included in the EU PAS Register | **57** | **3** | **60** |

# ENCePP Guide on Methodological Standards in Pharmacoepidemiology

## Foreword to 8th Revision: ENCePP Guide supports strong observational research for the COVID-19 pandemic

The rapid progression of the COVID-19 pandemic has generated several hypotheses on the safety and effectiveness of therapeutic interventions, such as repurposed medicines. The need for quick answers triggered the initiation of observational studies carried-out with fast data collection, analysis and reporting. In a pandemic situation, the same methodological standards as those applied in any other circumstance should nevertheless be used to provide valid and reliable evidence supporting rapid treatment decisions by clinicians and regulators. Adherence to existing guidance on the appropriate design and conduct of pharmacoepidemiologic studies is therefore of utmost importance. ENCePP believes that this 8$^{th}$ Revision of the Guide on Methodological Standards in Pharmacoepidemiology should be the backdrop against which observational studies related to the COVID-19 pandemic should be conducted.

Pottegård et al. provide methodological considerations for the conduct of pharmacoepidemiological studies in relation to the COVID-19 pandemic across eight domains. The ENCePP Guide addresses each of these domains: (1) timeliness of evidence generation, including the need to prioritise some questions over others in the acute phase of the pandemic (addressed in Chapter 2); (2) the need to align observational and interventional research on efficacy (Chapter 10.1); (3) the specific challenges related to “real-time epidemiology” during an ongoing pandemic (Chapters 4.1, 4.2 and 4.3); (4) what design to use to answer a specific question (Chapter 5); (5) considerations on the definition of exposures (Chapter 5.1); (6) what covariates to collect (Chapter 5.1); (7) considerations on the definition of outcomes (Chapter 5.1); and (8) the need for transparent reporting (Chapter 8).

The methodological challenges described by Pottegård et al. are illustrated by studies that examined the differences in the incidence and severity of the SARS-CoV -2 virus infection between patients receiving angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) and those not receiving ACEi/ARB, which may help to inform hypertension treatment decisions. In these studies, the subset of patients being tested was not a random and unbiased sample of the total population, which may lead to the selection bias described in Chapter 5.2. Patients with symptoms and

ispe International Society for Pharmacoepidemiology

MyISPE Login

ISPE Exchange

Search

About ISPE | Communities | Meetings | Strategic Initiatives | Get Involved | Resources

Home

# STRATEGIC INITIATIVES

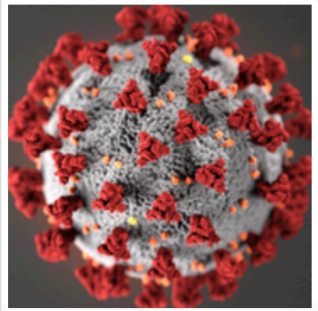
## ISPE MEMBERS COVID-19 WORK

- ISPE Members COVID-19 Work
  - Special COVID-19 Sessions

RWE Task Force

RWE for Regulatory Decision Making

COVID-19 has emphasized the importance of epidemiologic expertise on many levels, including our work in pharmacoepidemiology. This webpage is dedicated to featuring ISPE members' work aimed at addressing the pandemic. ISPE members work on every continent and on a broad range of initiatives from determining what drives transmission and prognosis to finding safe and effective treatment and vaccines, from helping to shape policy and guidance to design and govern valid research to integrating relevant topics in educational and outreach activities. Examples of ISPE members' rapidly evolving work are listed below.



# Conclusions

- Careful consideration of pharmacoepidemiological principles for:
  - Design and analysis
  - Interpretation
  - Transparancy
- International collaboration to generate consistent and reliable evidence using:
  - Common protocols
  - Common Data Models
- Link to networks outside EU (ASIA, US, Canada…)

Utrecht University

# DISCLAIMER

The information in this presentation has been compiled with the utmost care,
but no rights can be derived from its contents.