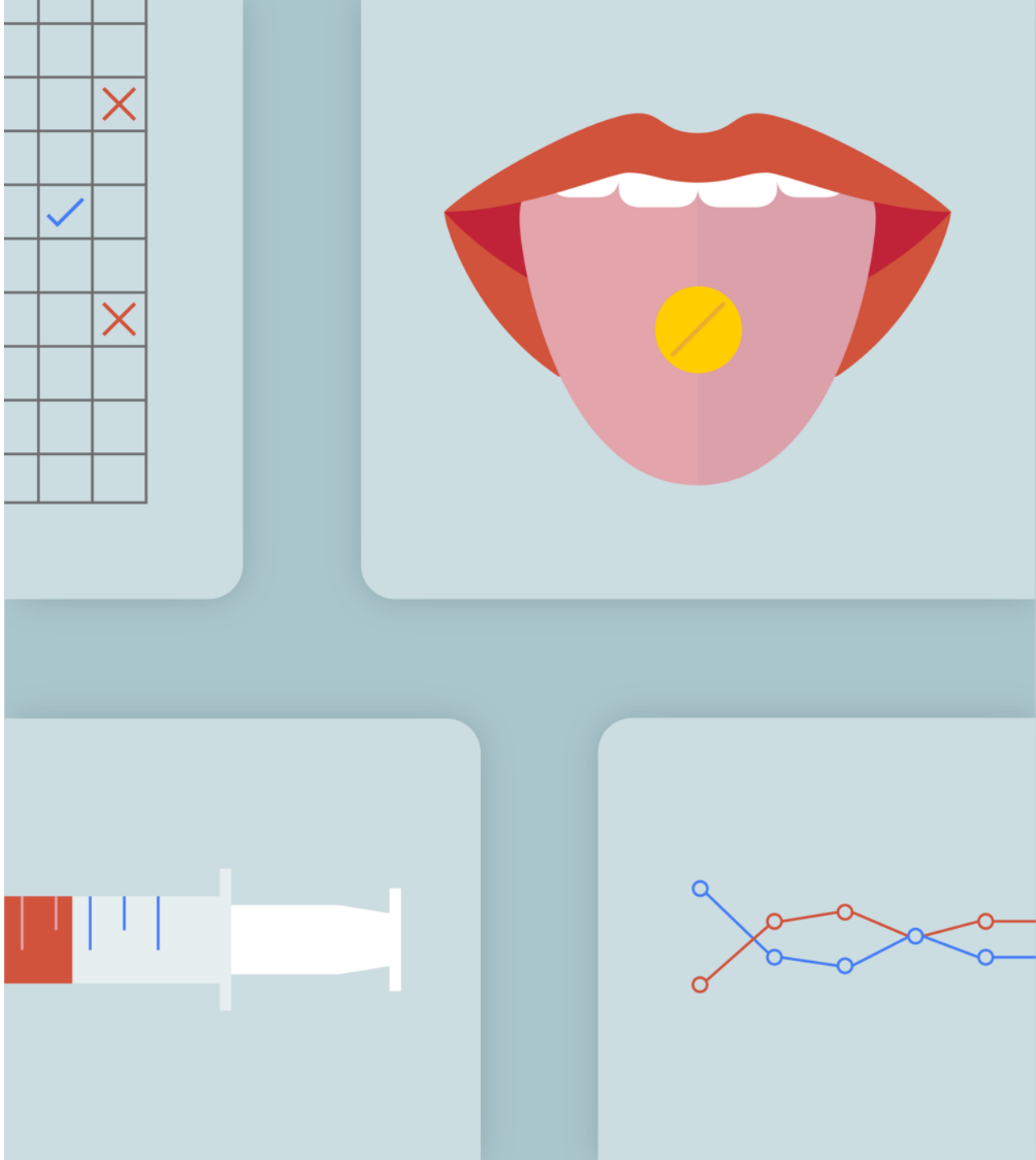
ENCePP and COVID-19:

Consideration on good practice in observational research on COVID-19

Helga Gardarsdottir, PharmD, PhD
Associate professor



Utrecht University

Pharmacoepidemiology
and Clinical Pharmacology

Many hypotheses/rumours about specific medicines

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, Fang Lei, Juan-Juan Qin, Jing Xie, Ye-Mao Liu, Yan-Ci Zhao, Xuewei Huang, Lijin Lin, Meng Xia, Ming-Ming Chen, Xu Cheng, Xiao Zhang, ... See all authors

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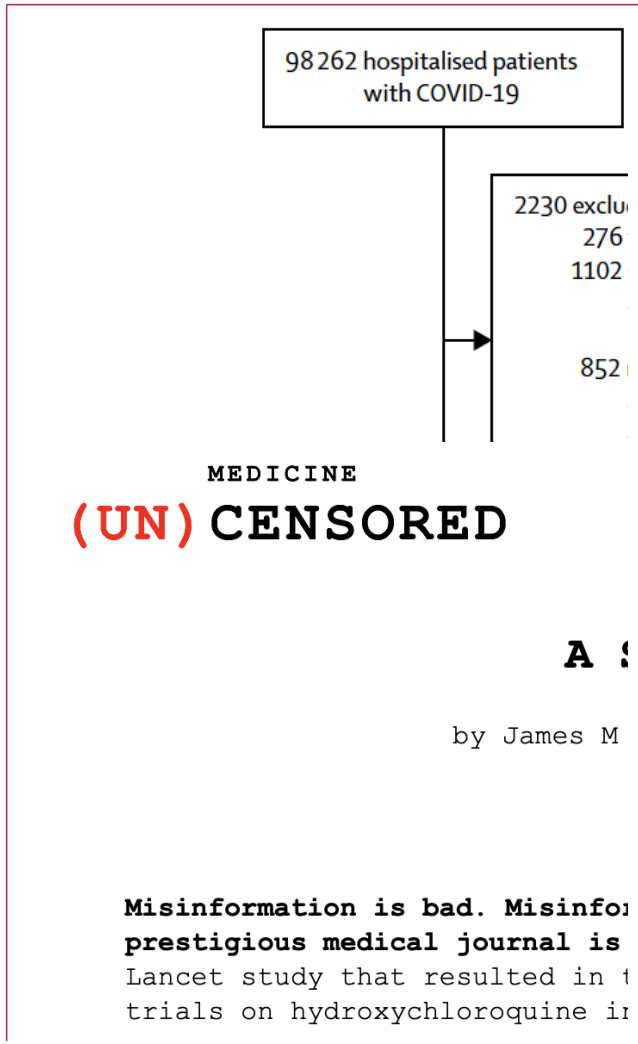
Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

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

Hydroxychloroquine or chloroquine with or without a ma… multinational reg…

Mandee…



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

Articles

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. Although …nerally …e whe… used for approved indications such as autoimmune disease or malaria, the safety and bene… f 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 … 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 … f 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), w… mpared wi… ortality in the control group (9·3%), hydroxychloroquine (18·0%; hazard ratio 1·335, 95%… 1·2… 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 … f in-hospital mortality. Compared with the control group (0·3%), hydroxychloroquine (6… ; 2·36… 935–2·90…), 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… d risk of de-novo ventricular arrhythmia during hospitalisation.

Interpretati… 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… …ey Distinguished Chair in Advanced Cardiovascular Medicine at Brigham and Women's Hospital.

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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

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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.

Clinical Pharmacology & Therapeutics

State of the Art | Free Access

Real-World Evidence for Assessing Pharmaceutical Treatments in the Context of COVID-19

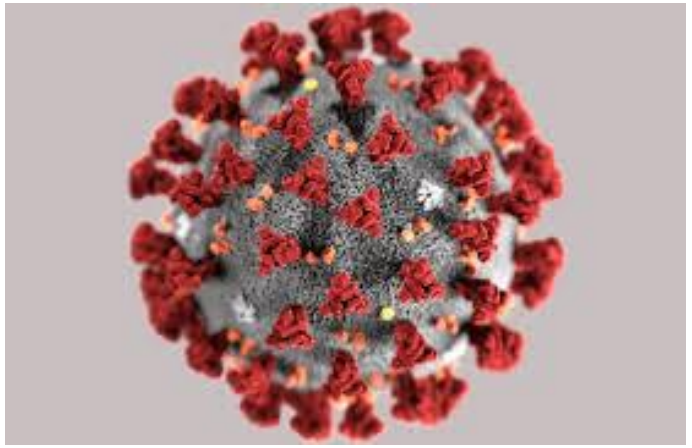
Jessica M. Franklin, Kueiyu Joshua Lin, Nicolle M. Gatto, Jeremy A. Rassen, Robert J. Glynn, Sebastian Schneeweiss

First published: 02 February 2021 | https://doi.org/10.1002/cpt.2185

Observational studies on efficacy

Challenges of real-time epidemiology

Timeliness of evidence



Appropriate study design

Transparent reporting

Ascertainment of exposure

Defining the outcome properly

Selection of covariates for risk studies

Exposure

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

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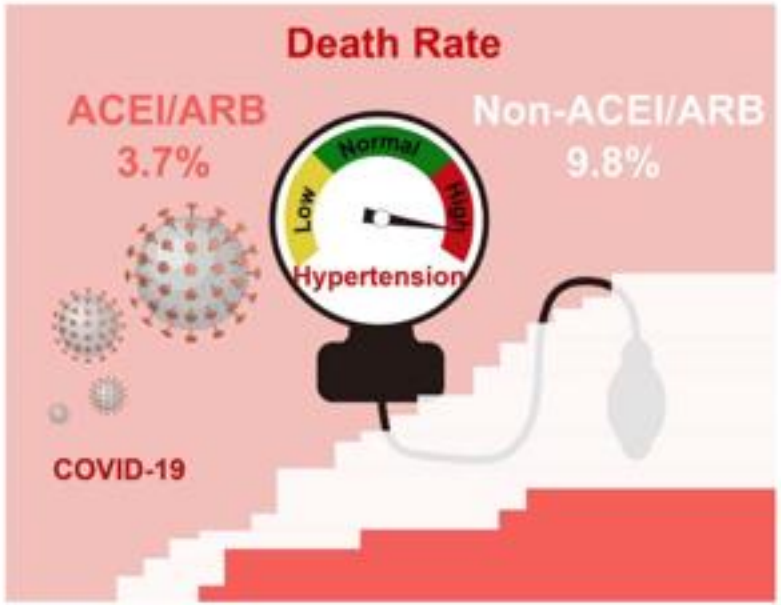
to February 20, 2020. Unadjusted mortality rate was lower in the ACEI/ARB group versus the non-ACEI/ARB group (3.7% vs. 9.8%; $P = 0.01$). In mixed-effect Cox model treating site as a random effect, after adjusting for age, gender, comorbidities, and in-hospital medications, the detected risk for all-cause 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



Exposure

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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*

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.

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

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.

Renin–angiotensin system blockers and susceptibility to COVID-19: an international, open science, cohort analysis

Daniel R Morales, Mitchell M Conover, Seng Chan You, Nicole Pratt, Kristin Kostka, Talita Duarte-Salles, Sergio Fernández-Bertolín, Maria Aragón, Scott L DuVall, Kristine Lynch, Thomas Falconer, Kees van Bochove, Cynthia Sung, Michael E Matheny, Christophe G Lambert, Fredrik Nyberg, Thamir M Alshammari, Andrew E Williams, Rae Woong Park, James Weaver, Anthony G Sena, Martijn J Schuemie, Peter R Rijnbeek, Ross D Williams, Jennifer C E Lane, Albert Prats-Uribe, Lin Zhang, Carlos Areia, Harlan M Krumholz, Daniel Prieto-Alhambra, Patrick B Ryan, George Hripcsak, Marc A Suchard

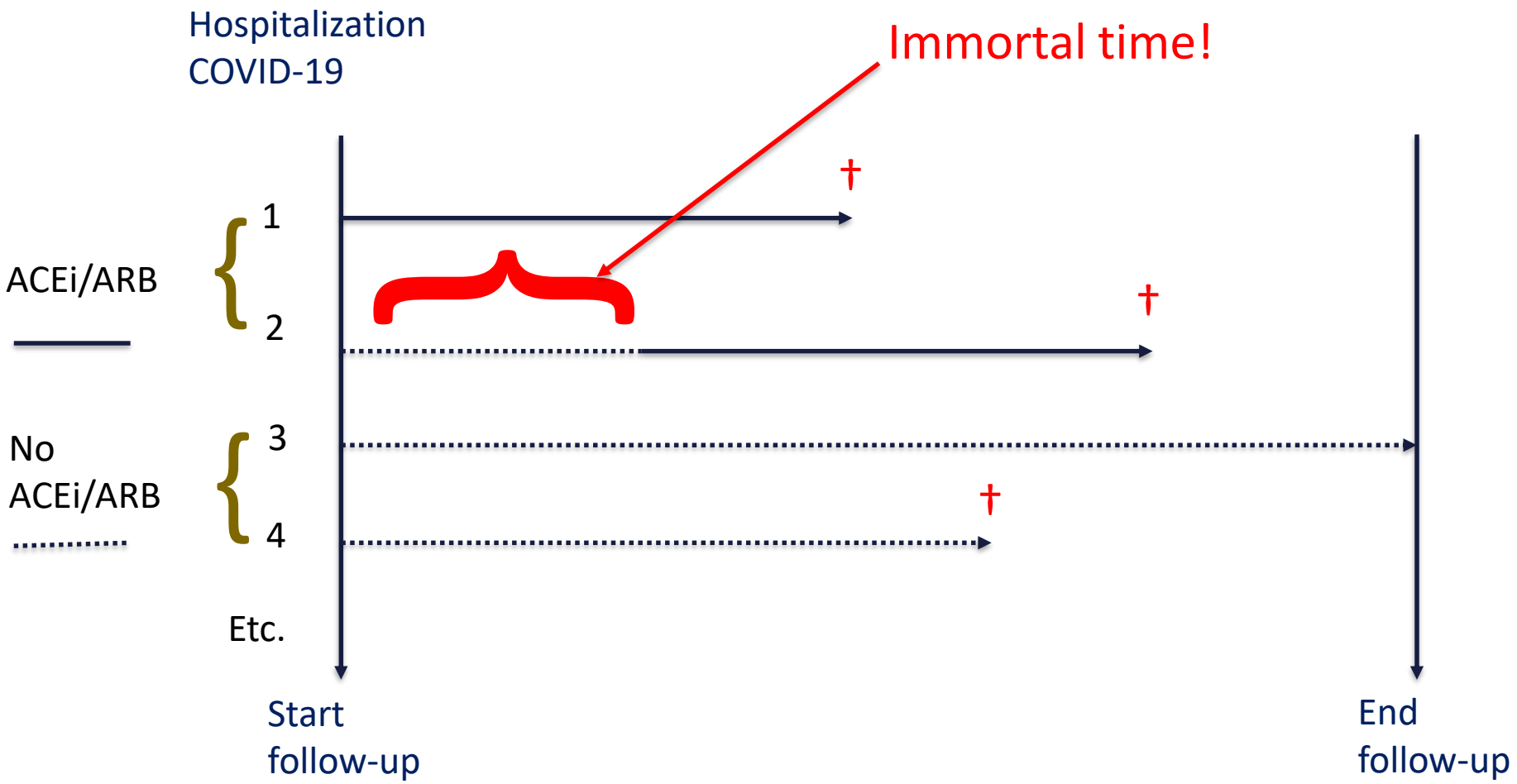
Interpretation No clinically significant increased risk of COVID-19 diagnosis or hospital admission-related outcomes associated with ACEI or ARB use was observed, suggesting users should not discontinue or change their treatment to decrease their risk of COVID-19.

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

HYDROXYCHLOROQUINE EXPOSURE

Patients were defined as receiving hydroxychloroquine if they were receiving it at study baseline or received it during the follow-up period before intubation or death. Study baseline was defined as 24 hours after arrival at the emergency department.

Immortal time bias



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> Am J Epidemiol. 2021 Feb 10;kwab028. doi: 10.1093/aje/kwab028. Online ahead of print.

Biases in evaluating the safety and effectiveness of drugs for covid-19: designing real-world evidence studies

Christel Renoux [1 2 3], Laurent Azoulay [1 2 4], Samy Suissa [1 2]

Future considerations

Use of data from 2020 (and 2021) in observational studies

How have our databases been affected?

- Heterogeneicity
- Different patterns of health care usage
  - HCP visits, hospital based care etc
- National health care systems versus employment dependant health care coverage
- Patient adherence
- etc

Capturing confounders, measuring outcomes

Diagnosis of physical and mental health conditions in primary care during the COVID-19 pandemic: a retrospective cohort study

Richard Williams, David A Jenkins, Darren M Ashcroft, Ben Brown, Stephen Campbell, Matthew J Carr, Sudeh Cheraghi-sohi, Navneet Kapur, Owain Thomas, Roger T Webb, Niels Peek

Findings Between March 1 and May 31, 2020, 1073 first diagnoses of common mental health problems were reported compared with 2147 expected cases (95% CI 1821 to 2489) based on preceding years, representing a 50·0% reduction (95% CI 41·1 to 56·9). Compared with expected numbers, 456 fewer diagnoses of circulatory system diseases (43·3% reduction, 95% CI 29·6 to 53·5), and 135 fewer type 2 diabetes diagnoses (49·0% reduction, 23·8 to 63·1) were observed. The number of first prescriptions of associated medications was also lower than expected for the same time period. However, the gap between observed and expected cancer diagnoses (31 fewer; 16·0% reduction, –18·1 to 36·6) during this time period was not statistically significant.

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https://www.sfk.nl/publicaties/PW/2020/door-coronacrisis-19-mider-eerste-uitgiften

Kristoffersen *et al. The Journal of Headache and Pain* (2020) 21:128
https://doi.org/10.1186/s10194-020-01195-2

The Journal of Headache and Pain

RESEARCH ARTICLE Open Access

Hospital-based headache care during the Covid-19 pandemic in Denmark and Norway

Espen Saxhaug Kristoffersen[1,2*], Kashif Waqar Faiz[1], Else Charlotte Sandset[3,4], Anette Margrethe Storstein[5], Simon Stefansen[6], Bendik Slagsvold Winsvold[3,7†] and Jakob Møller Hansen[6,8†]

Conclusion

Hospital-based headache care and research was impacted in Denmark and Norway during the initial phase of the Covid-19-pandemic. More research on imple-

JCO Clinical Cancer Informatics > List of Issues > Volume 4 >

ORIGINAL REPORTS

Effects of the COVID-19 Pandemic on Cancer-Related Patient Encounters

Jack W. London, PhD[1]; Elnara Fazio-Eynullayeva, MA[2]; Matvey B. Palchuk, MD, MS[2]; Peter Sankey, MBChB[3]; and Christopher McNair, PhD[1]

CONCLUSION

Trends seen in the CCRN clearly suggest a significant decrease in all cancer-related patient encounters as a result of the pandemic. The steep decreases in cancer screening and patients with a new incidence of cancer suggest the possibility of a future increase in patients with later-stage cancer being seen initially as well as an increased demand for cancer screening procedures as delayed tests are rescheduled.

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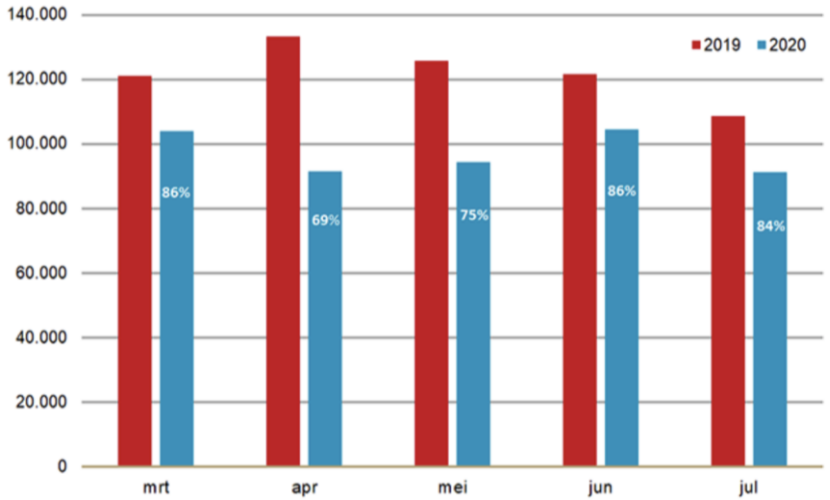

19% decrease in initiation of therapy (first prescriptions)

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The role of ENCePP

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Coordinated by the European Medicines Agency (EMA), the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) brings together expertise and resources in pharmacoepidemiology and pharmacovigilance across Europe.

ENCePP aims to strengthen the monitoring of the **benefit-risk balance** of medicines, primarily by facilitating the conduct of high quality, multi-centre, independent **post-authorisation studies** (PAS) with a focus on observational research.

Collective knowledge

Multinational collaborations

Development of Standards and Guidances

Transparency (EU PAS Register)

Careful consideration of pharmacoepidemiological principles

Utrecht University

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