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Antihypertensive drugs in COVID-19 infection

Hypertension predisposes a poor outcome of COVID-19.[1] It has been speculated that specific antihypertensive drugs may underlie this association.[2] In particular, angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs) may up-regulate ACE2—the receptor used by SARS-CoV-2 to enter host cells—which has been suggested to lead to an increased risk of infection;[2] however, by limiting the effects of angiotensin II, ACE2 could also protect against a more severe COVID-19 infection.[3]

We studied patients diagnosed with COVID-19 (by PCR, CT scan, or both), hospitalized between 1 March and 8 April 2020 in six Munich hospitals and 4 medical centres across the Netherlands (characteristics available upon request).

A mild course of COVID-19 was defined as documented discharge from the hospital within 10 days without treatment at an intensive care unit (ICU). A severe course was defined as any treatment at an ICU, or death. Patients still hospitalized on 8 April 2020 on a regular ward and missing data of ICU admission or death or number of days hospitalized were excluded from the analysis.

Requirement for informed consent was waived by the Medical Ethics Commission of the Amsterdam UMC on 20 March 2020 (registration number 2020-156) and by the ethics committee of the University Hospital rechts der Isar, Technische Hochschule München on 4 April 2020 (registration number 183/20S).

Data on the course of the disease and medication use were extracted from electronic medical records.

We used least absolute shrinkage and selection operator (lasso) logistic regression on the German patient data to identify comorbidities and patient characteristics predictive for the clinical outcome, including the following regressors: obesity, hypertension, diabetes mellitus, coronary heart disease, congestive heart failure, chronic obstructive pulmonary disease, asthma, chronic kidney disease, cancer, human immunodeficiency virus infection, chronic liver disease, age, and sex. Five-fold cross-validation was then used to find a suitable value for the regularization parameter, using the one-standard deviation rule. Multivariate logistic regression was used to analyse the effect of each individual antihypertensive medication on disease severity. Covariates were chosen by best subset selection, comparing all 16 models that include the five drugs as predictors and combinations of the variables age, sex, hypertension, and diabetes. The best-performing model both in terms of Akaike and Bayesian information criteria included only the variables age, sex, and diabetes in addition to the five antihypertensive medications [*Figure 1*; additional parameters and standard errors: age 0.028 (0.0057); sex, male 0.66 (0.16); diabetes 0.58 (0.19); intercept: −2.5 (0.4)]. We used SPSS version 26 and MATLAB version 2018a.

We checked the resulting model for collinearity based on condition number and variance decomposition analysis.[4] The largest condition index was 15.0, indicating mild to moderate collinearity. The variance decomposition analysis further showed that the detected collinearity is between age and the intercept variable (which both still have point estimates significantly different from zero); no further collinearity was detected.

We included n = 1134 COVID-19 patients, admitted to a hospital in Munich (n = 311) or the Netherlands (n = 823). We excluded 254 patients from the analysis because of an undefined outcome. The remaining 880 patients were grouped into severe outcome (n = 415) and mild outcome (n = 465). A total of 414 (47%) were treated before hospital admittance with at least one antihypertensive agent. In the lasso logistic regression analysis, hypertension was found to have the greatest importance among a number of relevant comorbidities in the German cohort. Following suitable regularization, additional variables with non-zero coefficients were: diabetes, age, sex, obesity, chronic obstructive pulmonary disease, asthma, and chronic kidney disease. The observed relationship between hypertension and severity of disease may not only be caused by hypertension *per se*, but could be caused by the underlying antihypertensive drugs used. Multivariate analysis showed a nominally significant association with poor outcome in patients treated

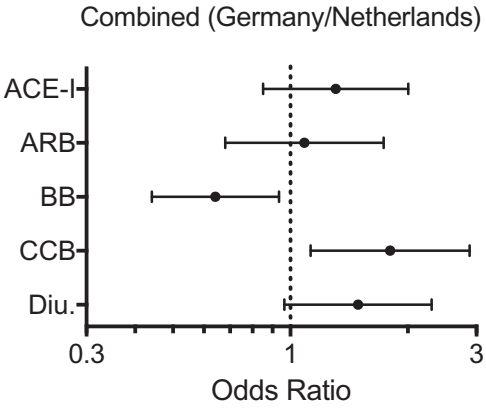

Figure 1 Association between antihypertensive drugs used and outcomes in the two cohorts combined, corrected for age, sex, and diabetes. An odds ratio >1 indicates a higher chance of treatment in an intensive care unit or death (error bars indicate 95% confidence limits; ACE-I, ACE inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; Diu, diuretic).

with a calcium channel blocker, whereas use of a beta-blocker was associated with a milder course after admission to the hospital in both cohorts separately and combined (*Figure 1*).

In conclusion, we find no evidence for adverse outcomes in severely affected COVID-19 patients that used ARBs prior to admission. The use of beta-blockers was associated with a significantly better outcome, whereas the use of calcium channel blockers was associated with poorer outcomes.

Interestingly, recent comparable studies in patients admitted for COVID-19 likewise observed a neutral role for prior use of ARBs[5,6] and a beneficial role for beta-blockers[5] as we describe here. However, given the known caveats of these observational studies, there is an urgent need for prospective studies on this subject.

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Sara-Joan Pinto-Sietsma[1†], Michael Flossdorf[2†], Veit R. Buchholz[2], Joost Offerhaus[1], Hidde Bleijendaal[1], Martijn Beudel[1], Paul G.A. Volders[3], Rachel M.A. ter Bekke[3], Tom Dormans[4], Peter-Paul Zwetsloot[5], Peter de Jager[5], Steffen Massberg[6], Patrick Rämer[7], Clemens Wendtner[7], Ellen Hoffmann[8], Kathrin Rothe[2], Susanne Feihl[9], Thorsten Kessler[10], Yigal M. Pinto[1‡], and Heribert Schunkert[10‡]

[1]University of Amsterdam, Amsterdam, The Netherlands, [2]Institute for Medical Microbiology, Immunology and Hygiene, Technische Universität München, Deutsches Zentrum für Infektionsforschung, München, Germany, [3]Maastricht University, Maastricht, The Netherlands, [4]Zuyderland Hospital, Heerlen, The Netherlands, [5]Jeroen Bosch Hospital, 's-Hertogenbosch, The Netherlands, [6]Department of Cardiology. Klinikum der Ludwig-Maximilians-Universität and Deutsches Zentrum für Herz-Kreislauf-Forschung, München, Germany, [7]Department of Hospital Hygiene and infection prevention, Munich Municipal Hospital Group, München, Germany, [8]Department of Cardiology and Internal Intensive Care Medicine, Heart Center Munich-Bogenhausen, Munich Municipal Hospital Group, Englschalkinger Str. 77, Munich, Germany, [9]Klinikum Rechts der Isar, Technische Universität München, München, Germany; and , [10]Department of Cardiology, Technische Universität München, Deutsches Zentrum für Herz-Kreislauf-Forschung, Munich Heart Alliance; München, Germany

*Corresponding author. Department of Experimental Cardiology, Amsterdam Universitair Medische Centra, meibergdreef 9, 1105AZ Amsterdam, The Netherlands: Tel: +31 205664688, Fax: +31 205664687, Email: y.pinto@amsterdamumc.nl

†These authors contributed equally to this work.
‡These author should be considered as joint senior authors.