European Journal of Clinical and Experimental Medicine

ONLINE FIRST

Authors: Dmytro Ivanov, Antolii Gozhenko, Mariia Ivanova, Zavalna Iryna, Tommy Crestanello

Article type: Original Article

Received: 13 December 2022

Accepted: 20 January 2023

Published online: 14 April 2023

eISSN: 2544-1361

Eur J Clin Exp Med

doi: 10.15584/ejcem.2023.2.3

The dynamics of hypertension and renal function in CKD and non-CKD patients affected with COVID-19 – final results of BIRCOV trial

Dmytro Ivanov [1], Antolii Gozhenko [2], Mariia Ivanova [1], Zavalna Iryna [1], Tommy Crestanello [3]

[1] Shupyk National Healthcare University of Ukraine, Kyiv, Ukraine, Bogomolets National Medical University
Kyiv, Ukraine
[2] Ukrainian Research Institute of Transport Medicine of the Ministry of Health of Ukraine, Odessa, Ukraine
[3] Ukrainian Association of Nephrology, Kyiv, Ukraine

Corresponding author: Dmytro D. Ivanov, e-mail: drivanovdd@gmail.com

ORCID
DI: https://orcid.org/0000-0003-2609-0051
AG: https://orcid.org/0000-0001-7413-4173
MI: https://orcid.org/0000-0002-7636-1000
ZI: https://orcid.org/0000-0002-5541-7351

ABSTRACT

Introduction and aim. There is evidence in the literature about a change in the effectiveness of inhibitors of the renin-angiotensin system (iRAS) in people with COVID-19. Considering different mechanisms of pressure reduction by different iRAS groups, one can expect differences in people with COVID-19 receiving these drugs. The aim of angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB) and direct renin inhibitors (DRi) usage in COVID-19 (BIRCOV study) was to pinpoint clinical and laboratory differences in people with hypertension who received iRAS and suffered coronavirus infection.

Material and methods. An open prospective trial of 108 patients was performed in subjects suffering from COVID-19 who have been receiving iRAS: ACEi, ARB or DRi as basic antihypertensive therapy. The disease follow-up was 12 and 24 weeks. A blood pressure (BP) measurement was performed the week before COVID-19 and up to 24 weeks from the disease onset. Subanalysis in patients with chronic kidney disease (CKD) was performed.

Results. In patients with COVID-19, a change in the effectiveness of antihypertensive therapy depending on the type of drug in the iRAS group has been documented in the first 4 weeks from the onset of the disease. The use of ACEi had significantly increased the risk of severe hypotension, unlike ARBs that do

not cause hypotension. The synchronous decline of estimated glomerular filtration rate (eGFR) and systolic BP was more pronounced in CKD patients followed by albuminuria incidence. The greatest decrease in eGFR was in people taking ACEi.

Conclusion. People with grade 1-2 hypertension who are constantly receiving RAS inhibitors suffering from COVID-19 may develop hypotension with ACEi. COVID-19 leads to transient albuminuria and decreased glomerular filtration rate, which is especially dangerous for people with CKD 4-5.

Keywords. ACEi, ARB, BIRCOV trial, COVID-19, DRi, iRAS

Introduction

The global COVID-19 pandemic evoked certain changes in approach to chronic kidney disease (CKD) patients with hypertension. Since the beginning of the COVID-19 pandemic, there have been reports of increased mortality among patients, receiving treatment for hypertension and the role of the renin-angiotensin system inhibitors (iRAS) has been discussed. It is well-known that SARS-CoV-2 uses an angiotensin-converting enzyme 2 (ACE2) receptor and furin site of S glycoprotein facilitating virus entry into host cells.[1-4] Given that ACE2 levels may vary in hypertensive subjects, the severity of COVID-19 disease and blood pressure levels might be different and it's natural to assume that SARS-CoV-2 affects the state of the renin-angiotensin system.[5] Available data remain controversial indicating positive, neutral, or negative effects of iRAS in COVID-19 infected patients in the clinical setting.[2,3,6,7] Current international guidelines suggest continuing the usage of antihypertensive drugs, in particular iRAS, in people with hypertension who become ill with COVID-19 with no reported differences between different classes of antihypertensive agents.[8,9] Although most studies do not point out a negative effect of the virus on blood pressure levels, there is information about the different iRAS classes' effects. Mandeep R et al (2020) found some differences between the effects of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) and a possible difference in direct renin inhibitors administration (DRi) is presumed.[5,10] Considering the different mechanisms of pressure reduction by iRAS, one can expect differences in people with COVID-19 receiving these drugs.

Aim

In this regard, in March 2020, we initiated a study which was aimed to pinpoint possible clinical and laboratory differences in people with hypertension who received iRAS and suffered coronavirus infection.

Material and methods

Ethics approval

Local ethic commission (21.02.2020 №1) and Shupyk National Healthcare University of Ukraine, Kyiv, Ukraine (24.04.2020 №16) approved the study.

Study design

BIRCOV trial (AR**B**, ACE**I**, D**R**i in **COV**ID-19) registered in ClinicalTrials.gov (NCT04364984) was accepted and completed. The study began on April 1, 2020, primary completion was achieved on July 24, 2021, and final results were available on August 1, 2021 (https://clinicaltrials.gov/ct2/show/results/NCT04364984?term=NCT04364984&cntry=UA&draw=1&rank=1). The study protocol originates from POEM (Patient-Oriented Evidence that Matters) (https://wilkes.libguides.com/c.php?g=191942&p=1266516) intervention that was performed as an open prospective randomized two medical center trial in subjects suffering from COVID-19 who have been receiving iRAS: either ACEi, ARB or DRi as basic antihypertensive therapy.

120 people with hypertension and confirmed COVID-19 infection have been screened and 112 Caucasian patients with confirmed COVID-19 and stage 1-2 hypertension receiving iRAS at the onset of COVID-19 had been included and inspected for 24 weeks. The stage of hypertension has been assessed according to the 2018 ESC/ESH Guidelines.[11] The sampling method was of a non-probability type, including male and female patients with an age range of 18-90 years old. The inclusion criteria were hypertension, stage 1-2 and confirmed COVID-19 infection. The exclusion criteria were hypertension stage 3, HF (NYHA) 3-4.[12] The cohort has been subdivided into three groups based on the iRAS type prescribed.

COVID-19 infection was confirmed by a PCR test and defined into alpha, beta, gamma, and delta subtypes according to CDC (www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html). Detailed features of the detected coronavirus SARS-CoV-2 strains were presented as following variants (strains):

1. del69-70, N501Y, 144del, A570D, D614G, P681H, T716I, S982A, D1118H Alpha B.1.1.7 British Variant 50% increased transmission Potential increased severity based on hospitalizations and case fatality rates No impact on susceptibility to EUA* monoclonal antibody treatments Minimal impact on neutralization by convalescent and post-vaccination sera.
2. E484K, N501Y, del242-244, D80A, D215G, K417N Beta B.1.351 South-African Variant 50% increased transmission Significantly reduced susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment, but other EUA* monoclonal antibody treatments are available. Reduced neutralization by convalescent and post-vaccination sera
3. E484K, N501Y, L18F, T20N, P26S, D138Y, R190S, K417T, D614G, H655Y, T1027I Gamma P.1, B.1.1.28.1 Japan-Brazilian Variant No impact on transmissibility Significantly reduced susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment, but other EUA* monoclonal antibody treatments are available Reduced neutralization by convalescent and post-vaccination sera.

4. T19R, T95I, G142D, E156-R158G, L452R, T478K, D614G, P681R, K417N Delta B.1.617.2 /Delta Plus AY.1&2 Indian Variant increased transmissibility Potential reduction in neutralization by some EUA* monoclonal antibody treatments Reduced neutralization by post-vaccination sera

To date, 45 patients (42%) have received the vaccinations against COVID-19 before the disease's onset.

The BIRCOV trial establishment sought to analyze the clinical data (Clinical arm) of included patients with the follow-up checkpoints of 12 and 24 weeks. Additionally, we highlighted a group of CKD patients from the whole cohort (Kidney arm), where the CKD stage had been assessed by eGFR according to 2012 KDIGO guidelines.[13] All the patients were randomized from the family doctor (clinical arm) and nephrology clinic (kidney arm).

The disease follow-up had two checkpoints: 12- and 24-weeks. The primary outcome measure was blood pressure (BP) levels in mm Hg, measured using ambulatory BP monitoring (ABPM), or home BP monitoring (HBPM) one week before COVID-19 infection and tested during the disease onset on weeks 2, 4, 12, 24 using in-clinic monitoring in case of hospitalization. Low blood pressure was defined below 90/60mmHg.The secondary outcome measures were: the number of patients with fever (above 37.2°C) up to 3 weeks after COVID-19 onset, the number of patients with cough (12 weeks after onset), the number of patients with throat pain (2 weeks after onset), the number of patients with diarrhea (2 weeks after onset) and the number of patients who needed hospital admission and intensive care unit (24 weeks after onset). The additional outcome measures for the Kidney arm were the estimated glomerular filtration rate (eGFR) measures as primary and the albuminuria levels as secondary. Figure 1 represents the summary of the study design.

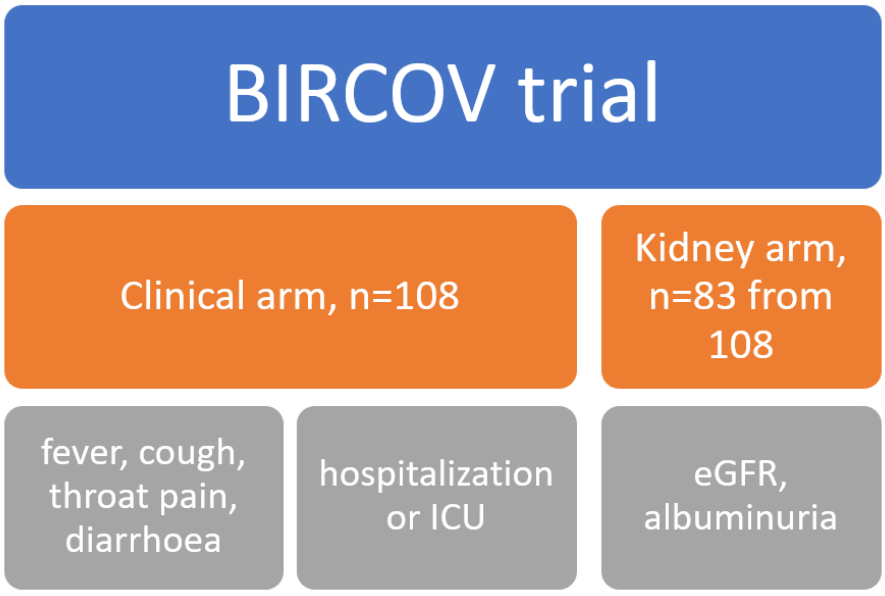

Fig. 1. The summary of the Study design. Total number of patients admitted (108) were included in the Clinical arm of the design, where 83 patients were eligible for the Kidney arm. The endpoints included

fever, cough, throat pain, diarrhea, hospitalization or intensive care unit (ICU) admission, estimated glomerular filtration rate (eGFR) and albuminuria levels

Additionally, the Hydration status of patients according to Ivanova et al. was assessed.[14]

Statistical evaluation of the research results was carried out in the package of medical statistics (https://www.gigacalculator.com/calculators/). The type of statistical test was superiority. The tool used for statistical analysis of outcome measure data and the calculated p-value was ANOVA. The estimation parameter used was Cox Proportional Hazard, parameter dispersion type was standard deviation.

The risk of progression to kidney failure requiring dialysis or transplantation (using the Kidney Failure Risk Equation) (https://qxmd.com/calculate/calculator_308/kidney-failure-risk-equation-4-variable) had been calculated for all patients of the Kidney arm on 2, 4, 12 and 24 weeks from COVID-19 onset.

All patients gave their consent to submit their personal data.

The complete diagram of the statistical analysis plan is presented in Figure 2.

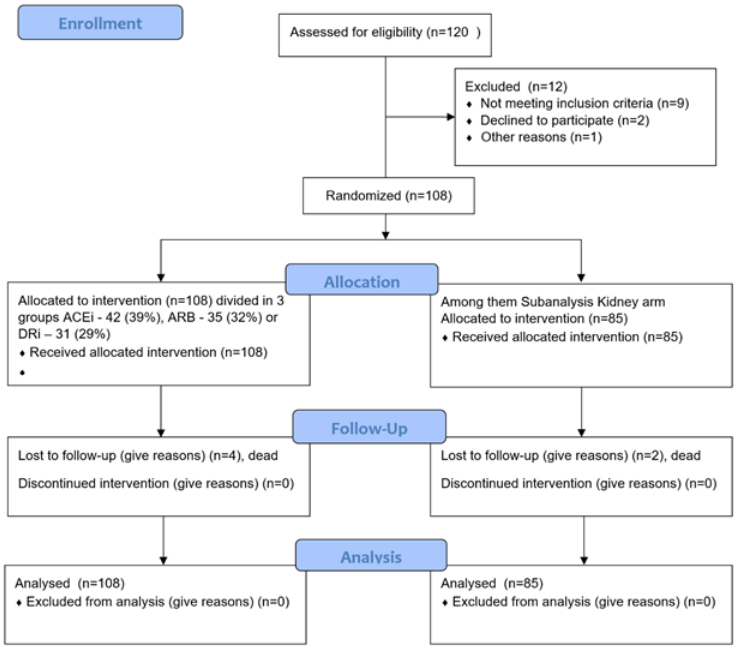

Fig. 2. The Diagram of Statistical Analysis Plan (CONSORT – transparent reporting of trials)

Results

We have conducted a screening of 120 outpatient subjects with COVID-19 and hypertension; 112 were enrolled; 108 (96%) completed the study; 60 (56%) males and 48 (44%) females, mean age of 55±1,12 (18-87; coefficient of variation 0.210514, coefficient of asymmetry -0.261873) years old. Four (3,7%) patients (2 males, 2 females) had died during the first 2 months of COVID-19 onset.

Coronavirus SARS-CoV-2 strains of enrolled patients are represented in Table 1.

Table 1. Characteristics of the type of coronavirus strains revealed in enrolled patients

Coronavirus SARS-CoV-2 strains	Number of people, n=108
Alpha, abs, %	16 (15%)
Beta, abs, %	23 (21%)
Gamma, abs, %	22 (20%)
Delta, abs,%	47 (44%)

Among 108 hypertensive patients enrolled in our trial, 35 (32%) had stage 1 hypertension, and 73 (68%) had stage 2.

Eighty-three (77%) subjects had CKD, ranging from 1 to 4 stages: CKD 1 – 23 (27%), CKD 2 – 46 (56%), CKD 3 – 10 (12%), CKD 4 – 4 (5%).

All patients were randomized into 3 groups who received iRAS: ACEi - 42 (39%), ARB - 35 (32%), or DRi – 31 (29%). Among the participants of the study, 11 (10%) people were over 65 years of age, among them, from each group, 6 people (14.29%) received ACEi, 4 (11.4%) ARB, and one (3.23%) DRi. Eighty-four subjects (78%) received the combined therapy of iRAS with calcium channel blockers (CCB) and diuretics, 17 (16%), combined iRAS with B-blockers, 7 (6%) received iRAS monotherapy.

Clinical arm

The reason for the prescription of iRAS and its combination with other antihypertensive agents was the presence of hypertension itself. Among 108 (96%) hypertensive persons who finished the trial 35 (32%) previously had stage 1 hypertension, and 73 (68%) had stage 2. Thus, a week before the development of COVID-19, the mean blood pressure was 137±0.9/83±0.6 mm Hg (coefficient of variation 0.067728, coefficient of asymmetry 1.029771). The dynamics of changes in blood pressure by control points are shown in Table 2 and Figure 3.

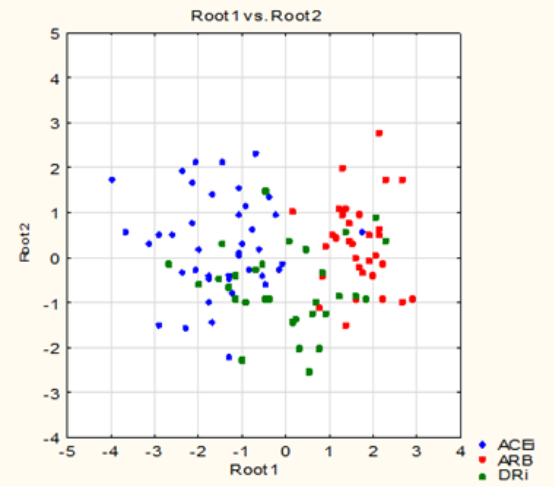

Fig. 3. Systolic and diastolic blood pressure values 2 weeks after the onset of COVID-19. Root 1, diastolic BP; Root 2, systolic BP, 0- 120/80 mm Hg, step - 10 mm Hg, ACEi – angiotensin-converting enzyme inhibitors; ARB – angiotensin receptor blockers; DRi – direct renin inhibitors

Table 2 which presents the baseline BP numbers in dynamics according to weeks and groups of antihypertensive treatment has shown that the BP changes did not have significant statistical differences between the chosen medicine one week before enrolment.

Table 2. The baseline BP mm Hg values before the COVID-19 onset and with a follow-up of 2, 4, 12 and 24 weeks in ACEi, ARB and DRi groups*

Drug group/Week	**-1**	**0**	**2**	**4**	**12**	**24**	**p** (1-0)	**p** (0-2)
ACEi. n=42	138±1.1/ 83±1.2	126±1.2/ 77±0.7	104±0.9/ 68±0.6	114±1.1/ 72±0.7	128±1.2/ 77±1.0	137±1.2/ 81±1.2	<0.01	<0.01
ARB.n=35	136±1.1/ 82±1.2	132±1.0/ 78±0.7	131±1.0/ 77±0.6	133±1.0/ 78±0.6	135±1.1/ 79±0.9	137±1.2/ 82±1.2	0.02	<0.01
DRi. n=31	134±1.4/ 82±1.2	127±1.2/ 79±0.6	115±0.9/ 70±0.6	121±0.9/ 74±0.6	125±1.0/ 79±0.8	129±1.2/ 80±1.2	<0.01	<0.01

* ACEi – angiotensin-converting enzyme inhibitors; ARB – angiotensin receptor blockers; DRi – direct renin inhibitors

However, we had a documented trend of BP lowering in the first two weeks of the COVID-19 disease (Figure 3) with its gradual return to baseline values up to the 12th week. Twenty-three (21%) patients had withdrawn medicine for up to 2 weeks due to severe hypotension. The BP values after COVID-19 in most subjects however remained lower than the baseline for 4 weeks of follow-up.

The analysis of individual data demonstrated that 16 (38%) patients with hypertension taking ACEi had to cancel the medicine or lower the dosage in the first 10-14 days of the COVID-19 disease due to pronounced hypotension development. From the group of patients taking DRi, 7 (23%) had a mildly softer decline in

BP. Patients in the ARB group had little to no decline in BP. This decline had no relation to dehydration or fever.

The data obtained indicate that the use of ACE inhibitors significantly increases the risk of withdrawal compared to DRi (RR 1.648 95% CI 0.772–3.519, NNT 7.0) and ARB (RR 13.023 95% CI 1.815–93.426, NNT 2.9) due to COVID-19.

No less interesting was the restoration of normotensives after the onset of coronavirus infection. It turned out that in the group of those taking DRi, after 4 weeks there were practically no significant differences from the starting BP, and after 12 weeks the consequences of hypotension were completely eliminated. On the contrary, in people who took ACEi, lower blood pressure values were still maintained in the post-COVID period.

The secondary outcomes measures: number of patients with fever (above 37.2C) (follow-up: 12 weeks), number of patients with cough (up to 12 weeks), number of patients with throat pain (up to 2 weeks), number of patients with diarrhea (up to 2 weeks) and number of patients who needed hospitalization and intensive care unit (up to 24 weeks), representing the course of COVID-19 in the BIRCOV study, are shown in Table 3.

Table 3. The secondary outcomes characteristics with a follow-up of 2, 4, 12 and 24 weeks in ACEi, ARB and DRi groups

Number of participants with clinical presentation, % / time frame in weeks	**Onset**	**2 weeks**	**3 weeks**	**4 weeks**	**12 weeks**	**Relative risk**
Fever (above 37.2°C)	101 (ACEi – 39, ARB – 32, DRi – 30) (90%)	12 (11%)	0	2 (2%)	0	Onset – 3 weeks: RR 8.417 95% CI 4.926–14.382, NNT 1.213
Cough	87 (ACEi –30, ARB– 29, DRi– 28) (78%)	78 (70%)	0	0	3 (3%)	
Throat pain	56 (ACEi – 21, ARB 19, DRi –16) (50%)	1 (1%)	0	0	0	
Diarrhea	8 (ACEi– 4, ARB –3, DRi –1) (7%)	0	0	0	0	
Hospital and intensive care unit	4 (ACEi – 2, ARB – 2, DRi – 0) (3.5%)	18 (16%)	4 (4%)	1 (1%)	0	Onset – 2 weeks: RR 0.222 95% CI 0.078–0.635, NNT 7.714

Died	3 (2.6%)	1 (1%)	0	3 to 4 weeks: RR 3.00 95% CI 0.317–28.390, NNT 54.00

ACEi – angiotensin-converting enzyme inhibitors; ARB – angiotensin receptor blockers; DRi – direct renin inhibitors

Analysis of clinical symptoms did not reveal any dependence on the type of antihypertensive therapy with an iRAS. The mortality rate was 3.7% (4 patients). Two of the patients received an ACEi and two received an ARB. The absolute risk for ARB compared to DRi was 0.057, for ACEi – 0.048 versus DRi. Thus, the absolute risk of death in people with COVID-19 receiving ARB was higher than in people taking ACEi, despite the presence of more severe hypotension in the first 4 weeks from COVID-19 onset.

Other complaints in people with COVID-19 included fatigue (58%), headache (44%), attention deficit disorder (27%) and shortness of breath (24%) in the first 2 weeks after the disease onset. Significant differences were found only on the clinical complaint of fatigue between ACEi and ARB groups (Fisher's criterion (bilateral) 0.00135, $p<0.01$; RR 2.197 95% CI 1.294–3.731, NNT 2.658).

In addition, a common manifestation of COVID-19 in people taking iRAS were severe symptoms of poor odor recognition (77%), partial loss of taste (18%), nasal vasculitis (6%) and persistent angioedema (3%).

Kidney arm

Characteristics of the causes of CKD were determined according to KDIGO, 2012 criteria.[13] They were presented by diabetes mellitus types 1 and 2 – 30 (36%), arterial hypertension – 15 (18%), kidney disease of unknown reason – 10 (12%), polycystic kidney disease 5 (6%) as ADPKD 3 and ARPKD 2 persons and other causes – 23 (28%), presented by urology diseases – 17 (CACUT syndrome - 6, chronic pyelonephritis - 11), glomerulonephritis – 5 (the kidney biopsy has been performed to 4 from 5 patients), and 1 with lupus nephritis class IV.

Mean arterial pressure did not differ statistically in the group of patients with CKD compared with the entire sample of people included in the study.

Twenty-three (21%) patients required dose reduction or discontinuation of antihypertensive drugs for up to 2 weeks due to severe hypotension. Among them, 16 (70%) people were taking ACEi and 7 (30%) – DRi. Post-COVID-19 BP values remained below baseline for the majority of subjects for the next 4 weeks. A more significant decrease in BP was observed in patients with grade 1 hypertension: 20 (57%) versus 29 (39%) with grade 2 hypertension (RR 1.438 95% CI 0.962–2.152, NNT 5.742) and in people with CKD: 62 (75 %) vs. 9 (36%) without CKD (RR 2.075 95% CI 1.212–3.552, NNT 2.584). This decrease was not associated with dehydration due to hyperthermia. Patients in the ARB group did not experience a significant decrease in blood pressure.

Findings show that the use of ACEi significantly increases the risk of discontinuation compared with DRi (RR 1.648 95% CI 0.772–3.519, NNT 7.0) and ARB (RR 13.023 95% CI 1.815–93.426, NNT 2.9) in patients affected with COVID-19.

To date, in this group of patients, normotension was restored after the onset of coronavirus infection. In the group taking DRi after 4 weeks there were practically no significant differences from the initial pressure, and after 12 weeks the effects of hypotension were completely eliminated. In contrast, people who took ACEi still had lower blood pressure values in the post-COVID-19 period.

Of 4 people who died during the study, two of the patients received an ACEi, and two received an ARB, and each group featured one CKD patient respectively. The risk of death was lowest for those receiving DRi, the absolute risk for ARB versus DRis was 0.057 (number of patients to be treated (NNT) 17,500), for ACEi versus DRi 0.048, and the number of patients to be treated – 21.000; the absolute risk for anti-ACEi ARBs was 0.057 (RR 1.200 95% CI 0.178–8.087, NNT 105.0).

Table 4 represents the baseline eGFR values with a follow-up every 2, 4, 12 and 24 weeks in ACEi, ARB and DRi groups.

Table 4. The changes in eGFR (ml/min/1.73 m^2) and ACR (mg/mmol) are presented in dynamics according to weeks and groups of antihypertensive treatment*

Drug/week	**0**	**2**	**4**	**12**	**24**	**p (0-2)**	**p (0-4)**
ACEi, n=42	69±1.7	52±1.1	51±0.9	58±2.0	68±1.9	<0.01	<0.01
ARB, n=35	72±1.7	70±1.8	73±1.5	70±1.6	71±1.8	not reliable	
DRi, n=31	71±1.8	70±1.6	69±1.5	72±1.7	70±1.7		
Urine/week, interquartile range	0	2	4	12	24		
ACR, mg/mmol	226.5	473.5		550.5	372.0	p (0-2, 0-12) <0.01	

* ACEi – angiotensin-converting enzyme inhibitors; ARB – angiotensin receptor blockers; DRi – direct renin inhibitors

The synchronous decline of eGFR and systolic BP was more pronounced in CKD patients. The greatest decrease in eGFR was noted in people who had been taking ACEi, weeks 0–24: the correlation coefficient (r) is 0.815, the relationship between the studied features was direct, the strength of the relationship according to the Chaddock scale was high, the number of degrees of freedom (f) is 3, the Student's t-test was 2.432, although the dependence of the features was statistically insignificant (p=0.1356).

The individual analysis demonstrated that eGFR decline correlated directly with the advancement of CKD. The drop in eGFR ranged from 23% in CKD 1 to 45% in CKD stage 4. Two people required short-term dialysis.

The analysis of secondary outcome points demonstrated that 23% of people without 3-12 months available preceding albuminuria had developed the A2 range albuminuria according to KDIGO, 2012 (13). During 12 weeks of observation, 81% of patients had spontaneous albuminuria withdrawal. Post COVID-19 (above 12 weeks) albuminuria remained in 19% of patients, and 90% of them have had CKD.

Patients with preceding CKD had an increase in albuminuria in 78% of cases and its return to the past results were observed only in 24% of patients by the 12th week and 49% in 24 weeks respectively. The interquartile range of albumin/creatinine ratio (ACR) was estimated in 24 patients with CKD. The ACR ratio in patients treated with ACEi, ARB, and DRi was 530, 161.5, and 9, respectively, but the mean values were not statistically distinguishable due to the large scatter of values due to varying degrees of severity of the primary renal process. The risk of a three-fold increase of ACR in the first 2 weeks from the onset of COVID-19 was 2.068 (95% CI 0.816-5.241, NNT 3.043) in the ACEi group, 0.75 95% CI 0.270-2.080, NNT 8.000) in the ARB group and 0.422 (95% CI 0.069–2.596, NNT 3.654) in the DRi group.

The post-COVID-19 syndrome was presented by the development of albuminuria in patients that were previously clear of it, and worsening albuminuria in patients that had it previously.

In people with COVID-19, by the second week from the onset of the disease, there had been a decrease in eGFR and, probably a reciprocal, increase in the level of uric acid in the blood, significantly higher from the baseline. Comparison of the two indicators in dynamics revealed a correlation coefficient of -0.871, the relationship between the studied features was inverse, and the strength of the connection according to the Chaddock scale was high, but the dependence of the features is not statistically significant (p=0.0914).

Discussion

The SARS-CoV-2 virus is ingested into the body through ACE2 receptors in the nose, penetrating the cells in other areas afterwards, de-allocating in other ACE2 receptors sites: the intestines, blood vessels and heart. These, possibly, explain the symptoms of heart disease, acute kidney injury and intestinal symptoms.[15,16] In children, who are known to have a lower expression of ACE2, the illness usually does not manifest with significant symptoms.[17]

If the SARS-CoV-2 virus inhibits the activation of ACE2 receptors in the muscles, they are expressed at low to medium levels, including ligands, explaining that in children, mature people without hypertension, and especially older people without hypertension, the symptoms of the disease can show up under the hour of COVID-19.[18]

ACEis perform their effect through the ACE1 receptor, while the SARS-CoV-2 uses the ACE2 receptor. Sequential metabolism of angiotensin 1–9, then angiotensin 1–7 goes two ways: 1) acts as an agonist through the Mas-1 receptors leading to vasodilation; 2) acts as an antagonist of angiotensin AT 1 receptor, enhancing vasodilation.[19]

Thus, the SARS-CoV-2 may be similar in ARB action, which explains hypotension in the acute period of coronavirus infection documented in BIRCOV trial. If the patients had taken ACEi and caught SARS-CoV-2 we documented the largest blood pressure decrease, and those who had taken ARB had practically no effect on blood pressure. This was some trend in increasing the risk of death in people with COVID-19 who are taking ARBs as an antihypertensive agent.[5]

Cohen et al. presented three possible mechanisms of the effect of RAS inhibitors, two of which, representing the detrimental role of ACEi and the neutral or beneficial role of ARB were replicated in the data of the BIRCOV study.[20] At the same time, a small triple-blind study has shown no reduction in blood pressure when using ACEi/ARB medications in hypertensive COVID-19 patients. Perhaps, observations in intensive care units and hospitals do not allow us to clearly depict the features that were established by us on an outpatient basis.[21]

There is a well-grounded idea that if the virus implements RAS changes, it should be done before the body's mechanisms for regulating bradykinin go out of whack. Receptors for bradykinin are restored, and the body also ceases to efficiently break down bradykinin (ACE ruins bradykinin, but if the virus suppresses it, you can't work it so effectively.) As bradykinin storm develops, we observe moderate arrhythmias and a decrease in BP.[22] Possibly, a stronger bradykinin storm led to an increase in the side effects of COVID-19 in apparently subacute angioedema in three patients in the BIRCOV study.

According to the data of the Italian registry, prospectively investigating 566 COVID-19 patients taking ACEi or ARB, those in ARB group have reduced the death rate of hospitalized patients, but this was not the case for the ACEi administration. Mortality due to both causes and hours of hospitalization was the primary outcome.[23]

However, these data are contradictory. The results of ACEI-COVID trial have shown that the discontinuation of RAS blockers in COVID-19 may lead to faster and better recovery.[24] Jia et al. (2021) concluded that patients with COVID-19 and hypertension may benefit from using ACEIs/ARBs.[25]

Most publications indicate the absence of negative effects of iRAS in people with COVID-19.[24,26] However, according to Reyes et al., COVID-19 patients with hypertension were more likely to suffer severe outcomes, hospitalizations and deaths compared with those without hypertension.[27] Wherein, the use of either beta-blockers, calcium-channel blockers, or diuretics was associated with a higher risk of COVID-19 hospitalization and mortality compared to ACEi use (adjusted OR (95%CI): 1.66 [1.43–1.93]) and ARB use (1.53 [1.30–1.81]).[28]

Adverse effects during the development of COVID-19 develop mostly in people with comorbid conditions which was confirmed in the present study.[29] The second most important result of the BIRCOV study was a transient decrease in renal function by eGFR for healthy people and quite pronounced for people with CKD, accompanied by an increase in albuminuria. These data are in good agreement with the known ones, claiming higher morbidity and mortality in patients with CKD.[8,30]

One of the most common COVID-19 side effects is the development of acute kidney injury (AKI). Simple risk scores using age, sex, a complete blood cell count, C-reactive protein and D-dimer are highly predictive of AKI and death and can help simplify and better inform clinical decision-making.[15] In the present study, 2 patients were identified and had a sharp deterioration in kidney function. At the same time, ACEi usage might help individualize pharmacological treatment and improve clinical outcomes,[31] which does not contradict our data. Polymorphism of ACE genes may also be of some importance: additional meta-analyses uncovered that both ACE1 rs4646994 DD-genotype and ACE2 rs2285666 GG-genotype carriers had a significantly increased risk of developing severe COVID-19 (OR=2.06, 95% CI: 1.45, 2.93; OR=2.14, 95% CI: 1.26, 3.66; respectively). Genetic polymorphisms of ACE1 rs4646994 DD-genotype, ACE2 rs2285666 GG-genotype, and TMPRSS2 rs12329760 CC-genotype and C-allele may serve as predictive models of COVID-19 severity.[32]

The BIRCOV study supports the available data on the absence of a negative effect of iRAS inhibitors on COVID-19 [20]. Further studies are required the profoundly discover the characteristics of the course of COVID-19 infection in people with concomitant diseases, including hypertension and CKD in the ongoing clinical trials and meta-analyses of randomized trials to elucidate the optimal use of iRAS in patients with COVID-19.

Study limitations were determined by unavailable tools of outpatient ACR and uric acid measurements for some subjects.

- What is already known about this subject:

- It is known that SARS-CoV-2 uses an ACE2 receptor facilitating virus entry into host cells.
- There are three known possible effects of ACEi and ARB in COVID-19 in clinical practice: condition worsening, neutral or helpful.
- Considering the different mechanisms of iRAS pressure reduction, one can expect differences in people with COVID-19.

- What this study adds:

- People with mild hypertension, infected with COVID-19, develop hypotension while constantly receiving iRAS.
- People with CKD stage 4-5 are at the highest risk of kidney function loss while infected with COVID-19.
- Of the iRAS group, ACEi have demonstrated the highest risk of severe hypotension, eGFR decline and onset of albuminuria.

- What impact this may have on practice or policy:

- Patients with hypertension and/or CKD should be carefully monitored when receiving iRAS administration during COVID-19 infection.
- We should carefully follow the BP, eGFR and albuminuria levels in CKD patients, receiving iRAS administration during COVID-19 infection.

Conclusion

COVID-19 has been shown to induce reversible hypotension in outpatients if they receive an ACEi for hypertension. The working hypothesis indicates DRi as the safest antihypertensive treatment drug in 24 weeks' follow-up observation with the least volatility of BP and mortality. The nature of BP reduction in people with hypertension of grades 1-2, taking iRAS, allows comparing the effect of SARS-CoV-2 with the action similar to ARB, i.e. in people taking ACEi, the effect of BP reduction was the most sufficient. Hypertensive patients, affected by COVID-19, may experience a transitory renal function deterioration with an incidence of albuminuria but this statement needs more research in parallel groups. In patients with hypertension and CKD, these effects were more pronounced and correlated with eGFR levels. Not all patients with CKD had a return to baseline albuminuria and renal function after COVID-19.

Declarations

Funding

Study was funded by prof. D. Ivanov Medical Practice.

Author contributions

Conceptualization, D.I. and A.G.; Methodology, D.I.; Software, T.C.; Validation, T.C.; Formal Analysis, T.C.; Investigation, Z.I. and D.I.; Resources, Z.I., M.I. and D.I.; Data Curation, Z.I.; Writing – Original Draft Preparation, D.I.; Writing – Review & Editing, D.I and M.I.; Visualization M.I.; Supervision, D.I. and A.G.; Project Administration, M.I.; Funding Acquisition, Z.I.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

Data available on request from the authors.

Ethics approval

Local ethic commission (21.02.2020 №1) and Shupyk National Healthcare University of Ukraine, Kyiv, Ukraine (24.04.2020 №16) approved the study.

References

1. Beyerstedt S, Casaro EB, Rangel É B. COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. *Eur J Clin Microbiol Infect Dis*. 2021;40(5):905-919. doi: 10.1007/s10096-020-04138-6
2. Bojkova D, Klann K, Koch B, et al. Proteomics of SARS-CoV-2-infected host cells reveals therapy targets. *Nature*. 2020;583(7816):469-472. doi: 10.1038/s41586-020-2332-7.
3. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med.* 2020;8(4):e21. doi: 10.1016/S2213-2600(20)30116-8
4. Davidson AD, Williamson MK, Lewis S, et al. Characterisation of the transcriptome and proteome of SARS-CoV-2 reveals a cell passage induced in-frame deletion of the furin-like cleavage site from the spike glycoprotein. *Genome Med.* 2020;12(1):68. doi: 10.1186/s13073-020-00763-0
5. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. *N Engl J Med.* 2020;382(25):e102. doi: 10.1056/NEJMoa2007621
6. Kerneis M, Montalescot G. RAS inhibition and COVID-19: more questions than answers? *Lancet Respir Med.* 2021;9(8):807-809. doi: 10.1016/S2213-2600(21)00233-2
7. Bauer A, Schreinlechner M, Sappler N, et al. Discontinuation versus continuation of renin-angiotensin-system inhibitors in COVID-19 (ACEI-COVID): a prospective, parallel group, randomised, controlled, open-label trial *Lancet Respir Med.* 2021;9(8):863-872. doi: 10.1016/S2213-2600(21)00214-9
8. ERA-EDTA Council; ERACODA Working Group. Chronic kidney disease is a key risk factor for severe COVID-19: a call to action by the ERA-EDTA. *Nephrol Dial Transplant.* 2021;36(1):87-94. doi: 10.1093/ndt/gfaa314
9. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-Angiotensin-Aldosterone System Inhibitors and Risk of Covid-19. *N Engl J Med.* 2020;382(25):2441-2448. doi: 10.1056/NEJMoa2008975
10. Mourad JJ, Levy BI. Interaction between RAAS inhibitors and ACE2 in the context of COVID-19. *Nat Rev Cardiol.* 2020;17(5):313. doi: 10.1038/s41569-020-0368-x
11. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension *Eur Heart J.* 2018;39(33):3021-3104. doi: 10.1093/eurheartj/ehy339

12. Flack JM, Adekola B. Blood pressure and the new ACC/AHA hypertension guidelines. *Trends Cardiovasc Med.* 2020;30(3):160-164. doi: 10.1016/j.tcm.2019.05.003
13. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. *Kidney Int.* 2021;99(3S):S1-S87. doi: 10.1016/j.kint.2020.11.003
14. Ivanova MD, Gozhenko AI, Crestanello T, Ivanov DD. Early Coaching to Increase Water Intake in CKD. *Ann Nutr Metab.* 2020;76, 1:69-70. doi: 10.1159/000515276
15. Li D, Ren H, Varelmann DJ, et al. Risk assessment for acute kidney injury and death among new COVID-19 positive adult patients without chronic kidney disease: retrospective cohort study among three US hospitals. *BMJ Open.* 2022;12(2):e053635. doi: 10.1136/bmjopen-2021-053635
16. Norsa L, Valle C, Morotti D, Bonaffini PA, Indriolo A, Sonzogni A. Intestinal ischemia in the COVID-19 era. *Dig Liver Dis.* 2020;52(10):1090-1091. doi: 10.1016/j.dld.2020.05.030
17. Yazıcıoğlu B, Bakkaloğlu SA; European Society for Pediatric Nephrology. Impact of coronavirus disease-2019 on pediatric nephrology practice and education: an ESPN survey. *Pediatr Nephrol.* 2022;37(8):1867-1875. doi: 10.1007/s00467-021-05226-1
18. Gheblawi M, Wang K, Viveiros A, et al. Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System: Celebrating the 20th Anniversary of the Discovery of ACE2. *Circ Res.* 2020;126(10):1456-1474. doi: 10.1161/CIRCRESAHA.120.317015
19. Aronson JK, Ferner RE. Drugs and the renin-angiotensin system in covid-19. *BMJ.* 2020;369:m1313. doi: 10.1136/bmj.m1313
20. Cohen JB, South AM, Shaltout HA, Sinclair MR, Sparks MA. Renin-angiotensin system blockade in the COVID-19 pandemic. *Clin Kidney J.* 2021;14(1):i48-i59. doi: 10.1093/ckj/sfab026
21. Najmeddin F, Solhjoo M, Ashraf H, Salehi M, Rasooli F, Ghoghaei M, Soleimani A, Bahreini M. Effects of Renin-Angiotensin-Aldosterone Inhibitors on Early Outcomes of Hypertensive COVID-19 Patients: A Randomized Triple-Blind Clinical Trial. *Am J Hypertens.* 2021;20;34(11):1217-1226. doi: 10.1093/ajh/hpab111. PMID: 34265044; PMCID: PMC8344947.
22. Roche JA, Roche R. A hypothesized role for dysregulated bradykinin signaling in COVID-19 respiratory complications. *FASEB J.* 2020;34(6):7265-7269. doi: 10.1096/fj.202000967
23. Angeli F, Verdecchia P, Balestrino A, et al. Renin Angiotensin System Blockers and Risk of Mortality in Hypertensive Patients Hospitalized for COVID-19: An Italian Registry. *J Cardiovasc Dev Dis.* 2022;9(1):15. doi: 10.3390/jcdd9010015
24. Theodorakopoulou MP, Alexandrou ME, Boutou AK, Ferro CJ, Ortiz A, Sarafidis P. Renin-angiotensin system blockers during the COVID-19 pandemic: an update for patients with

hypertension and chronic kidney disease. *Clin Kidney J.* 2021;15(3):397-406. doi: 10.1093/ckj/sfab272

25. Jia N, Zhang G, Sun X, et al. Influence of angiotensin converting enzyme inhibitors/angiotensin receptor blockers on the risk of all-cause mortality and other clinical outcomes in patients with confirmed COVID-19: A systemic review and meta-analysis. *J Clin Hypertens (Greenwich).* 2021;23(9):1651-1663. doi: 10.1111/jch.14329
26. Kang SH, Lee DH, Han KD, et al. Hypertension, renin-angiotensin-aldosterone-system-blocking agents, and COVID-19. *Clin Hypertens.* 2021;27(1):11. doi: 10.1186/s40885-021-00168-0
27. Reyes C, Pistillo A, Fernández-Bertolín S, et al. Characteristics and outcomes of patients with COVID-19 with and without prevalent hypertension: a multinational cohort study. *BMJ Open.* 2021;11(12):e057632. doi: 10.1136/bmjopen-2021-057632
28. Safizadeh F, Nguyen TNM, Brenner H, Schöttker B. Association of renin-angiotensin-aldosterone system inhibition with Covid-19 hospitalization and all-cause mortality in the UK biobank. *Br J Clin Pharmacol.* 2022;88(6):2830-2842. doi: 10.1111/bcp.15192
29. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep.* 2021;11(1):16144. doi: 10.1038/s41598-021-95565-8
30. Chung EYM, Palmer SC, Natale P, et al. Incidence and Outcomes of COVID-19 in People With CKD: A Systematic Review and Meta-analysis. *Am J Kidney Dis.* 2021;78(6):804-815. doi: 10.1053/j.ajkd.2021.07.003
31. Tylicki P, Polewska K, Och A, et al. Angiotensin Converting Enzyme Inhibitors May Increase While Active Vitamin D May Decrease the Risk of Severe Pneumonia in SARS-CoV-2 Infected Patients with Chronic Kidney Disease on Maintenance Hemodialysis. *Viruses.* 2022;14(3):451. doi: 10.3390/v14030451
32. Saengsiwaritt W, Jittikoon J, Chaikledkaew U, Udomsinprasert W. Genetic polymorphisms of ACE1, ACE2, and TMPRSS2 associated with COVID-19 severity: A systematic review with meta-analysis. *Rev Med Virol.* 2022;32(4):e2323. doi: 10.1002/rmv.2323