НИРКИ ПОЧКИ KIDNEYS

UDC 616.12-008.46 *DOI: https://doi.org/10.22141/2307-1257.10.3.2021.239591*

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Final results of BIRCOV trial (ARB, ACEI, DRi in COVID-19)

For citation: Počki. 2021;10(3):143-149. doi: 10.22141/2307-1257.10.3.2021.239591

Abstract. ***Background.*** *The question of the possible effect of the inhibitors of the renin-angiotensin system (iRAS) on hypertensive subjects who fell ill with COVID-19 has been discussed in the literature. SARS-CoV-2 is well-known to use an angiotensin-converting enzyme 2 receptors facilitating virus entry into host cells. There are three possible mechanisms of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) effect in COVID-19 in clinical practice: with worsening, neutral, or helpful function. Considering the different mechanisms of blood pressure reduction by iRAS, one can expect differences in people with COVID-19 receiving these drugs. The purpose of the BIRCOV study is to pinpoint possible clinical and laboratory differences in hypertensive people who received iRAS and suffered from coronavirus infection.* ***Materials and methods.*** *Patient-Oriented Evidence that Matters (POEM) intervention was designed as an open prospective randomized two medical centers trial in subjects suffering from COVID-19 who have been receiving iRAS, either ACEi, ARB, or direct renin inhibitor (DRi) as basic antihypertensive therapy. One hundred and twenty people with stage 1–2 hypertension have been screened, 108 subjects were enrolled in the BIRCOV study. COVID-19 was confirmed by a PCR test; the disease follow-up was divided into 2 periods: up to 12 weeks and up to 24 weeks. The primary outcome measure was as follows: blood pressure (BP) was known one week before COVID-19 onset and was measured during the disease on weeks 2, 4, 12, 24. The secondary outcome measures were clinical features. Subanalysis in patients with chronic kidney disease (CKD) was performed.* ***Results.*** *All patients were randomized into 3 groups who received: ACEi — 42 (39 %), ARB — 35 (32 %), or DRi — 31 (29 %). The BIRCOV trial documented the trend of BP lowering in the first two weeks of the COVID-19 disease with its gradual return to baseline values up to the 12th week. Twenty-three (21 %) patients have withdrawn medicine for up to 2 weeks due to severe hypotension. However, the BP values after COVID-19 in most subjects remained lower than the baseline ones for 4 weeks. The use of ACE inhibitors significantly increased 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. The synchronous decline of estimated glomerular filtration rate (eGFR) and systolic BP was more pronounced in CKD patients. The greatest decrease in eGFR was noted in people who have been taking ACEi. The drop in eGFR ranged from 23 % in CKD stage 1 to 45 % in CKD stage 4. Two people required short-term dialysis. The analysis of secondary outcome points demonstrated that in 23 % of people without preceding albuminuria it developed in the A2 range. During 12 weeks of observation, 81 % of patients had spontaneous albuminuria reduction. Post-COVID-19 (above 12 weeks) albuminuria remained in 19 % of patients, 90 % of them had a history of CKD. Patients with preceding CKD had an increase in albuminuria in 78 % of cases, and its return to the baseline was observed only in 24 % of patients by the 12th week and in 49 % of individuals in 24 weeks.* ***Conclusions.*** *People with stage 1–2 hypertension who are receiving chronic iRAS and suffer from COVID-19 may develop hypotension with ACE inhibitors. COVID-19 leads to transient albuminuria and decreased glomerular filtration rate, which is especially dangerous for people with CKD.*

Keywords: *renin-angiotensin system inhibitors; angiotensin receptor blockers; angiotensin-converting enzyme inhibitors; direct renin inhibitor; COVID-19; BIRCOV trial*

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Background

Current international guidelines suggest continuing the usage of antihypertensive drugs, in particular inhibitors of the renin-angiotensin-aldosterone system, in hypertensive people who become ill with COVID-19 [1] with no differences between the five classes of antihypertensive agents [2].

It is well-known that the SARS-CoV-2 uses an angiotensin-converting enzyme 2 (ACE2) receptor and furin to enter the cell [3–5]. So if ACE2 levels are higher or lower in some hypertensive subjects, then the severity of disease and blood pressure (BP) level might be different [6]. It is natural to assume that SARS-CoV-2 can affect the state of the inhibitors of the renin-angiotensin system (iRAS).

Although most studies do not point out a negative effect of the virus on blood pressure levels, there is information about the different effects of various RAS inhibitors. Mandeep R. et al. (2020) found some differences between angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) [7]. Probably, there also could be a difference for direct renin inhibitor (DRi) [8].

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

Materials and methods

The BIRCOV trial (AR**B**, ACE**I**, D**R**i in **COV**ID-19) is registered in ClinicalTrials.gov (NCT04364984, https://clinicaltrials.gov/ct2/show/NCT04364984). The study began on April 1, 2020; the primary completion was achieved on July 24, 2021, and final results were available on August 1, 2021.

Study protocol. Patient-Oriented Evidence that Matters (POEM) [10] intervention was designed as an open prospective randomized two medical centers trial in subjects suffering from COVID-19 who have been receiving iRAS, either ACEi, ARB, or DRi as basic antihypertensive therapy.

One hundred and twenty people with stage 1–2 hypertension were screened.

Study population: patients with proved COVID-19 and preliminary stage 1–2 hypertension receiving iRAS at the onset of COVID-19 were being observed for 24 weeks.

Sampling method: non-probability sample. Minimum age:18 years; maximum age: 90 years.

Sex: all.

Inclusion criteria: hypertension, stage 1–2.

Exclusion criteria: hypertension, stage 3, heart failure (NYHA) 3–4.

COVID-19 was confirmed by a PCR test, the disease follow-up was divided into 2 periods: up to 12 weeks and up to 24 weeks.

Primary outcome measure: BP was known one week before COVID-19 and was measured during the disease course on weeks 2, 4, 12, 24. Secondary outcome measures: the number of patients with fever (above 37.2 °C) up to 3 weeks after COVID-19 onset; the number of patients with cough (time frame: 12 weeks); the number of patients with throat pain (time frame: 2 weeks); the number of patients with diarrhoea (time frame: 2 weeks), and the number of patients who needed hospital admission and intensive care unit (time frame: 24 weeks).

Informed consent form — optional under 42 CFR Part 11, all patients gave their verbal consent to submit personal data.

The BIRCOV trial included subanalysis of patients with chronic kidney disease (CKD) — kidney arm, with the primary endpoints: BP and estimated glomerular filtration rate (eGFR) measuring and the secondary endpoint — albuminuria grade (Fig. 1).

Hydration status was elevated by the method of Ivanova M.D. et al. [10]. Statistical evaluation of the research results was carried out in the package of medical statistics [11]. The risk of progression to kidney failure requiring dialysis or transplantation (using the Kidney Failure Risk Equation) [12] was calculated for all patients of kidney arm on weeks 2, 4, 12, and 24 from COVID-19 onset.

Results

One hundred and twenty outpatient subjects were screened; 112 were enrolled; 108 (96 %) completed the study (4 died); 60 (56 %) males and 48 (44 %) females; mean age 55.0 ± 1.12 years old (18–87; coefficient of variation 0.210514, coefficient of asymmetry –0.261873). Among hypertensive patients, 35 (32 %) had stage 1 hypertension, 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: ACEi — 42 (39 %), ARB — 35 (32 %), or DRi — 31 (29 %). Eighty-four (78 %) patients had combined iRAS with calcium channel blockers and diuretics, 17 (16 %) combined iRAS with B-blockers, 7 (6 %) received iRAS monotherapy.

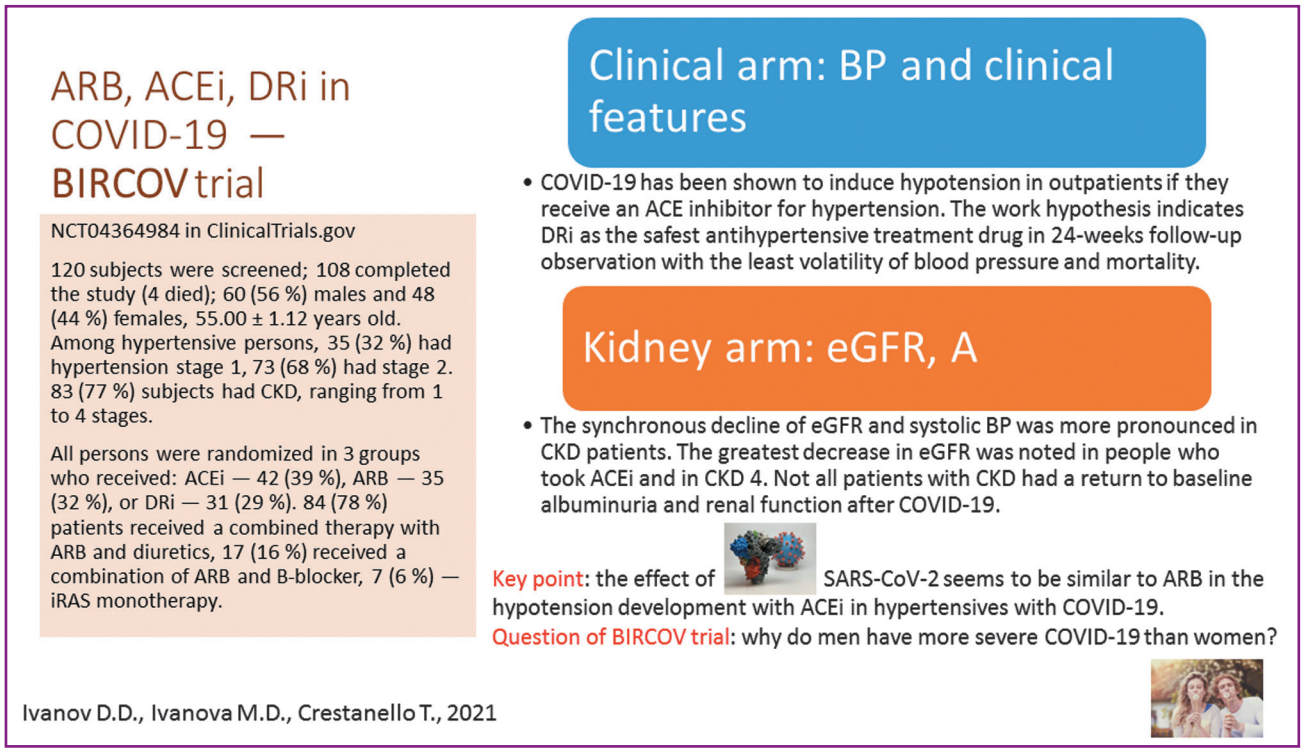
Clinical features arm

Primary outcome measure: blood pressure

The reason for the prescription of iRAS and its combination with other antihypertensive agents was the presence of hypertension itself. At the beginning of the trial, 35 patients have had stage 1 hypertension, 77 — stage 2. Four patients (2 males, 2 females) died within the first 2 months from the COVID-19 onset. Among 108 hypertensive persons who finished the trial, 35 (32 %) previously had stage 1 hypertension, 73 (68 %) had stage 2 before getting prescribed drugs. Thus, a week before the development of COVID-19, the mean blood pressure was 137.0 ± 0.9 / 83.0 ± 0.6 mm Hg (coefficient of variation 0.067728, coefficient of asymmetry 1.029771). The dynamics in blood pressure by control points are shown in Table 1. Table 1 presents the baseline BP values with a follow-up of 2, 4, 12, and 24 weeks in ACEi, ARB and DRi groups.

The BP changes did not have significant statistical differences between the chosen medicine one week before enrolment. However, we had a clear documented trend of BP lowering in the first two weeks of the COVID-19 disease (Fig. 2) with its gradual return to baseline values up to the 12th week. Twenty-three (21 %) patients discontinued a

Infographics



Notes: ARB — angiotensin receptor blockers; ACEi — angiotensin-converting enzyme inhibitors; DRi — direct renin inhibitor; eGFR — estimated glomerular filtration rate.

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 ones for 4 weeks.

The analysis of individual values demonstrated that 16 (38 %) patients with hypertension taking ACEi had to discontinue the medicine or lower the dosage in the first 10–14 days of the COVID-19 disease due to pronounced hypotension development. In the group of patients taking DRi, 7 (23 %) individuals had a mildly softer decline in BP. Patients in ARB group had little to no decline in BP. This decline had no relation to dehydration or fever.

The data obtained indicated 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 normotensiveness 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 baseline BP values, and after 12 weeks, the consequences of hypotension were eliminated. On the contrary, in people who took ACE inhibitors, lower blood pressure values were still maintained in the post-COVID period.

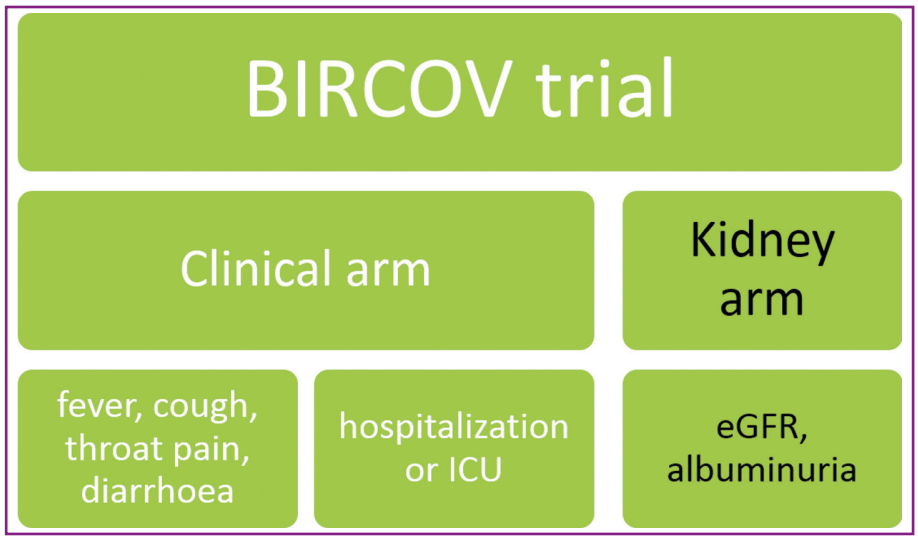


Figure 1. The BIRCOV trial

The Table 2 shows the **secondary outcomes measure**:

— the number of patients with fever (above 37.2 °C) up to 3 weeks,

— the number of patients with cough (time frame: 12 weeks),

— the number of patients with throat pain (time frame: 2 weeks),

— the number of patients with diarrhoea (time frame: 2 weeks),

— the number of patients who needed hospitalization and intensive care unit (time frame: 24 weeks).

The data in Table 2 characterizes the course of COVID-19 in

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

Kidney arm

Table 3 represents the baseline eGFR values with a follow-up of weeks 2, 4, 12, and 24 in ACEi, ARB, and DRi groups.

The synchronous decline of eGFR and systolic BP was more pronounced in CKD patients. The greatest decrease in eGFR was noted in people who took ACEi, weeks 0–24: the correlation coefficient (r) is 0.815; the relationship between the studied features is direct; the tightness (strength) of the relationship according to the Chaddock scale is high, the number of degrees of freedom (f) is 3; the Student's t-test is 2.432; although the dependence of the features was statistically insignificant (p = 0.135563).

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 the secondary outcome points demonstrated that 23 % of people without preceding albuminuria had developed the A2 range. During 12 weeks of observation, 81 % of patients had spontaneous albuminuria reduction. The post-COVID-19 (above 12 weeks) albuminuria remained in 19 % of patients, 90 % of them had CKD.

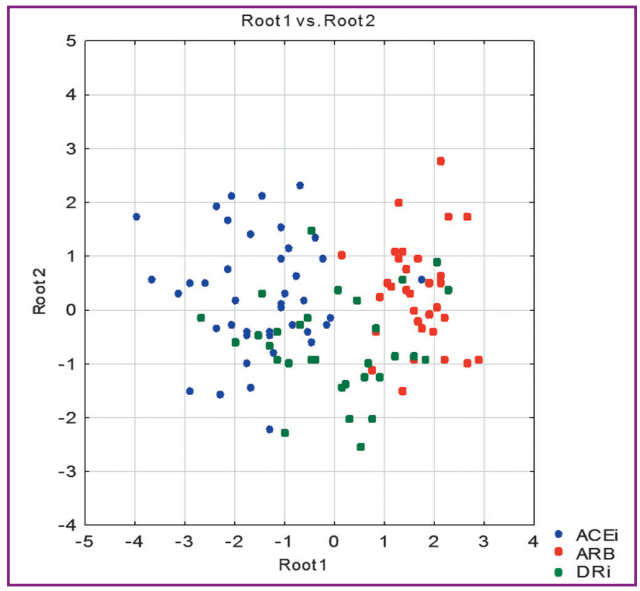


Figure 2. Systolic and diastolic blood pressure values 2 weeks after the onset of COVID-19

Table 1. The baseline BP values in dynamics by the weeks and groups of antihypertensive treatment

Drug/Week	–1	0	2	4	12	24	P value –1–0	P value 0–2
ACEi, n = 42	138.0 ± 1.1 / 83.0 ± 1.2	126.0 ± 1.2 / 77.0 ± 0.7	104.0 ± 0.9 / 68.0 ± 0.6	114.0 ± 1.1 / 72.0 ± 0.7	128.0 ± 1.2 / 77.0 ± 1.0	137.0 ± 1.2 / 81.0 ± 1.2	P ≤ 0.01	P ≤ 0.01
ARB, n = 35	136.0 ± 1.1 / 82.0 ± 1.2	132.0 ± 1.0 / 78.0 ± 0.7	131.0 ± 1.0 / 77.0 ± 0.6	133.0 ± 1.0 / 78.0 ± 0.6	135.0 ± 1.1 / 79.0 ± 0.9	137.0 ± 1.2 / 82.0 ± 1.2	P = 0.02	P ≤ 0.01
DRi, n = 31	134.0 ± 1.4 / 82.0 ± 1.2	127.0 ± 1.2 / 79.0 ± 0.6	115.0 ± 0.9 / 70.0 ± 0.6	121.0 ± 0.9 / 74.0 ± 0.6	125.0 ± 1.0 / 79.0 ± 0.8	129.0 ± 1.2 / 80.0 ± 1.2	P ≤ 0.01	P ≤ 0.01

Table 2. Data on the secondary outcome measure, N (%)

Patients	Time						Relative risk
	onset	2 weeks	3 weeks	4 weeks	12 weeks	24 weeks	
with fever (above 37.2 °C)	101 (90)	–	12 (11)	–	0	0	Onset — 3 weeks: RR 8.417; 95% CI 4.926–14.382; NNT 1.213
with cough	87 (78)	78 (70)	–	–	3 (3)	0	–
with throat pain	56 (50)	1 (1)	–	–	0	0	–
with diarrhoea	8 (7)	0	–	–	–	0	–
who needed hospitalization and intensive care unit	4 (3.5)	18 (16)	4 (4)	1 (1)	0	0	Onset — 2 weeks: RR 0.222; 95% CI 0.078–0.635; NNT 7.714
who died	–	–	3 (2.6)	1 (1)	0	0	3 to 4 weeks: RR 3.00; 95% CI 0.317–28.390; NNT 54.00

Seventy-eight percent of patients with preceding CKD had an increase in albuminuria and its return to the baseline values was observed only in 24 % of patients by the 12th week and in 49 % in 24 weeks.

An albumin/creatinine ratio was available in 24 patients with CKD. A two- and five-year prognosis of the risk of developing end-stage renal failure was calculated for them (Tables 4, 5).

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 already had it.

Discussion

ACE inhibitors form their effect through the ACE1 receptors, while the SARS-CoV-2 uses the ACE2 receptors [13]. Sequential metabolism of angiotensin 1–9, then angiotensin 1–7 goes two ways: 1) acting as an agonist through the Mas-1 receptors leading to vasodilation, 2) acting as an antagonist of the angiotensin AT1 receptor, enhancing vasodilation [14].

Thus, the SARS-CoV-2 seems similar in its mechanism of action to ARB that explains hypotension in the acute period of coronavirus infection. A double block of ACE inhibitors and ARB (the SARS-CoV-2) is accompanied by the largest blood pressure decrease, a double block of DRi and ARB (the SARS-CoV-2) is characterized by a smaller decrease in pressure, and a double block of ARB + ARB (the SARS-CoV-2) has practically no effect on blood pressure. This is associated with a trend that increases the risk of death in people with COVID-19 who are taking ARB as an antihypertensive agent [15].

Jordana B. Cohen et al. (2021) presented three possible mechanisms of the effect of RAS inhibitors, one of which, in our opinion, was shown in the results of the BIRKOV study [15]. At the same time, a small triple-blind study has shown no reduction in blood pressure. Perhaps, staying in intensive care units and hospitals does not allow us to depict the features that were established by us on an outpatient basis [16].

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 [17, 18].

The BIRKOV study supplements the available data on the absence of a negative effect of RAS inhibitors on the COVID-19 course [20]. Further studies are required for profound discovery of the characteristics of the course of COVID-19 infection in people with concomitant diseases, including hypertension and CKD [19].

Conclusions

COVID-19 has been shown to induce hypotension in outpatients if they receive an ACE inhibitor 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 stage 1–2 hypertension, taking iRAS allows comparing the effect of SARS-CoV-2 with the action similar to ARB, i.e. in people taking ACE inhibitors, the effect of BP reduction was comparable to the double block of iRAS: ACE inhibitors + ARB.

The synchronous decline of eGFR and systolic BP was more pronounced in CKD patients. The greatest decrease in eGFR was noted in people who took ACEi and in CKD 4. Not all patients with CKD had a return to baseline albuminuria and renal function after COVID-19.

Table 3. The changes in eGFR (ml/min/1.73 m²) in patients by the weeks and groups of antihypertensive treatment

Drug	Week					P value 0–2	P value 0–4
	0	2	4	12	24		
ACEi, n = 42	69.0 ± 1.7	52.0 ± 1.1	51.0 ± 0.9	58.0 ± 2.0	68.0 ± 1.9	P ≤ 0.01	P ≤ 0.01
ARB, n = 35	72.0 ± 1.7	70.0 ± 1.8	73.0 ± 1.5	70.0 ± 1.6	71.0 ± 1.8	Not reliable	
DRi, n = 31	71.0 ± 1.8	70.0 ± 1.6	69.0 ± 1.5	72.0 ± 1.7	70.0 ± 1.7		

Table 4. Risk of progression to kidney failure requiring dialysis or transplantation (using the Kidney Failure Risk Equation) in men (n = 14), %

Control check/risks	2 weeks	12 weeks	24 weeks
Over 2 years	0.1	0.1	0
Over 5 years	0.4	0.3	0.1

Table 5. Risk of progression to kidney failure requiring dialysis or transplantation (using the Kidney Failure Risk Equation) in women (n = 10), %

Control check/risks	2 weeks	12 weeks	24 weeks
Over 2 years	0.1	0.1	0
Over 5 years	0.3	0.2	0

References

1. *European Renal Association - European Dialysis and Transplant Association (ERA-EDTA). COVID-19: news and information. Available from: www.era-edta.org/en/covid-19-news-and-information/toggle-id-8.*
2. *Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-Angiotensin-Aldosterone System Inhibitors and Risk of Covid-19. N Engl J Med. 2020 Jun 18;382(25):2441-2448. doi:10.1056/NEJMoa2008975.*
3. *Lei Y, Zhang J, Schiavon CR, et al. SARS-CoV-2 Spike Protein Impairs Endothelial Function via Downregulation of ACE 2. Circ Res. 2021 Apr 30;128(9):1323-1326. doi:10.1161/CIRCRESAHA.121.318902.*
4. *Bojkova D, Klann K, Koch B, et al. Proteomics of SARS-CoV-2-infected host cells reveals therapy targets. Nature. 2020 Jul;583(7816):469-472. doi:10.1038/s41586-020-2332-7.*
5. *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 Jul 28;12(1):68. doi:10.1186/s13073-020-00763-0.*
6. *Nephrology Journal Club (NephJC). ACE2 and hypertension. Available from: http://www.nephjc.com/news/covidace2. Accessed: October 4, 2020.*
7. *Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. N Engl J Med. 2020 Jun 18;382(25):e102. doi:10.1056/NEJMoa2007621.*
8. *Mourad JJ, Levy BI. Interaction between RAAS inhibitors and ACE2 in the context of COVID-19. Nat Rev Cardiol. 2020 May;17(5):313. doi:10.1038/s41569-020-0368-x.*
9. *Evidence-Based Practice and Information Mastery: POEMs and DOEs. Available from: https://wilkes.libguides.com/c.php?g=191942&p=1266516.*
10. *Ivanova MD, Gozhenko AI, Crestanello T, Ivanov DD. Early Coaching to Increase Water Intake in CKD. Ann Nutr Metab. 2020;76(Suppl 1):69-70. doi:10.1159/000515276.*
11. *GIGA Online Calculators. Available from: https://www.gigacalculator.com/calculators/.*
12. *Kidney Failure Risk Equation (4 Variable): Calculator. Available from: https://qxmd.com/calculate/calculator_308/kidney-failure-risk-equation-4-variable.*
13. *Nephrology Journal Club (NephJC). COVID-19. Available from: http://www.nephjc.com/covid19.*
14. *Aronson JK, Ferner RE. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers in COVID-19. Available from: http://www.cebm.net/covid-19/angiotensin-converting-enzyme-ace-inhibitors-and-angiotensin-receptor-blockers-in-covid-19/. Accessed: March 31, 2020.*
15. *Cohen JB, South AM, Shaltout HA, Sinclair MR, Sparks MA. Renin-angiotensin system blockade in the COVID-19 pandemic. Clin Kidney J. 2021 Feb 2;14(Suppl 1):i48-i59. doi:10.1093/ckj/sfab026.*
16. *Najmeddin F, Solhjoo M, Ashraf H, et al. Effects of Renin-Angiotensin-Aldosterone Inhibitors on Early Outcomes of Hypertensive COVID-19 Patients: A Randomized Triple-Blind Clinical Trial. Am J Hypertens. 2021 Jul 15:hpab111. doi:10.1093/ajh/hpab111.*
17. *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 Jan 1;36(1):87-94. doi:10.1093/ndt/gfaa314.*
18. *Chung EY, 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 Aug 5:S0272-6386(21)00771-X. doi:10.1053/j.ajkd.2021.07.003.*
19. *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 Jul 28. doi:10.1111/jch.14329.*
20. *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 Aug 9;11(1):16144. doi:10.1038/s41598-021-95565-8.*

Received 20.08.2021
Revised 02.09.2021
Accepted 06.09.2021

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Conflicts of interests. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.
Information about funding: financially supported by Prof D. Ivanov Medical Practice.

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Підсумкові результати дослідження BIRCOV (БРА, ІАПФ, ПІР при COVID-19)

Резюме. Актуальність. У літературі дискутується питання про можливий вплив інгібіторів ренін-ангіотензин-альдостеронової системи (іРААС) на стан людей з гіпертензією, які захворіли на COVID-19. Основою для такої дискусії є використання коронавірусом рецептора ангіотензинперетворюючого фермента 2 (АПФ) для проникнення в клітину. Три можливі механізми взаємодії іРААС з коронавірусом можуть бути реалізовані в клінічній практиці: погіршення перебігу інфекції, нейтральний або той, що допомагає організму чинити опір COVID-19. З огляду на різні механізми зниження тиску інгібіторами РААС можна очікувати й відмінностей в стані людей з COVID-19, які отримують названі препарати. **Метою** дослідження було вивчення клінічних особливостей і лабораторних показників у пацієнтів із гіпертензією 1–2-го ступеня, які отримували іРААС і захворіли на COVID-19. **Матеріали та методи.** Дослідження POEM (Докази, орієнтовані на пацієнта, що мають значення) проводилося як відкрите перспективне рандомізоване в двох медичних центрах у пацієнтів, які захворіли на COVID-19, що попередньо отримували іАПФ, або блокатори рецепторів ангіотензину (БРА), або прямі інгібітори реніну (ПІР) як основну антигіпертензивну терапію. Було обстежено 120 людей з гіперто-

нічною хворобою 1–2-ї стадії, 108 увійшли до дослідження BIRCOV. COVID-19 був підтверджений тестом ПЛР, спостереження за хворобою поділили на 2 періоди: до 12 тижнів і до 24 тижнів. Первинна кінцева точка: артеріальний тиск (АТ), який був відомий за тиждень до розвитку COVID-19 і контролювався під час початку захворювання, на 2, 4, 12, 24-й тижні після дебюту коронавірусної інфекції. Вторинні кінцеві точки — клінічні ознаки COVID-19. Окремо проведений субаналіз у пацієнтів із хронічною хворобою нирок (ХХН). **Результати.** Усі пацієнти були рандомізовані в 3 групи й отримували: ІАПФ — 42 (39 %), БРА — 35 (32 %) або ПІР — 31 (29 %). Дослідження BIRCOV задокументувало тенденцію зниження АТ протягом перших двох тижнів захворювання на COVID-19 з поступовим поверненням до вихідних значень до 12-го тижня. 23 (21 %) пацієнти відмінили ліки на термін до 2 тижнів через тяжку гіпотензію. Однак показники АТ після COVID-19 у більшості учасників залишалися нижчими за вихідні протягом 4 тижнів. Застосування інгібіторів АПФ значно збільшувало ризик відміни порівняно з ПІР (RR 1,648; 95% ДІ 0,772–3,519; NNT 7,0) та БРА (RR 13,023; 95% ДІ 1,815–93,426; NNT 2,9) при COVID-19. Синхронне зниження розрахункової швидкості клубочкової фільтрації (рШКФ) та систолічного АТ було більш вираженим у пацієнтів із ХХН. Найбільше зниження рШКФ було відзначене в людей, які приймали іАПФ. Зниження рШКФ коливалося від 23 % при ХХН стадії 1 до 45 % на 4-й стадії ХХН. Двом людям був потрібен короткочасний діаліз. Аналіз вторинних результатів показав, що в 23 % людей без попередньої альбумінурії дана патологія сформувалася в діапазоні А2. Протягом 12 тижнів спостереження у 81 % пацієнтів спостерігалася спонтанна ліквідація альбумінурії. Після COVID-19 (спостереження понад 12 тижнів) альбумінурія зберігалася в 19 % пацієнтів, 90 % з них мали ХХН. У пацієнтів із попередньо визначеною ХХН спостерігалося збільшення альбумінурії в 78 % випадків, і її повернення до вихідного рівня спостерігалося лише в 24 % пацієнтів до 12-го тижня та в 49 % через 24 тижні. **Висновки.** У людей із гіпертензією 1–2-го ступеня, що постійно отримують інгібітори РААС, при захворюванні на COVID-19 може розвинутись гіпотензія в разі прийому іАПФ. COVID-19 призводить до транзиторного виникнення альбумінурії та зниження швидкості клубочкової фільтрації, що особливо небезпечно для людей із ХХН.

Ключові слова: інгібітори ренін-ангіотензин-альдостеронової системи; інгібітори ангіотензинперетворюючого фермента; блокатори рецепторів ангіотензину; прямі інгібітори реніну; COVID-19; дослідження BIRCOV

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Результаты исследования BIRCOV (БРА, ИАПФ, ПИР при COVID-19)

Резюме. Актуальность. В литературе дискутируется вопрос о возможном влиянии ингибиторов ренин-ангиотензин-альдостероновой системы (иРААС) на состояние людей с гипертензией, которые заболели COVID-19. Основой для такой дискуссии является использование коронавирусом рецептора ангиотензинпревращающего фермента 2 (АПФ) для проникновения в клетку. Три возможных механизма взаимодействия иРААС с коронавирусом могут быть реализованы в клинической практике: усугубляющий течение инфекции, нейтральный или помогающий организму. Учитывая различный механизм снижения давления ингибиторами РААС, можно ожидать и различия в состоянии людей с COVID-19, получающих названные препараты. **Целью** исследования явилось изучение клинических особенностей и лабораторных показателей у пациентов с гипертензией 1–2-й степени, получавших иРААС и заболевших COVID-19. **Материалы и методы.** Исследование POEM (Доказательства, ориентированные на пациента и имеющие значение) проводилось как открытое проспективное рандомизированное исследование в двух медицинских центрах с участием людей, которые заболели COVID-19 и получали иАПФ, блокаторы рецепторов ангиотензина (БРА) или прямые ингибиторы ренина (ПИР) в качестве базовой антигипертензивной терапии. Отобрано 120 человек с гипертензией 1–2-й стадии, 108 из них участвовали в исследовании BIRCOV. COVID-19 был подтвержден с помощью ПЦР-теста, наблюдение за заболеванием разделено на 2 периода: до 12 недель и до 24 недель. Первичная конечная точка: артериальное давление (АД), которое было известно за неделю до COVID-19 и затем мониторировалось во время начала заболевания, на 2, 4, 12, 24-й неделе от его дебюта. Вторичными конечными точками были клинические характеристики. Отдельно был проведен субанализ пациентов с хронической болезнью почек (ХБП). **Результаты.** Все пациенты были рандомизированы в 3 группы, которые соответственно получали: ИАПФ — 42 (39 %), БРА — 35 (32 %) или ПИР — 31 (29 %). Исследование BIRCOV зафиксировало тенденцию к снижению АД в первые две недели заболевания COVID-19 с его постепенным возвращением к исходным значениям вплоть до 12-й недели. У 23 (21 %) пациентов был отменен прием лекарств на срок до 2 недель из-за тяжелой гипотензии. Однако значения АД после COVID-19 у большинства испытуемых оставались ниже исходного уровня в течение 4 недель. Использование ингибиторов АПФ значительно увеличивало риск синдрома отмены по сравнению с ПИР (ОР 1,648; 95% ДИ 0,772–3,519; NNT 7,0) и БРА (ОР 13,023; 95% ДИ 1,815–93,426; NNT 2,9) из-за COVID-19. Синхронное снижение расчетной скорости клубочковой фильтрации (рСКФ) и систолического АД было более выражено у пациентов с ХБП. Наибольшее снижение рСКФ было отмечено у людей, принимавших иАПФ. Снижение рСКФ варьировало от 23 % при ХБП 1-й стадии до 45 % при ХБП 4-й стадии. Два человека нуждались в кратковременном диализе. Анализ вторичной конечной точки показал, что у 23 % людей без предшествующей альбуминурии она появилась в диапазоне А2. В течение 12 недель наблюдения у 81 % пациентов наблюдалась спонтанная ликвидация альбуминурии. После COVID-19 (сроки наблюдения свыше 12 недель) альбуминурия сохранялась у 19 % пациентов, 90 % из них имели ХБП. У пациентов с предшествующей ХБП наблюдалось увеличение альбуминурии в 78 % случаев, а ее возврат к исходному уровню отмечен только у 24 % пациентов к 12-й неделе и 49 % через 24 недели. **Выводы.** У людей с гипертензией 1–2-й степени, постоянно получающих ингибиторы РААС при заболевании COVID-19, может развиваться гипотензия при приеме иАПФ. COVID-19 приводит к транзиторному возникновению альбуминурии и снижению скорости клубочковой фильтрации, что особенно опасно для людей с ХБП.

Ключевые слова: ингибиторы ренин-ангиотензин-альдостероновой системы; ингибитор ангиотензинпревращающего фермента; блокаторы рецепторов ангиотензина; прямые ингибиторы ренина; COVID-19; исследование BIRCOV