Hypertension

ORIGINAL ARTICLE

# Impact of Arterial Hypertension and Use of Antihypertensive Pharmacotherapy on Mortality in Patients Hospitalized due to COVID-19: The CRACoV-HHS Study

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**BACKGROUND:** Cardiovascular diseases including arterial hypertension are common comorbidities among patients hospitalized due to COVID-19. We assessed the influence of preexisting hypertension and its pharmacological treatment on in-hospital mortality in patients hospitalized with COVID-19.

**METHODS:** We studied all consecutive patients who were admitted to the University Hospital in Krakow, Poland, due to COVID-19 between March 2020 and May 2021. Data of 5191 patients (mean age 61.9±16.7 years, 45.2% female) were analyzed.

**RESULTS:** The median hospitalization time was 14 days, and the mortality rate was 18.4%. About a quarter of patients had an established cardiovascular disease including coronary artery disease (16.6%) or stroke (7.6%). Patients with hypertension (58.3%) were older and had more comorbidities than patients without hypertension. In multivariable logistic regression analysis, age above median (64 years), male gender, history of heart failure or chronic kidney disease, and higher C-reactive protein level, but not preexisting hypertension, were independent risk factors for in-hospital death in the whole study group. Patients with hypertension already treated (n=1723) with any first-line antihypertensive drug (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, or thiazide/thiazide-like diuretics) had a significantly lower risk of in-hospital death (odds ratio, 0.25 [95% CI, 0.2–0.3]; $P<0.001$) compared to nontreated hypertensives (n=1305).

**CONCLUSIONS:** Although the diagnosis of preexisting hypertension per se had no significant impact on in-hospital mortality among patients with COVID-19, treatment with any first-line blood pressure–lowering drug had a profound beneficial effect on survival in patients with hypertension. These data support the need for antihypertensive pharmacological treatment during the COVID-19 pandemic. **(*Hypertension*. 2022;79:2601–2610. DOI: 10.1161/HYPERTENSIONAHA.122.19575.)**

• **Supplemental Material**

**Key Words:** blood pressure ■ COVID-19 ■ hypertension ■ pandemic ■ mortality ■ risk factors

It would be difficult to indicate another phenomenon in recent history that has changed the lives of people around the world as significantly as the COVID-19.[1] Indeed, COVID-19, despite unprecedented restrictions in daily life, has led to a crisis in health care systems causing millions of serious health complications and over 6.3 million deaths worldwide.[2] Cardiovascular diseases, arterial hypertension, and diabetes were identified very

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## NOVELTY AND RELEVANCE

### What Is New?

Our study for the first time confirms the importance of antihypertensive treatment for the improvement of survival in patients with hypertension hospitalized due to COVID-19.

### What Is Relevant?

The use of each main antihypertensive drug class improves the prognosis of patients with hypertension hospitalized with COVID-19.

### Clinical/Pathophysiological Implications?

Study results provide strong support for the use of antihypertensive treatment during the COVID-19 pandemic, thus there is no reason to discontinue or change the given antihypertensive drug only because of the fact of the SARS-CoV-2 infection.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **ACE** | angiotensin-converting enzyme |
| **ARB** | angiotensin receptor blocker |
| **BP** | blood pressure |
| **HF** | heart failure |
| **ICU** | intensive care units |
| **IL** | interleukin |
| **NT-proBNP** | N-terminal pro-brain natriuretic peptide |

early as common comorbidities, particularly in patients hospitalized due to COVID-19.[3,4] Further publications have provided evidence for the prognostic significance of these diseases for the COVID-19 severity and mortality.[5-7] Accordingly, the World Health Organization stated that people with preexisting noncommunicable diseases, including hypertension, appeared to be more vulnerable to developing a severe form of COVID-19.[8] Initial studies also reported arterial hypertension as an independent predictor of COVID-19 severity as indicated by the need for hospitalization, occurrence of acute respiratory distress syndrome, admission to intensive care units (ICU), and mortality.[7-9] However, recent studies have shown that hypertension may not represent an independent predictor of mortality in COVID-19, particularly after accounting for age and other comorbidities in adjusted analyses.[10-13] The role of antihypertensive treatment and more specifically, the relevance of renin-angiotensin-system blockers was also extensively discussed and investigated during the initial phase of the COVID-19 pandemic.[1,10,13-15] This was largely driven by the hypothesis that treatment with renin-angiotensin-system-blockers, that is, ACE (angiotensin-converting enzyme) inhibitors or angiotensin receptor blockers (ARB), may increase the risk for COVID-19 based on an unfavorable interaction with ACE2 representing the cell-entry receptor for the SARS-CoV2 virus.[16] However, a large number of original studies and meta-analyses discarded the initial findings suggesting poorer COVID-19 outcomes in patients using ACE inhibitors/ARB.[17] Nevertheless, the relevance of preexisting hypertension, its treatment as well as blood pressure (BP) control through treatment among patients with COVID-19 are still not clear and represent important knowledge gaps.[13,18]

The aim of the current study was to assess the influence of diagnosed arterial hypertension and its treatment with first-line BP-lowering drugs on in-hospital mortality in patients with COVID-19, including the impact of other risk factors and comorbidities.

## METHODS

In this retrospective study, all consecutive patients who were admitted between 6 March 2020 and 13 May 2021 to the University Hospital in Krakow (Poland), which was converted temporarily into an infectious disease hospital dedicated only to COVID-19 treatment, were included in this study (CRACoV-HHS Study [Cracow in COVID Pandemics - Home, Hospital and Staff]). Data available on request from the authors. Patients were admitted from the whole Malopolska Voivodship and neighboring regions. The Małopolska Voivodship is one of 16 administrative regions in Poland with its capital in Krakow. Over 3.4 million people live in an area of 15 108 square kilometers, mostly Poles of White descent.

Patients were diagnosed with COVID-19 according to World Health Organization and Polish guidelines with the use of real-time polymerase chain reaction.[19-21] The treatment algorithm for COVID-19 was in accordance with the recommendations of the Polish Association of Epidemiologists and Infectiologists.[20,21] Individual patient data were obtained from the Hospital Information System. Information on diagnosis of hypertension, other cardiovascular risk factors, and comorbidities were identified based on the medical history of prehospital diagnoses. Importantly, the diagnosis of hypertension was based on prehospital data about hypertension diagnosis or treatment. Diagnosis of hypertension was based on the current European Society of Cardiology Guidelines,[22] that is, systolic BP ≥140 mm Hg or diastolic ≥90 mm Hg measured at two different ambulatory visits. BP values obtained at admission to the hospital due to COVID-19 were not considered as a criterion for hypertension diagnosis. Prehospital diagnosis of hyperlipidemia and diabetes was established according to criteria provided by the European Guidelines,[23,24] whereas obesity was defined as body mass index ≥30 kg/m$^2$. Data on

drug treatment including antihypertensive treatment were also obtained from in-hospital medical records. The primary end point of our study was in-hospital mortality from any cause. The study was approved by the Jagiellonian University Ethics Committee, decision number 1072.6120.278.2020. The retrospective nature of the analysis precluded the collection of separate informed consents. Before admission, each patient signed an agreement to be hospitalized and to have their data processed. Approval by the Local Ethics committee was granted to use anonymized data from Hospital Information System for this study.

### Statistical Analysis

We used the SAS software, version 9.3 (SAS Institute, Cary, NC), for database management and statistical analysis. The results were expressed as numerical values and percentages for categorical variables and mean values and SD if normally distributed (assessed using the Kolmogorov-Smirnov test) or median and interquartile range for continuous variables. To test the differences between patients with COVID-19 with and without preexisting hypertension and between treated and untreated hypertensives in means and proportions, we applied the $t$ test and the $\chi^2$ statistic, respectively, while in the case of nonparametric data, the Wilcoxon Rank-sum test was used. We also adjusted these differences for age by means of a general regression model. In multivariable logistic regression, we searched for possible covariates of the likelihood of in-hospital death. Then odds ratios and corresponding 95% CI were calculated for covariates influencing in-hospital death. Then, separate models were constructed for patients with and without hypertension, treated and untreated hypertensives as well as for patients with cardiovascular risk factors but without comorbidities, that is, coronary artery disease and stroke or heart failure and chronic kidney disease and selected drugs used in pharmacological treatment. We also constructed separate models for each antihypertensive drug class to assess the effect of their use in patients with hypertension (each model besides the antihypertensive drug class use versus not use, included: age, gender, diabetes, atrial fibrillation, coronary artery disease, heart failure, stroke, chronic kidney disease, chronic obstructive pulmonary disease, cancer, and increase of highly sensitive C-reactive protein). Patients with missing data were excluded from regression analyses. In all analyses, a $P$ value of ≤0.05 was considered statistically significant.

## RESULTS

During analyzed period a total of 5191 patients (mean age, 61.9± 16.7 years) were hospitalized due to COVID-19 and completed their hospital course (ie, from admission to discharge or death). The study sample comprised 2348 women (mean age, 62.6±17.9 years) and 2843 men (mean age 61.2±15.6 years). A preexisting diagnosis of arterial hypertension was recorded in 3028 patients (58%), rendering this diagnosis the most common cardiovascular risk factor, followed by diabetes (26.2%), hyperlipidemia (20.7%), and obesity (17.5%, Table 1). The prevalence of preexisting chronic diseases is summarized in Table 1; about a quarter of patients had an established cardiovascular disease, that is, coronary artery disease (16.6%) or stroke (7.6%).

The median time of hospitalization was 14 days (Table 2). Admission to the ICU was needed in 12.2% of patients, and the median length of ICU stay was 11 days. The overall in-hospital mortality was 18.4% (953 of 5191 patients, Table 2). In-hospital mortality was significantly higher among patients older than 64 years (the median age in the study cohort) compared to younger patients (14.7% versus 3.6%, $P<0.01$).

Overall, 33.2% of patients were treated with first-line BP-lowering drugs, including 14.7% of patients using ACE inhibitors, 5.3% ARBs, 28.9% ß-blockers, 13.5% calcium channel blockers, 6.5% thiazide or thiazide-like diuretics; 30% were treated with loop diuretics. Statins were used in 13.9%, antiplatelet drugs in 14.6%, new oral anticoagulants in 6.1%, and vitamin K antagonists in 1.0% of patients (Table 2).

### Comparison of Patients With and Without Hypertension

Patients with hypertension were older and had a higher prevalence of other cardiovascular risk factors including hyperlipidemia (31.2% versus 6.2%), diabetes (37.2% versus 10.8%), and obesity (20.0% versus 13.9%) than those without hypertension after adjusting for age ($P<0.0001$). Patients with hypertension had also more comorbidities and were more frequently treated with cardiovascular medications, including BP-lowering drugs (Tables 1 and 2). The prevalence of in-hospital death in patients with hypertension was almost 2× higher than in patients without hypertension (22.2% versus 12.9%, $P=0.02$, after adjusting for age). The median length of hospitalization was longer in hypertensives than in patients without hypertension (Table 2); however, the need for admission to the ICU and the length of stay in the ICU were similar in both groups (Table 2). Compared with patients without hypertension, patients with hypertension had (at admission) higher systolic BP, mean BP, and pulse pressure, but not diastolic BP. Patients with hypertension had significantly higher respiratory rates and NT-proBNP levels than patients without hypertension ($P<0.05$ after adjusting for age; Table 2), whereas blood oxygen saturation, heart rate, and immune-inflammatory markers at admission were similar in both groups (Table 2).

### Comparison of Patients With Hypertension Treated and Untreated With First-Line BP-Lowering Drugs

Among 3028 patients with hypertension, 1723 (57%) were treated with first-line BP-lowering medications, whereas 1305 (43%) were not. In comparison to untreated patients, those with treated hypertension

**Table 1. Initial Characteristics of the Patients**

| Characteristics | All | History of hypertension | | Of 3028 patients with history of hypertension | | *P* value† |
|---|---|---|---|---|---|---|
| | | No | Yes | Treated* | Untreated* | |
| Number | 5191 | 2163 | 3028 | 1723 | 1305 | |
| Age‡, y | 61.9 (16.7) | 52.8 (17.3) | 68.3 (12.7) | 68.1 (12.8) | 68.8 (12.6) | 0.21 |
| Female, n (%) | 2348 (45.2) | 998 (46.1) | 1350 (44.6) | 798 (46.3) | 552 (42.3) | 0.028 |
| BMI,§ kg/m$^2$ | 29.1 (5.78) | 27.9 (5.47) | 30.0 (5.84)‖ | 30.1 (6.0) | 29.9 (5.6) | 0.70 |
| Preexisting disorders, n (%) | | | | | | |
| Hyperlipidemia | 1075 (20.7) | 134 (6.20) | 941 (31.1) ‖ | 591 (34.3) | 350 (26.8) | <0.0001 |
| Diabetes | 1361 (26.2) | 233 (10.8) | 1128 (37.2) ‖ | 652 (37.8) | 476 (36.5) | 0.44 |
| Coronary artery disease | 864 (16.6) | 119 (5.50) | 745 (24.60) ‖ | 429 (24.9) | 316 (24.2) | 0.66 |
| Stroke | 394 (7.59) | 65 (3.01) | 329 (10.9) ‖ | 206 (12.0) | 123 (9.4) | 0.027 |
| Heart failure | 509 (9.81) | 87 (4.02) | 422 (13.9) ‖ | 237 (13.8) | 185 (14.2) | 0.74 |
| Atrial fibrillation | 641 (12.3) | 112 (5.18) | 529 (17.5) ‖ | 304 (17.6) | 225 (17.2) | 0.77 |
| Asthma | 316 (6.09) | 109 (5.04) | 207 (6.84) | 110 (6.4) | 97 (7.4) | 0.26 |
| COPD | 276 (5.32) | 54 (2.50) | 222 (7.33) ‖ | 106 (6.15) | 116 (8.9) | 0.004 |
| CKD | 483 (9.3) | 92 (4.25) | 391 (12.9) ‖ | 212 (12.3) | 179 (13.7) | 0.25 |
| Cancer | 624 (12.0) | 238 (11.0) | 386 (12.7) | 214 (12.4) | 172 (13.2) | 0.53 |

Data are presented as mean (SD) or median (interquartile range) or number (%). BMI indicates body mass index; CKD, chronic kidney disease; and COPD, chronic obstructive pulmonary disease.

*Treatment with any of first-line antihypertensive drugs (ie, β-blockers, angiotensin-converting enzyme inhibitors; angiotensin receptor blockers; thiazide diuretics, calcium channel blockers).

†*P* for differences between patients with hypertension treated and untreated due to hypertension.

‡Age median=64 (Q1–Q3: 51–74);

§Data are available in 2403 patients.

‖*P*<0.05 for adjusted to age differences between patients with and without hypertension.

were more commonly women and had higher prehospital prevalence of diagnosed hypercholesterolemia and stroke but less frequently chronic obstructive pulmonary disease (Table 1). Treated hypertensive individuals were also characterized by higher BP values and oxygen saturation at admission, while lower heart rate, respiratory rate, CRP (C-reactive protein), IL (interleukin) 6, and D-Dimer levels than untreated hypertensives (Table 2). Of note is that the number of in-hospital deaths in patients with hypertension who were treated by any drug belonging to the first-line BP-lowering drug class (ie, ACE inhibitors, ARB, β-blockers, calcium channel blockers, or thiazide/thiazide-like diuretics) was significantly lower than in untreated hypertensives (Table 2).

## Independent Predictors of In-Hospital Death

We used multivariable logistic regression analysis to identify independent predictors of in-hospital death. In these analyses, age above a median of the cohort, male gender, and a history of heart failure or chronic kidney disease as well as increased hsCRP (high-sensitivity CRP) level were independent predictors of in-hospital death, while a preexisting diagnosis of hypertension was not (Figure 1). The use of first-line BP-lowering drugs, however, improved in-hospital survival in the whole study group (Figure S1). In sensitivity analysis, we also assessed whether differences between pandemic periods may have influenced the relationship between hypertension and its treatment with mortality outcome. Accordingly, the pandemic period in our study was divided into three separate periods (waves) reflecting the trends of admission increase: (1) from March 6 to July 31, 2020; (2) from August 1 to January 31, 2021; (3) from February 1, 2021 to May 13, 2021. Independently of admission period, hypertension diagnosis did not influence in-hospital mortality, whereas BP-lowering drug use improved prognosis (Figure S1).

In further analysis, we assessed in more detail the role of treatment status with first-line BP-lowering drugs in patients with hypertension. This analysis revealed that use of any drug belonging to the first-line BP-lowering drug classes was associated with reduced mortality (odds ratio, 0.25 [95% CI, 0.20–0.30]; *P*<0.001) (Figure 2). In this analysis, older age, increased hsCRP, history of coronary artery disease, heart failure, and chronic kidney disease were also independent predictors of in-hospital death (Figure 2; Figure S2A and S2B). The positive influence of antihypertensive drug treatment on survival in COVID-19 persisted after inclusion into the model the treatment with other cardiovascular drugs including statins, antiplatelet drugs, heparins, and new oral anticoagulants (Figure S3A and S3B).

**Table 2. Clinical Characteristics, Drug Therapy, and Outcomes During Hospitalization**

| Characteristics | All | History of hypertension | | Of 3028 patients with history of hypertension | | *P* value† |
|---|---|---|---|---|---|---|
| | | No | Yes | Treated* | Untreated* | |
| Number | 5191 | 2163 | 3028 | 1723 | 1305 | |
| Parameters on admission | | | | | | |
| SBP,‡ mm Hg | 130.5 (22.3) | 127.3 (19.5) | 132.6 (23.7)§ | 135.4 (23.0) | 128.9 (24.2) | <0.001 |
| DBP,‡ mm Hg | 79.0 (14.3) | 79.3 (13.3) | 78.9 (14.9) | 80.5 (14.5) | 76.8 (15.2) | <0.001 |
| PP,‡ mm Hg | 51.4 (16.7) | 48.0 (14.3) | 53.7 (17.8) § | 54.9 (17.9) | 52.1 (17.5) | <0.001 |
| MAP,‡ mm Hg | 96.2 (15.5) | 95.3 (14.1) | 96.8 (16.3) § | 98.8 (15.7) | 94.2 (16.8) | <0.001 |
| Heart rate‡/min | 85.7 (16.4) | 87.1 (16.7) | 84.9 (16.2) | 83.6 (14.9) | 86.6 (17.7) | <0.001 |
| Respiratory rate‡/min | 15 (12–18) | 14 (12–16) | 16 (14–18) § | 14 (12–18) | 16 (14–20) | <0.001 |
| Oxygen saturation,‡ % | 95 (92–97) | 95 (93–97) | 94 (92–97) | 95 (92–97) | 94 (91–96) | <0.001 |
| hsCRP,‡ mg/L | 50.9 (15.2–103.5) | 42.8 (9.78–98.9) | 55.1 (20.1–106) | 46.8 (14.9–93) | 69.9 (28.3–119) | <0.001 |
| D-dimer,‡ µg/mL | 0.95 (0.53–2.02) | 0.84 (0.47–1.85) | 1.02 (0.57–2.12) | 0.94 (0.55–1.83) | 1.14 (0.62–2.65) | <0.001 |
| IL6, pg/mL‡ | 32.8 (12.3–75.5) | 28.2 (10.8–70.3) | 35.3 (14.2–77.9) | 31.6 (11.9–73.5) | 39.2 (17.1–85.0) | <0.001 |
| NT-proBNP,‡ pg/mL | 484.0 (145–1839) | 219 (80–958) | 712 (225–2440) § | 738 (237–2355) | 700 (206–2596) | 0.33 |
| Cardiovascular therapy | | | | | | |
| ACE inhibitor | 763 (14.7) | 102 (4.72) | 661 (21.8) § | 661 (38.4) | | |
| ARB | 275 (5.3) | 13 (0.6) | 262 (8.6) § | 262 (15.2) | | |
| β-blocker | 1503 (28.9) | 310 (14.3) | 1193 (39.4) § | 1193 (69.2) | | |
| Calcium channel blockers | 703 (13.5) | 80 (3.7) | 623 (20.6) § | 623 (36.2) | | |
| Thiazide diuretics | 338 (6.5) | 23 (1.06) | 315 (10.4) § | 315 (18.3) | | |
| Loop diuretics | 1558 (30.0) | 418 (19.3) | 1140 (37.6) § | 770 (44.7) | 370 (28.3) | <0.001 |
| Statins | 721 (13.9) | 94 (4.35) | 627 (20.7) § | 555 (32.2) | 72 (5.5) | <0.001 |
| Antiplatelets‖ | 760 (14.6) | 142 (6.56) | 618 (20.4) § | 525 (30.5) | 93 (7.1) | <0.001 |
| Novel oral anticoagulants | 317 (6.11) | 72 (3.33) | 245 (8.09) § | 220 (12.8) | 25 (1.9) | <0.001 |
| Vitamin K antagonists | 52 (1.0) | 12 (0.55) | 40 (1.32) | 36 (2.09) | 4 (0.31) | <0.001 |
| Heparin | 2785 (53.6) | 1210 (55.9) | 1575 (52.0) | 1165 (67.6) | 410 (31.4) | <0.001 |
| Clinical course | | | | | | |
| In hospital death | 953 (18.4) | 281 (12.9) | 672 (22.2) § | 212 (12.3) | 460 (35.2) | <0.001 |
| Noninvasive oxygen therapy¶ | 1641 (31.6) | 624 (28.8) | 1017 (33.59) | 674 (39.1) | 343 (26.3) | <0.001 |
| Mechanical ventilation | 643 (12.4) | 244 (11.3) | 399 (13.2) | 176 (10.2) | 223 (17.1) | <0.001 |
| Admission to an ICU, n % | 634 (12.2) | 237 (10.9) | 397 (13.1) | 203 (11.8) | 194 (14.9) | 0.013 |
| Length of stay at ICU, d | 11 (6–21) | 12 (6–23) | 11 (6–19) | 14 (7–26) | 10 (5–16) | <0.001 |
| Length of hospital stay, d | 14 (9–21) | 12 (8–18) | 15 (10–23) § | 17 (12–27) | 12 (8–18) | <0.001 |

Data are presented as mean (SD), median (Q1–Q3), or number (%). ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; hsCRP, highly sensitive C-reactive protein; hscTn, high-sensitivity cardiac troponin; ICU, intensive care unit; IL6, interleukin 6; NT-proBNP, N-terminal pro-brain natriuretic peptide; PP, pulse pressure; and SBP, systolic blood pressure.

*Treatment with any of first-line antihypertensive drug (ie, β-blockers, angiotensin-converting enzyme inhibitors; angiotensin receptor blockers; thiazide diuretics, calcium channel blockers).

†*P* for differences between patients with hypertension treated and untreated due to hypertension.

‡Data available for SBP/DBP in 4361 patients, respiratory rate in 3623 patients, oxygen saturation in 4128 patients, hsCRP in 5020 patients, D-Dimer in 4572 patients, IL6 for 2991 patients, NT-proBNP in 3074 patients.

§*P*<0.05 adjusted for age differences between patients with and without hypertension.

‖Antiplatelet therapy included those treated with low-dose aspirin or clopidogrel, ticagrelor, or prasugrel.

¶At least 5 L/min.

Subsequent separate logistic regression analysis for the use of each first-line antihypertensive drug class confirmed the effect on in-hospital death reduction for each analyzed drug class (Table S1). The independent predictors of in-hospital death in treated and untreated patients with hypertension are summarized in Figure S4.

In patients without preexisting arterial hypertension, the main factors increasing the odds of in-hospital death were slightly different from patients with hypertension and included older age, history of heart failure or chronic kidney disease, and higher hsCRP, but not a history of cardiovascular disease. In this group, use of ACE inhibitors but not use of any other BP-lowering

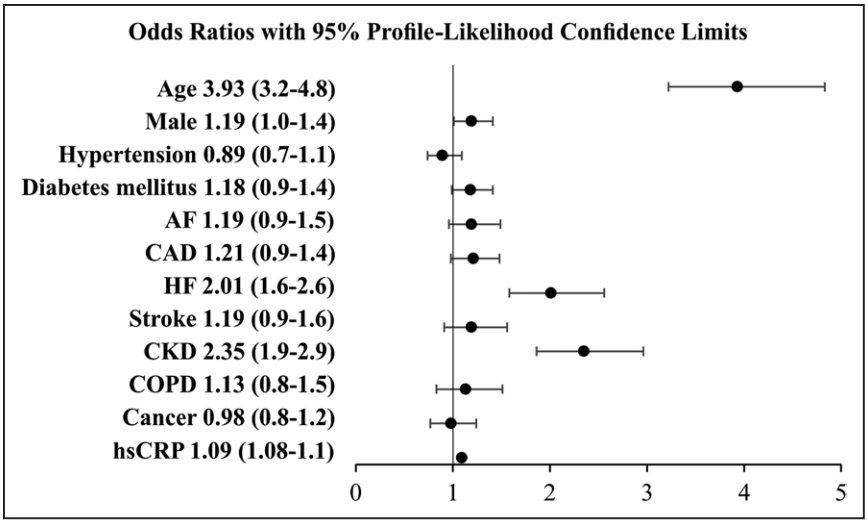


**Figure 1. Independent predictors of in-hospital death in multivariable logistic regression analysis in whole study group N= 5191 (171 patients excluded due to missing data.**
Age: indicates patients at age equal or above median for study group; AF - atrial fibrillation, CAD - coronary artery disease, HF - heart failure, Stroke; CKD - chronic kidney disease, COPD - chronic obstructive pulmonary disease; CRP (C-reactive protein) units - indicates increase in 10 mg/L of hsCRP (high-sensitivity C-reactive protein).

drug class was related to lower risk of in-hospital death (Figure S5).

In the subgroup of patients without preexisting established cardiovascular diseases or chronic kidney disease not treated with any cardiovascular medication, including BP-lowering drugs, multivariable logistic regression still showed that preexisting diagnosis of hypertension was a significant factor increasing the risk of in-hospital death (Figure 3).

## DISCUSSION

Hypertension was the most common clinical condition in the group of patients hospitalized due to COVID-19 in this study. This prevalence of about 60% was similar to the prevalence observed among subjects in the general population over 50 years of age in epidemiological studies from Poland.[25] Overall, patients with hypertension in our cohort were older and had more coexisting comorbidities with a potential impact on clinical outcome than patients without hypertension. Therefore, in-hospital mortality in patients with preexisting hypertension was higher in crude analysis than in patients without hypertension. However, the preexisting diagnosis of hypertension per se was not an independent predictor of in-hospital death. In contrast, significant predictors of death, besides older age and male sex were higher hsCRP levels, heart failure, and chronic kidney disease. The 2 latter conditions are widely recognized as a consequence of long-lasting hypertension.[22,24] Preexisting hypertension was an independent predictor of in-hospital death during COVID-19 only in patients free of cardiovascular diseases. This can be explained also as these patients had not been used to get medical treatment. Of interest, the treatment with first-line BP-lowering drugs had a significant impact on mortality in patients with hypertension, that is, the use of any class of first-line antihypertensive medications as recommended in guidelines[22,24] increased the probability of surviving COVID-19 hospitalization.

Prior studies have also shown that there is a high prevalence of hypertension ranging from 27% to 59%[3,6,10,11] in patients hospitalized due to COVID-19.

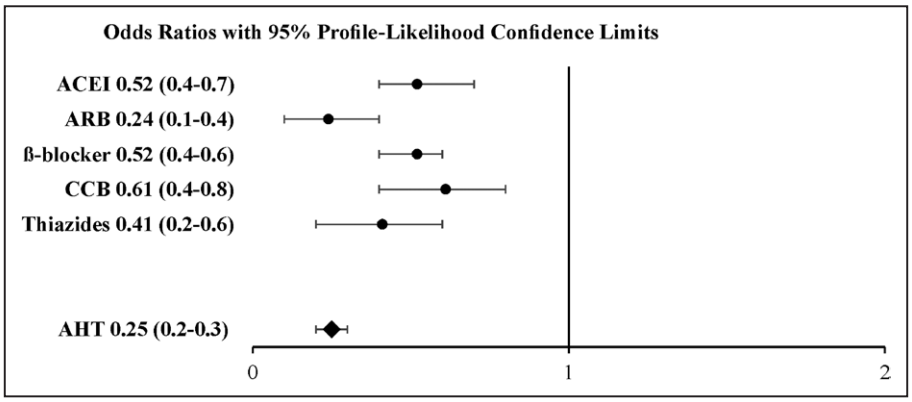


**Figure 2. Independent predictors of in-hospital death in multivariable logistic regression analysis in patients with hypertension N=3028 (59 patients excluded due to missing data).**
The models include age, sex, diabetes, atrial fibrillation, coronary artery disease, heart failure, stroke, chronic kidney disease, chronic obstructive pulmonary disease, cancer, and highly sensitive C-reactive protein level increase (the whole models are presented in Figure S2). ACE inhibitor indicates angiotensin-converting enzyme inhibitor; AHT, treatment with any class of main antihypertensive drugs; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; and Thiazides, thiazide diuretics or thiazides like diuretics.

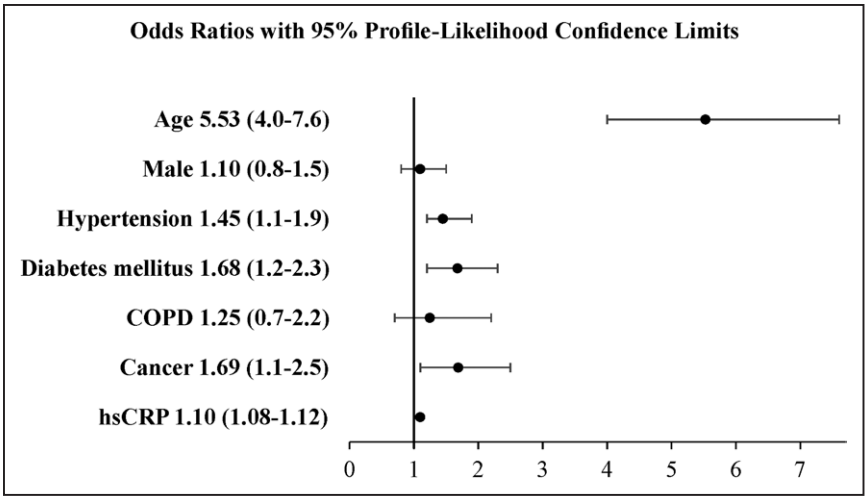


**Figure 3. Independent predictors of in-hospital death in multivariable logistic regression analysis in patients without history of the following disease: heart failure, coronary artery disease, chronic kidney disease, stroke, atrial fibrillation, and without antihypertensive treatment (nontreated with β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers or thiazide diuretics; 112 patients excluded due to missing data).** N= 2281 including 1061 women, 704 patients with arterial hypertension, 338 with diabetes; 66 with chronic obstructive pulmonary disease (COPD), and 238 with history of cancer. hsCRP indicates high-sensitivity C-reactive protein.

The prevalence was even higher, up to 70%, in those who died due to COVID-19.[10,11] Consequently, the question arises whether preexisting hypertension is a factor influencing in-hospital prognosis in patients hospitalized due to COVID-19, as it is a significant long-term prognostic factor in the general population.[27] Available data on the role of hypertension in COVID-19 prognosis are, however, equivocal.[5,6,10,12,17,28,29] In an early study from Wuhan, China, coexisting hypertension, observed in 28% of patients, was independently associated with all-cause mortality (hazard ratio, 1.8 [95% CI, 1.2–2.7]) in patients treated due to COVID-19.[5] Moreover, in the analyses of 13 early studies, which included a total of 3822 patients, there was a significant association of hypertension with mortality due to COVID-19.[28] However, in the study of Sun et al,[12] hypertension was a predictor of death but only in combination with diabetes (odds ratio, 3.02 [95% CI, 1.48–6.15]). Other recently published data did not confirm the previous observation about the negative influence of hypertension on prognosis in patients with COVID-19.[6] In a meta-analysis of 18 studies (14 558 individuals), the estimated pooled relative risk of mortality among patients with COVID-19 was significantly increased for comorbidities, including cardiovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, and cancer, but not for hypertension or diabetes.[6] In a study by the Italian Society of Hypertension of 1591 patients hospitalized due to COVID-19 in multivariable analyses, only older age, diabetes, chronic obstructive pulmonary disease, and chronic kidney disease but not hypertension predicted increased mortality.[10] In a different group of Italian patients hospitalized with COVID-19 and admitted to intensive care units, hypertension was also not an independent predictor of in-hospital mortality.[29] Similarly, in our results, we did not identify preexisting hypertension as an independent predictor of in-hospital death when analyzed along with other comorbidities and other risk factors. Among those comorbidities, only a history of heart failure or chronic kidney disease—well-known consequences of hypertension—were associated with in-hospital death.

In a Massachusetts community-based observational study, hypertension was an independent predictor of severe COVID-19 defined as need for hospitalization or death, only in patients younger than 65 years.[14] This finding is consistent with our results showing that hypertension predicts in-hospital death only among patients free of established cardiovascular diseases. This group in our study was also younger than patients with any cardiovascular disease (median of age 56 versus 70 years).

The importance of antihypertensive treatment for COVID-19 morbidity and mortality was a subject of interest from the very beginning of the pandemic, mainly due to the mechanisms of virus incorporation into cells in the respiratory tract via angiotensin-converting enzyme 2 and a postulated interaction of ACE inhibitors and ARB treatment with this mechanism.[30-32] However, the majority of data obtained in observational studies and randomized trials have shown and reassured that treatment with ACE inhibitors or ARB has a neutral impact on the outcomes of patients with COVID-19.[33-37]

In one of the largest population-based case-controlled analyses in the United Kingdom, there was no evidence that the use of antihypertensive medication is associated with increased risk of COVID-19 diagnosis or mortality.[38]

It is of interest that some studies indicated that treatment with ACE inhibitors or ARB may even protect against infection and reduce mortality in COVID-19.[12,15,18] In the study by the Italian Society of Hypertension, there was no interference of antihypertensive therapy with COVID-19 mortality.[10] In the study of Ran et al,[39] ARBs did not increase the risk of adverse events in patients with hypertension; moreover, poor BP control was independently associated with higher risks of adverse outcomes of COVID-19, including heart failure, which in our study was a main determinant of in-hospital mortality. With respect to medical treatment, Bauer et al. found that therapy with any first-line antihypertensive drug does not worsen COVID-19 severity.[14] Another

large observational study suggests a lower risk of worse COVID-19 outcome (hospitalization and death or intubation) in patients with hypertension treated over a long period with ACE inhibitors or ARBs compared to those treated with calcium channel blockers.[40] However, some limitations of the evidence on the role of antihypertensive treatment in patients with COVID-19 presented to date should also be taken into consideration. A high proportion of studies was based on small sample sizes, and many studies failed to include adequate adjustments for confounding variables.

In our study, the use of any first-line BP-lowering drug had a profound beneficial effect on survival in patients with COVID-19 with hypertension, after adjustment for covariates. Consequently, the treatment status in patients with preexisting hypertension had a major influence on mortality during hospitalization due to COVID-19, irrespective of the drug class used. There is also a possibility that treated patients with antihypertensive medications were admitted earlier than untreated attributable to a potentially higher socioeconomic status or education level resulting in higher health awareness and earlier reach out for medical care. This may also partially explain the between-group differences in clinical condition on admission. However, it appears still important to emphasize that the positive effect of antihypertensive treatment on the prognosis in multivariable logistic regression was independent of inflammation severity at admission as assessed by hsCRP level. Based on the available data in our study, we cannot precisely identify the decisive factors for whether attending physicians treat their patients with a recommended first-line BP-lowering pharmacotherapy. It appears conceivable that the untreated patients may represent patients with a lower risk or a more recent diagnosis of hypertension, with the treating physicians initiating treatment with lifestyle changes but not with pharmacotherapy. However, the patient characteristics (as evident from Table 1) showed only subtle differences between the treated and untreated groups of patients with hypertension. Interestingly, all BP values measured at admission to the hospital were significantly higher in the patients under antihypertensive pharmacotherapy, which would confirm more advanced hypertension in this group. In a recent study by Sheppard et al,[15] better BP control in the period before admission to hospital was shown to be associated with a worse COVID-19 outcome. The authors explained this phenomenon by a potentially more advanced target organ damage in patients with better BP control because their corresponding patients were older, had more comorbidities, and had been diagnosed with hypertension for a longer period of time.[15] The positive influence of antihypertensive treatment on prognosis in patients with hypertension hospitalized due to COVID-19 might be explained by 2 well-known facts. First, the results of numerous RCT studies from the prepandemic era show that each antihypertensive treatment improves prognosis irrespective of the drug class used.[22,24] A second explanation is the positive effect of different antihypertensive drugs on the endothelium as it is a well-known fact that the endothelium is widely involved in COVID-19 pathogenesis and its complications.[41,42]

## Limitations

The lack of detailed data about the preadmission period of the included patients should be considered as a first limitation of our study. Such data might have shed more light on our finding indicating a relevant beneficial prognostic effect of pharmacological treatment status in patient with preexisting hypertension and acute COVID-19 disease. We analyzed drug classes and not individual medications and could not take into account dosage of different drugs, treatment duration before admission, or adherence to therapy. A second limitation is that this is a retrospective observational study, and despite controlling for various comorbidities, some other unknown confounders might therefore play a role in affecting our results. However, we presented the data of a large cohort from a single center with a uniform hospital information system and a standardized COVID-19 management with reliable data from medical records directly available to us. Additionally, our results of reduced mortality in consecutive COVID-19 pandemic waves confirmed that COVID-19 treatment strategy improved during pandemic waves.

## Conclusions

Preexisting hypertension in patients hospitalized due to COVID-19 is not overall an independent predictor of in-hospital death. However, the use of any antihypertensive drug, regardless of the class to which it belongs, resulted in a profound reduction of in-hospital mortality in patients with hypertension.

## Perspectives

The future of the COVID-19 pandemic remains unpredictable, but cardiovascular risk factors and diseases including hypertension should be treated continuously to obtain a better long-term prognosis in patients with these conditions as well as for reducing COVID-19 mortality. The following indication should be considered for patients with hypertension: continuation of antihypertensive treatment during hospitalization due to COVID-19, and all antihypertensive drug classes might be recommended equally in this indication.

## ARTICLE INFORMATION

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## Disclosures

None.

## REFERENCES


1. Kreutz R, Dobrowolski P, Prejbisz A, Algharably EAE, Bilo G, Creutzig F, Grassi G, Kotsis V, Lovic D, Lurbe E, et al; European Society of Hypertension COVID-19 Task Force Review. Lifestyle, psychological, socioeconomic and environmental factors and their impact on hypertension during the coronavirus disease 2019 pandemic. *J Hypertens*. 2021;39:1077–1089. doi: 10.1097/HJH.0000000000002770
2. World Health Organization Coronavirus Disease (COVID-19) Dashboard. Accessed July 1, 2022 . https://covid19.who.int/
3. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, et al. Risk Factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180:934–943. doi: 10.1001/jamainternmed.2020.0994
4. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054–1062. doi: 10.1016/S0140-6736(20)30566-3
5. Pan W, Zhang J, Wang M, Ye J, Xu Y, Shen B, He H, Wang Z, Ye D, Zhao M, et al. Clinical features of COVID-19 in patients with essential hypertension and the impacts of renin-angiotensin-aldosterone system inhibitors on the prognosis of COVID-19 patients. *Hypertension*. 2020;76:732–741. doi: 10.1161/HYPERTENSIONAHA.120.15289
6. Singh AK, Gillies CL, Singh R, Singh A, Chudasama Y, Coles B, Seidu S, Zaccardi F, Davies MJ, Khunti K. Prevalence of co-morbidities and their association with mortality in patients with COVID-19: A systematic review and meta-analysis. *Diabetes Obes Metab*. 2020;22:1915–1924. doi: 10.1111/dom.14124
7. Wang Z, Deng H, Ou C, Liang J, Wang Y, Jiang M, Li S. Clinical symptoms, comorbidities and complications in severe and non-severe patients with COVID-19: A systematic review and meta-analysis without cases duplication. *Medicine (Baltimore)*. 2020;99:e23327. doi: 10.1097/MD.0000000000023327
8. World Helth Organization. Information note on COVID-19 and non-communicable diseases. https://www.who.int/publications/m/item/covid-19-and-ncds
9. Pranata R, Lim MA, Huang I, Raharjo SB, Lukito AA. Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: a systematic review, meta-analysis and meta-regression. *J Renin Angiotensin Aldosterone Syst*. 2020;21:1470320320926899. doi: 10.1177/1470320320926899
10. Iaccarino G, Grassi G, Borghi C, Ferri C, Salvetti M, Volpe M; SARS-RAS Investigators. Age and multimorbidity predict death among COVID-19 patients: results of the SARS-RAS study of the Italian Society of Hypertension. *Hypertension*. 2020;76:366–372. doi: 10.1161/HYPERTENSIONAHA.120.15324
11. Gupta S, Hayek SS, Wang W, Chan L, Mathews KS, Melamed ML, Brenner SK, Leonberg-Yoo A, Schenck EJ, Radbel J, et al; STOP-COVID Investigators. Factors associated with death in critically Ill patients with coronavirus disease 2019 in the US. *JAMA Intern Med*. 2020;180:1436–1447. doi: 10.1001/jamainternmed.2020.3596
12. Sun Y, Guan X, Jia L, Xing N, Cheng L, Liu B, Zhang S, He K. Independent and combined effects of hypertension and diabetes on clinical outcomes in patients with COVID-19: a retrospective cohort study of Huoshen Mountain Hospital and Guanggu Fangcang Shelter Hospital. *J Clin Hypertens (Greenwich)*. 2021;23:218–231. doi: 10.1111/jch.14146
13. Savoia C, Volpe M, Kreutz R. Hypertension, a moving target in COVID-19: current views and perspectives. *Circ Res*. 2021;128:1062–1079. doi: 10.1161/CIRCRESAHA.121.318054
14. Bauer AZ, Gore R, Sama SR, Rosiello R, Garber L, Sundaresan D, McDonald A, Arruda P, Kriebel D. Hypertension, medications, and risk of severe COVID-19: A Massachusetts community-based observational study. *J Clin Hypertens (Greenwich)*. 2021;23:21–27. doi: 10.1111/jch.14101
15. Sheppard JP, Nicholson BD, Lee J, McGagh D, Sherlock J, Koshiaris C, Oke J, Jones NR, Hinton W, Armitage L, et al. Association between blood pressure control and coronavirus disease 2019 outcomes in 45 418 symptomatic patients with hypertension: an observational cohort study. *Hypertension*. 2021;77:846–855. doi: 10.1161/HYPERTENSIONAHA.120.16472
16. Kreutz R, Algharably EAE, Azizi M, Dobrowolski P, Guzik T, Januszewicz A, Persu A, Prejbisz A, Riemer TG, Wang JG, et al. Hypertension, the renin-angiotensin system, and the risk of lower respiratory tract infections and lung injury: implications for COVID-19. *Cardiovasc Res*. 2020;116:1688–1699. doi: 10.1093/cvr/cvaa097
17. Tadic M, Saeed S, Guido Grassi G, Taddei S, Mancia G, Cuspidi C. Hypertension and COVID-19: Ongoing Controversies. *Front Cardiovasc Med*. 2021;8:639222. doi:10.3389/fcvm.2021.639222
18. World Health Organization. Hypertension and COVID-19: scientific brief, 17 June 2021. World Health Organization. 2021. https://apps.who.int/iris/handle/10665/341848
19. World Health Organization. Laboratory testing for coronavirus disease (COVID-19) in suspected human cases: interim guidance, 19 March 2020. World Health Organization. 2020. http://apps.who.int/iris/handle/10665/331501
20. Flisiak R, Horban A, Jaroszewicz J, Kozielewicz D, Pawłowska M, Parczewski M, Piekarska A, Simon K, Tomasiewicz K, Zarębska-Michaluk D. Management of SARS-CoV-2 infection: recommendations of the polish association of epidemiologists and infectiologists as of March 31, 2020. *Pol Arch Intern Med*. 2020;130:352–357. doi: 10.20452/pamw.15270
21. Flisiak R, Horban A, Jaroszewicz J, Kozielewicz D, Pawłowska M, Parczewski M, Piekarska A, Simon K, Tomasiewicz K, Zarębska-Michaluk D. Management of SARS-CoV-2 infection: recommendations of the polish association of epidemiologists and infectiologists. Annex no. 1 as of June 8, 2020. *Pol Arch Intern Med*. 2020;130:557–558. doi: 10.20452/pamw.15424
22. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, et al; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39:3021–3104. doi: 10.1093/eurheartj/ehy339
23. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, et al; ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J*. 2020;41:255–323. doi: 10.1093/eurheartj/ehz486
24. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, et al; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41:111–188. doi: 10.1093/eurheartj/ehz455
25. Niklas A, Marcinkowska J, Kozela M, Pająk A, Zdrojewski T, Drygas W, Piwońska A, Kwaśniewska M, Kozakiewicz K, Tykarski A. Blood pressure and cholesterol control in patients with hypertension and hypercholesterolemia: the results from the Polish multicenter national health survey WOBASZ II. *Pol Arch Intern Med*. 2019;129:864–873. doi: 10.20452/pamw.15013
26. Reboussin DM, Allen NB, Griswold ME, Guallar E, Hong Y, Lackland DT, Miller EPR 3rd, Polonsky T, Thompson-Paul AM, Vupputuri S. Systematic review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2018;138:e595–e616. doi: 10.1161/CIR.0000000000000601

27. Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, Alexander L, Estep K, Hassen Abate K, Akinyemiju TF, et al. Global Burden of Hypertension and Systolic Blood Pressure of at Least 110 to 115 mm Hg, 1990-2015. *JAMA*. 2017;317:165–182. doi: 10.1001/jama.2016.19043
28. de Almeida-Pititto B, Dualib PM, Zajdenverg L, Dantas JR, de Souza FD, Rodacki M, Bertoluci MC; Brazilian Diabetes Society Study Group (SBD). Severity and mortality of COVID 19 in patients with diabetes, hypertension and cardiovascular disease: a meta-analysis. *Diabetol Metab Syndr*. 2020;12:75. doi: 10.1186/s13098-020-00586-4
29. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, Bonanomi E, Cabrini L, Carlesso E, Castelli G, et al; COVID-19 Lombardy ICU Network. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. *JAMA Intern Med*. 2020;180:1345–1355. doi: 10.1001/jamainternmed.2020.3539
30. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 2020;579:270–273. doi: 10.1038/s41586-020-2012-7
31. Patel AB, Verma A. COVID-19 and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: what is the evidence? *JAMA*. 2020;323:1769–1770. doi: 10.1001/jama.2020.4812
32. Sparks MA, South AM, Badley AD, Baker-Smith CM, Batlle D, Bozkurt B, Cattaneo R, Crowley SD, Dell'Italia LJ, Ford AL, et al. Severe acute respiratory syndrome coronavirus 2, COVID-19, and the renin-angiotensin system: pressing needs and best research practices. *Hypertension*. 2020; 76:1350–1367. doi: 10.1161/HYPERTENSIONAHA.120.15948
33. Kjeldsen SE, Narkiewicz K, Burnier M, Oparil S. Potential protective effects of antihypertensive treatments during the Covid-19 pandemic: from inhibitors of the renin-angiotensin system to beta-adrenergic receptor blockers. *Blood Press*. 2021;30:1–3. doi: 10.1080/08037051.2021.1862483
34. de Abajo FJ, Rodríguez-Miguel A, Rodríguez-Martín S, Lerma V, García-Lledó A; MED-ACE2-COVID19 Study Group. Impact of in-hospital discontinuation with angiotensin receptor blockers or converting enzyme inhibitors on mortality of COVID-19 patients: a retrospective cohort study. *BMC Med*. 2021;19:118. doi: 10.1186/s12916-021-01992-9
35. Ren L, Yu S, Xu W, Overton JL, Chiamvimonvat N, Thai PN. Lack of association of antihypertensive drugs with the risk and severity of COVID-19: A meta-analysis. *J Cardiol*. 2021;77:482–491. doi: 10.1016/j.jjcc.2020.10.015
36. Singh S, Offringa-Hup AK, Logtenberg SJJ, Van der Linden PD, Janssen WMT, Klein H, Waanders F, Simsek S, de Jager CPC, Smits P, et al. Discontinuation of antihypertensive medications on the outcome of hospitalized patients with severe acute respiratory syndrome-coronavirus 2. *Hypertension*. 2021;78:165–173. doi: 10.1161/HYPERTENSIONAHA.121.17328
37. Shibata S, Arima H, Asayama K, Hoshide S, Ichihara A, Ishimitsu T, Kario K, Kishi T, Mogi M, Nishiyama A, et al. Hypertension and related diseases in the era of COVID-19: a report from the Japanese Society of Hypertension Task Force on COVID-19. *Hypertens Res*. 2020;43:1028–1046. doi: 10.1038/s41440-020-0515-0
38. Rezel-Potts E, Douiri A, Chowienczyk PJ, Gulliford MC. Antihypertensive medications and COVID-19 diagnosis and mortality: population-based case-control analysis in the United Kingdom. *Br J Clin Pharmacol*. 2021;87:4598–4607. doi: 10.1111/bcp.14873
39. Ran J, Song Y, Zhuang Z, Han L, Zhao S, Cao P, Geng Y, Xu L, Qin J, He D, et al. Blood pressure control and adverse outcomes of COVID-19 infection in patients with concomitant hypertension in Wuhan, China. *Hypertens Res*. 2020;43:1267–1276. doi: 10.1038/s41440-020-00541-w
40. Semenzato L, Botton J, Drouin J, Baricault B, Vabre C, Cuenot F, Penso L, Herlemont P, Sbidian E, Weill A, et al. Antihypertensive drugs and COVID-19 risk: a cohort study of 2 million hypertensive patients. *Hypertension*. 2021;77:833–842. doi: 10.1161/HYPERTENSIONAHA.120.16314
41. Rovas A, Osiaevi I, Buscher K, Sackarnd J, Tepasse PR, Fobker M, Kühn J, Braune S, Göbel U, Thölking G, et al. Microvascular dysfunction in COVID-19: the MYSTIC study. *Angiogenesis*. 2021;24:145–157. doi: 10.1007/s10456-020-09753-7
42. Bernard I, Limonta D, Mahal LK, Hobman TC. Endothelium infection and dysregulation by SARS-CoV-2: evidence and caveats in COVID-19. *Viruses*. 2020;13:E29. doi: 10.3390/v13010029