Antihypertensives and their relation to mortality by SARS-CoV-2 infection

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Abstract
The role of antihypertensives, especially Renin–Angiotensin–Aldosterone System inhibitors, is still debatable in COVID-19-related severity and outcome. Therefore, we search for a more global analysis of antihypertensive medication in relation to SARS-CoV-2 severity using prescription data worldwide. The association between the percentage use of different types of antihypertensive medications and mortality rates due to a SARS-CoV-2 infection during the first 3 weeks of the pandemic was analyzed using random effects linear regression models for 30 countries worldwide. Higher percentages of prescribed angiotensin receptor blockers (ARBs) (β, 95% confidence interval [CI]; −0.02 [−0.04 to −0.0012]; p = .042) and calcium channel blockers (CCBs) (β, 95% CI; −0.023 [−0.05 to −0.0028]; p = .0304) were associated with a lower first 3-week SARS-CoV-2–related death rate, whereas a higher percentage of prescribed angiotensin-converting enzyme inhibitors (ACEis) (β, 95% CI; 0.03 [0.0061–0.05]; p = .0103) was associated with a higher first 3-week death rate, even when adjusted for age and metformin use. There was no association between the amount of prescribed beta-blockers (BBs) and diuretics (Diu) and the first 3-week death rate. When analyzing the combination of drugs that is used by at least 50% of antihypertensive users, within the different countries, countries with the lowest first 3-week death rates had at least an angiotensin receptor blocker as one of the most often prescribed antihypertensive medications (ARBs/CCBs: [β, 95% CI; −0.02 [−0.03 to −0.004]; p = .009], ARBs/BBs: [β, 95% CI; −0.03 [−0.05 to −0.006]; p = .01]). Finally, countries prescribing high-potency ARBs had lower first 3-week ARBs. In conclusion, ARBs and CCB seem to have a protective effect against death from SARS-CoV-2 infection.

KEYWORDS
angiotensin-converting enzyme inhibitor, angiotensin receptor blockers, CVOID-19, RAAS blockers, SARS-CoV-2

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1 | INTRODUCTION

The current pandemic of the SARS-CoV-2 coronavirus has infected millions of people worldwide.1,2 Ongoing efforts globally are pursued to find an effective treatment. Early epidemiological data suggest that individuals with chronic underlying comorbidities such as hypertension, diabetes, and coronary artery disease were at particular risk for a severe infection,3-6 but it is not clear whether this is due to older age, and the associated impaired immune system, or the comorbidities themselves, which the elderly more often have. However, one of the existing hypotheses revolves around the widespread use of RAAS inhibitors, as it has been shown that the SARS-CoV-2 virus uses ACE2, a member of the RAAS system, to enter its host.3-5

It was shown that the SARS-CoV-2 virus uses the membrane-bound ACE2 receptor and enzyme to enter lung epithelial cells,7,8 and that by this process, it is broken down. It was, therefore, suggested that patients who use ACEi and ARBs are presumed to have increased ACE2 expression levels and are therefore prone to more severe SARS-CoV-2 infection, owing to which these antihypertensive medications should be temporarily discontinued.3-6 However, no confirmative evidence is given for this hypothesis. Most of the ACE2 is membrane-bound with a very low level in the soluble form,9-11 and shedding of ACE2 often increases in the pathological state.12,13 Besides, it was suggested that RAAS blocking agents could reverse this shedding, which could therefore increase the level of membrane-bound ACE2, and therefore of infectious sites. As most of the ACE2 is already membrane-bound, the decrease in shedding will not affect the proportional change of membrane-bound ACE2, and therefore will not lead to a meaningful change in SARS-CoV-2 binding.14 Besides, no confirmative evidence has shown that ACEi increases ACE2, neither the soluble nor the membrane-bound form, whereas for ARBs, an increase might be speculated.15-17 In contrast, it has also been suggested that ARBs could play a protective role, that is, they might restore the membrane-bound ACE2 levels, which are being broken down during SARS-CoV-2 infection of the cell.18,19 Besides, they could potentially block the deleterious effects of angiotensin II, which is no longer broken down by ACE2, as it is no longer available. These (by a viral infection) increased angiotensin II levels, lead to cellular apoptosis, cytokine release, lung oedema, and eventual ARDS.5,20-22

The debate on how RAAS inhibitors influence SARS-CoV-2 infections has been subject to many clinical investigations. A recently published meta-analysis suggested no significant increased risk for infection by SARS-CoV-2,23-26 or a more severe outcome in patients using RAAS inhibitors.27,28 Some of these observational studies even suggested that they lower disease severity due to a SARS-CoV-2 infection.23,24,27,29 The most important bias in this analysis is that both ACEi and ARBs are often combined in the analysis; however, they will not exert the same effect. Besides, when analyzing at-home antihypertensive medication within a hospital or even ICU admission, this poses a problem, as often antihypertensive medication will be withdrawn in patients with a severe disease.30,31 This will lead to a confounding effect and will cause bias, because the withdrawal of favorable medication will falsely lead to the assumption that it caused a deleterious outcome. Therefore, to get a broader view on how antihypertensive medication and particular RAAS inhibitors are associated with the severity of a SARS-CoV-2 infection, we analyzed global prescription data of 30 countries on antihypertensive medication and its relation to mortality due to the SARS-CoV-2 virus.

2 | METHODOLOGY

Medication prescription data on different types of antihypertensive medications (prescribed for hypertension or any other condition as a whole) and metformin were obtained for 30 countries worldwide, utilizing IQVIA MIDAS data. MIDAS is an overlay set of internationalization features, designed to standardize local output and make cross-country analysis possible and easier. MIDAS data are entirely based on the locally reported core data elements of selected local audits. Data for publication in local audits are entirely handled and collected at a local level. The core items of data collection across all IQVIA audits are the pack form, strength, size and volume, the product name, the manufacturer, and the number of packs delivered/sold through the measured channels. Besides, we identified SARS-CoV-2-related daily mortality data from the “Johns Hopkins University coronavirus resource center” website (https://coronavirus.jhu.edu/map.html) First, we collected mortality data from the first day that mortality for a particular country was reported until the third week. We only analyzed the first 3 weeks, as this would provide the least influenced death rate data, and in these first three weeks, the virus would be new to all countries around the world, and therefore there would be no standard adaptations to the virus within a country yet. Therefore, this will lead to the best outcome parameter to be used, to compare outcomes between countries. Second, as viral multiplication and spread, as well as death rates, behave exponentially, we log-transformed these deaths to the natural log (e) and plotted against time to generate a linear first 3-week death rate slope, which can be used in linear regression modeling. This slope (death rate) was plotted against the percentage use of individual antihypertensive medications.

The primary outcome of interest was the association between “first 3-week death rates” and the percentage use of different antihypertensive medications for a given country. Second, we created univariate regression models for the association of the use of ACE inhibitors, ARBs, beta-blockers, calcium channel blockers, and diuretics (Diu) with the death rates for each country. We used random effects models with inverse weighing with the squared standard error (SE) of the first 3-week death rate slope in the analysis. Third, we corrected our analysis for differences in the median age of the various populations and the number of individuals on metformin use within a specific country and showed mutually adjusted outcomes. This is important because we want to correct for the burden of comorbidities in aging countries and the burden of diabetes within a country. Besides, metformin use was shown to be significantly related to the first 3-week death rate, which can therefore be seen as a
confounder. As the relationship between antihypertensive medication and the first 3-week death rate will be driven by which medication is used by most individuals within a country, we also analyzed the weighted mean of the first 3-week death rate for countries in which ≥50% of antihypertensive users were using the same dual combination. This outcome was validated by logistic regression analysis of all possible dual combinations, irrespective of the percentages used within a country and its relationship with the mean of the first 3-week death rate, adjusted for the median age of a country and metformin use. Finally, to be able to substantiate our findings on ARB and its relation with the first 3-week death rate, we also analyzed our data, taking into consideration the different pharmacokinetics and pharmacodynamics properties that different ARBs might have. For that matter, we analyzed whether countries prescribing more potent ARBs would have a lower first 3-week death rate as compared with countries prescribing less potent ARBs. We have defined high or low potency according to receptor affinity and half-life, where, for instance, Losartan has a half-life of 3–6 h and a low receptor affinity, and Telmisartan has a half-life of 20–24 h and has the highest receptor affinity of all ARBs. Therefore, we grouped Telmisartan and Irbesartan as high-potency ARBs and the rest as low-potency ARBs. We used RStudio for the regression analysis and GraphPad QuickCalcs (https://www.graphpad.com/quickcalcs/) online tool for comparing the weighted means of a death rate.

3 | RESULTS

The most prescribed antihypertensive medications worldwide are diuretics (25%) and beta-blockers (25%), followed by calcium channel blockers (24%), ARBs (21%), and ACEi (19%) as the least prescribed antihypertensive medications (Table 1). The use of the different types of antihypertensive medications was very different between countries (Table 1). The percentage use of diuretics was 36% for Spain versus 14% for Japan, for beta-blockers, it was 37% for Belgium versus 12% for Japan, for calcium channel blockers, it was 46% for Japan versus 15% for South Africa, for ARBs, it was 51% for South Korea versus 12% for the UK, and for ACEi, it was 35% for Hungry versus 1% for South Korea. When analyzing the type of antihypertensive medication and its relation with the first 3-week death rate of a SARS-CoV-2 infection (Table 2), we observed that ARBs (β, 95% confidence interval [CI] −0.02 [−0.04 to −0.001]; p = .03) and CCB (β, 95% CI −0.02 [−0.05 to −0.002]; p = .03) were significantly associated with a lower first 3-week death rate, whereas ACEi (β, 95% CI 0.03 [0.006–0.05]; p = .01) was significantly associated with a higher first 3-week death rate of a SARS-CoV-2 infection (Figures 1–3), even after correcting for median age and metformin use within a country (Table 2). In addition, when analyzing the use of metformin and its relation to the first 3-week death rate, we found that metformin (β, 95% CI 0.02 [0.002–0.04]; p = .02) use was significantly associated with a higher first 3-week death rate, even after correcting for the median age (Table 2). When mutually correcting for all antihypertensive drugs, only the amount of prescribed BB (β, 95% CI −0.05 [−0.09 to −0.002]; p = .04) was independently associated with a lower first 3-week death rate.

A single antihypertensive drug analysis, as well as a mutually adjusting antihypertensive drug analysis, by no means determines which antihypertensive is the most important driver of its relationship with the first 3-week death rate, as only a small portion of individuals will either use a single drug or all five of them. Therefore, we also analyzed which dual combination of medications was used by at least 50% of the individuals on antihypertension medication within each country and analyzed the mean first 3-week death rate among countries with the same combinations (Table 3). Of the 10 possible dual combinations, 8 could be observed in more than 50% of the antihypertensive users in any of the countries. A dual combination with an ARB accounted for the lowest and second-lowest first 3-week death rates (0.48 for lowest death rate [ARB/CCB] and 0.71 for second-lowest first 3-week death rate [ARB/BB]), whereas a dual combination with a BB accounted for the highest and second-highest first 3-week death rate (1.72 highest death rate [BB/Diu] and 1.54 for second-highest death rate [BB/CCB]; Figure 3B). Besides, when analyzing all possible dual combinations in a logistic regression model, correcting for the median age and metformin use, similar results were obtained (Table 4).

To substantiate the finding that countries with the lowest death rate have the highest amount of ARB users, we analyzed whether a proxy of a dose–response relationship could be observed. Dose–response relationships often strengthen single observation and are therefore effective in crude analysis. For that matter, we analyzed whether countries prescribing a higher amount of more potent ARBs would have lower first 3-week death rates as compared with countries prescribing a higher amount of less potent ARBs. Interestingly, we were able to show that countries prescribing higher amounts of more potent ARBs had lower first 3-week death rates (β, 95% CI −0.01 [−0.03 to −0.0000]; p = .04). Unfortunately, due to lack of power owing to the small sample size, significance was lost (β, 95% CI −0.01 [−0.03 to 0.003]; p = .12) after adjusting for the median age and metformin use.

4 | DISCUSSION

In the present study, we show that countries that mainly prescribe antihypertensive drug combinations with an ARB had a lower first 3-week death rate due to a SARS-CoV-2 infection and even more so in countries prescribing a higher amount of more potent ARBs. However, beta-blocker was the only independent antihypertensive drug that was related to a lower first 3-week death rate. It remains to be elucidated whether this is due to blocking of the neurohumoral response or the combination with a high-potency ARB. In addition, countries with higher prescriptions of either an ACEi or a diuretic had worse outcomes in terms of mortality.

As mentioned in the introduction, most studies that investigated antihypertensive medication and its relationship with SARS-CoV-2 infection focused on the question that whether the
use of RAAS inhibitors could worsen the outcome of a SARS-CoV-2 infection. However, most of these studies have considered ARBs and ACEi together in the analysis. In addition, they were also biased, because at-home medication is often withdrawn in severely ill patients admitted to the hospital. We believe that in our analysis, we show a more global gradual effect of antihypertensive medication on the first 3-week death rate due to a SARS-CoV-2 infection, also taking into account individuals who have died outside the hospital.

A better way of analyzing the relationship between at-home antihypertensive medication and the severity of a SARS-CoV-2 infection would be to also include individuals who have died outside the hospital, rendering a better impression on the relationship between SARS-CoV-2 infection and mortality. Unfortunately, only a handful of studies investigated the effect of at-home antihypertensive medication and overall population mortality. For instance, the study by Reynolds et al. showed the relationship between at-home medication and SARS-CoV-2-positive tests in

| Country   | ACEi (%) | ARBs (%) | Diuretics (%) | Beta-blockers (%) | Calcium channel blockers (%) | Metformin (%) | Cumulative (%) |
|-----------|----------|----------|--------------|-----------------|-----------------------------|--------------|----------------|
| China     | 8        | 19       | 21           | 16              | 40                          | 44           | 104            |
| France    | 19       | 22       | 28           | 27              | 22                          | 64           | 118            |
| Italy     | 24       | 23       | 31           | 27              | 18                          | 74           | 123            |
| South Korea | 1       | 51       | 21           | 16              | 44                          | 59           | 133            |
| USA       | 20       | 15       | 26           | 30              | 17                          | 66           | 108            |
| Spain     | 24       | 27       | 36           | 20              | 15                          | 68           | 122            |
| UK        | 25       | 12       | 18           | 23              | 23                          | 70           | 101            |
| Netherlands | 20      | 16       | 25           | 29              | 17                          | 68           | 107            |
| Switzerland | 19     | 28       | 30           | 26              | 18                          | 73           | 121            |
| Belgium   | 23       | 16       | 27           | 37              | 20                          | 70           | 123            |
| Germany   | 22       | 20       | 25           | 28              | 16                          | 59           | 111            |
| Australia | 20       | 31       | 24           | 23              | 20                          | 62           | 118            |
| Austria   | 24       | 25       | 31           | 30              | 16                          | 67           | 126            |
| Canada    | 24       | 19       | 24           | 23              | 19                          | 67           | 109            |
| Greece    | 12       | 37       | 33           | 28              | 22                          | 70           | 132            |
| Ireland   | 22       | 21       | 21           | 24              | 24                          | 66           | 112            |
| Norway    | 12       | 31       | 25           | 29              | 19                          | 75           | 116            |
| Sweden    | 16       | 21       | 22           | 29              | 19                          | 78           | 107            |
| Bulgaria  | 22       | 19       | 29           | 31              | 22                          | 68           | 123            |
| Japan     | 3        | 35       | 14           | 12              | 46                          | 35           | 110            |
| Luxembourg | 14      | 33       | 27           | 32              | 16                          | 63           | 122            |
| Mexico    | 18       | 42       | 23           | 17              | 18                          | 79           | 118            |
| Poland    | 17       | 24       | 27           | 27              | 32                          | 76           | 127            |
| Portugal  | 25       | 27       | 36           | 22              | 21                          | 69           | 131            |
| Russia    | 29       | 15       | 24           | 26              | 16                          | 60           | 110            |
| Turkey    | 21       | 27       | 36           | 30              | 23                          | 63           | 137            |
| Czech Republic | 32 | 17       | 26           | 25              | 25                          | 71           | 125            |
| Finland   | 15       | 25       | 23           | 31              | 18                          | 79           | 112            |
| Hungary   | 35       | 12       | 26           | 31              | 23                          | 67           | 127            |
| South Africa | 24     | 27       | 36           | 20              | 15                          | 45           | 122            |
| Total     | 19%      | 21%      | 25%          | 25%             | 24%                         | 58%          |                |

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
TABLE 2  Association of individual antihypertensive medication and metformin with COVID-19-related first 3-week death rate

|                                | Unadjusted | Adjusted a |
|--------------------------------|------------|------------|
| Angiotensin II receptor blockers | −0.02 (−0.04 to −0.002)* | −0.02 (−0.04 to −0.001)* |
| Angiotensin converting enzyme inhibitor | 0.03 (0.01–0.06)* | 0.03 (0.006–0.05)* |
| Beta-blockers                   | 0.02 (−0.01 to 0.05) | −0.001 (−0.04 to 0.04) |
| Calcium channel blockers        | −0.03 (−0.05 to −0.009)* | −0.02 (−0.05 to −0.002)* |
| Diuretics                       | 0.02 (−0.02 to 0.05) | 0.01 (−0.02 to 0.05) |
| Metformin                       | 0.02 (0.003–0.04)* | 0.02 (0.002–0.04)* |

Abbreviation: CI, confidence interval.
aAdjusted antihypertensive = corrected for age and metformin; Adjusted metformin = corrected for age.
*p < .05.

FIGURE 1  (A) Percentage use of angiotensin-converting enzyme inhibitors in a country with COVID-19-related first 3-week death rate (β, 95% CI; 0.03 [0.01–0.06]; p = .003). (B) Percentage use of angiotensin II receptor blockers (ARBs) use in a country with COVID-19-related first 3-week death rate (β, 95% CI; −0.02 [−0.04 to −0.002]; p = .02). CI, confidence interval.

FIGURE 2  (A) Percentage use of calcium channel blockers used in a country with COVID-19-related first 3-week death rate (β, 95% CI; −0.03 [−0.05 to −0.009]; p = .004). (B) Percentage use of beta-blockers used in a country with COVID-19 related first 3-week death rate (β, 95% CI; 0.02 [−0.01 to 0.05]; p = .21). CI, confidence interval.
about 12,000 individuals of the general population. They observed no differences in the number of positive tests among any of the antihypertensive medications, as compared with individuals not using any medication, implying that antihypertensive medication does not prevent infection. In addition, others showed no significant increased risk of getting infected by the SARS-CoV-2 virus or a more severe outcome, that is, hospitalization, among individuals from the general population that used antihypertensive medication.\textsuperscript{24,25,33} From these data, one can conclude that the likelihood of getting infected is not different between individuals using antihypertensive medication and the ones who do not use such medication. By no means does this tell us that individuals using any of the antihypertensive medications have a worse outcome. Besides, individuals who use antihypertensive medication, even RAAS inhibitors, will still have a membrane-bound ACE2 that will be targeted by the virus, leading to infection, so no protection against infection was anticipated in the first place. Besides, all these studies used data of a limited amount of countries, where it is often the case that within a certain country, certain types and brands of drugs are preferably prescribed. By analyzing global prescription data, many different antihypertensive drugs can be analyzed, resulting in a better overall impression on the relationship of antihypertensive medication and their relationship with the severity of the disease.

4.1 Strength and limitations

In our study, we used the replication rate of the SARS-CoV-2, reflected as the first 3-week death rate as the outcome. Whether this is a true reflection of the virus replication rate is not known, even though many have used it that way. However, we believe that in the first 3 weeks that a country encounters this unknown virus, it is reasonable to assume that it reflects virus replication, as many countries will not take measures and will test most cases, especially the ones with a severe disease who at the end will succumb to it. Second, we also took into account out-of-hospital mortality when analyzing at-home antihypertensive medication and death from a SARS-CoV-2 infection, whereas most other studies only analyzed in-hospital mortality. Third, we tried to substantiate our findings in three different ways: first, by analyzing the effect of dual combination used by more than 50% of antihypertensive users within a country; second, by analyzing in a logistic regression analysis whether this dual combination when corrected for median age and metformin use would still render the same result; third, by analyzing whether there is a dose–response relationship in our observed results. We believe by being able to show that ARB medication is associated with a lower first 3-week death rate in a single antihypertensive drug analysis, two different dual combination of medications analyses and in a dose–response effect (ARB potency) analysis, underscores the strength of our study.

As most countries only prescribe low-potency angiotensin receptor blockers, with low affinity for the receptor, often dosed once a day while half-life is max 6 h, it can be argued whether sufficient angiotensin II type 1 (AT1) receptor blockade should be expected to fully block the deleterious effects of the high angiotensin II levels. However, we are aware that our results regarding the potency of ARB use lack potential, as significance was lost after adjusting for the median age and metformin use in a country. Finally, as we did not analyze patient-level data and therefore could not control for other underlying comorbidities, our results should be interpreted with caution.

It is important to keep in mind that although they are called antihypertensive medications, they need not be prescribed for hypertension alone, to be analyzed as a whole. We analyzed prescribed antihypertensive medication, irrespective of the underlying disease. This might lead to confounding, but the decision for each underlying condition to choose any of the antihypertensive medication will not differ so much between countries, as they are all bound by similar
guidelines. Besides, any confounding in that area also holds true for other publications on that matter, investigating antihypertensive medication. Major bias can be expected by differences in the quality of the healthcare systems of different countries. However, if this would be the case, the three countries most often with the top three best healthcare systems (the United Kingdom, Australia, and the Netherlands) did not have the lowest death rates. To strengthen the analysis, we corrected the data for the median age within a country and metformin use. By correcting for the median age in a country and metformin use, aging and, indirectly, the health status of a country is

**TABLE 3**

Antihypertensive dual combinations and their percentages of use within each country

| Countries      | ARB–CCB (%) | ARBs–BB (%) | Diu–CCB (%) | Diu–ACEI (%) | ACEI–BB (%) | Diu–ARB (%) | Diu–BB (%) | BB–CCB (%) |
|----------------|------------|------------|------------|-------------|-------------|-------------|------------|------------|
| South Korea    | 95 (51–44) | –          | –          | –           | –           | –           | –          | –          |
| Japan          | 81 (35–46) | –          | –          | –           | –           | –           | –          | –          |
| Total          | 88 (43–45) | –          | –          | –           | –           | –           | –          | –          |
| Finland        | –          | 56 (25–31) | –          | –           | –           | –           | –          | –          |
| Norway         | –          | 60 (31–29) | –          | –           | –           | –           | –          | –          |
| Luxembourg     | –          | 65 (33–32) | –          | –           | –           | –           | –          | –          |
| Total          | –          | 60 (30–30) | –          | –           | –           | –           | –          | –          |
| China          | –          | –          | 61 (21–40) | –           | –           | –           | –          | –          |
| Poland         | –          | –          | 59 (27–32) | –           | –           | –           | –          | –          |
| Total          | –          | –          | 60 (24–36) | –           | –           | –           | –          | –          |
| Canada         | –          | –          | –          | 48 (24–24)  | –           | –           | –          | –          |
| Czech          | –          | –          | –          | 58 (26–32)  | –           | –           | –          | –          |
| Total          | –          | –          | –          | 53 (25–28)  | –           | –           | –          | –          |
| Hungary        | –          | –          | –          | 66 (35–31)  | –           | –           | –          | –          |
| Russia         | –          | –          | –          | 55 (29–26)  | –           | –           | –          | –          |
| Uk             | –          | –          | –          | 48 (25–23)  | –           | –           | –          | –          |
| Total          | –          | –          | –          | 56 (30–26)  | –           | –           | –          | –          |
| Spain          | –          | –          | –          | –          | 63 (36–27)  | –           | –          | –          |
| Switzerland    | –          | –          | –          | –          | 58 (36–27)  | –           | –          | –          |
| Australia      | –          | –          | –          | –          | 55 (24–31)  | –           | –          | –          |
| Greece         | –          | –          | –          | –          | 70 (33–37)  | –           | –          | –          |
| Mexico         | –          | –          | –          | –          | 65 (23–42)  | –           | –          | –          |
| Portugal       | –          | –          | –          | –          | 63 (36–27)  | –           | –          | –          |
| South Africa   | –          | –          | –          | –          | 63 (36–27)  | –           | –          | –          |
| Total          | –          | –          | –          | –          | 62 (32–31)  | –           | –          | –          |
| France         | –          | –          | –          | –          | –          | 55 (28–27)  | –          | –          |
| Italy          | –          | –          | –          | –          | –          | 58 (31–27)  | –          | –          |
| USA            | –          | –          | –          | –          | –          | 56 (26–30)  | –          | –          |
| Netherlands    | –          | –          | –          | –          | –          | 54 (25–29)  | –          | –          |
| Belgium        | –          | –          | –          | –          | –          | 64 (27–37)  | –          | –          |
| Germany        | –          | –          | –          | –          | –          | 53 (25–28)  | –          | –          |
| Total          | –          | –          | –          | –          | –          | 57 (27–30)  | –          | –          |
| Ireland        | –          | –          | –          | –          | –          | –          | 48 (24–24) | –          |

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; Diu, diuretics.
TABLE 4  Association of COVID-19-related first 3-week death rate with any dual combination, irrespective of percentage use within a country

| Variables | β (95% CI) | Unadjusted | Adjusted* |
|-----------|------------|------------|-----------|
| ARBs/CCB | -0.02 (-0.03 to 0.007)* | -0.02 (-0.03 to 0.004)* |
| ARBs/BB | -0.02 (-0.04 to 0.006) | -0.03 (-0.05 to -0.006)* |
| ARBs/diuretics | -0.012 (-0.03 to 0.006) | -0.01 (-0.03 to 0.005) |
| ACEI/BB | 0.02 (0.005 to 0.04) | 0.01 (-0.004 to 0.03) |
| ACEI/diuretics | 0.02 (0.003 to 0.03)* | 0.02 (0.0000 to 0.03)* |
| BB/CCB | -0.03 (-0.06 to -0.005)* | -0.03 (-0.06 to -0.009)* |
| BB/diuretics | 0.01 (-0.007 to 0.03) | 0.004 (-0.02 to 0.03) |
| CCB/diuretics | -0.03 (-0.06 to -0.007)* | -0.02 (-0.05 to 0.002) |

*Adjusted for age and metformin.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta-blocker; CCB, calcium channel blocker.

*p < .05.

taken into account, as it reflects the number of individuals who have comorbidities and diabetes, and indirectly obesity. Besides, most diseases for which antihypertensive medication is prescribed, that is, hypertension, diabetes, and cardiovascular disease, have insulin resistance as a common denominator. Therefore, it can be anticipated that these diseases will not differ that much in whether they have an increased risk to a more severe SARS-CoV-2 infection. Finally, these assumptions are the same for each country and are therefore annulled when analyzing effects between countries.

5  CONCLUSION

Countries that mostly prescribed ARBs had the lowest first 3-week death rates, and BB was only independently related to a lower first 3-week death rate. On the contrary, the true beneficial effect of these medications might be obscured in countries in which less potent angiotensin receptor blockers are prescribed. However, it remains to be elucidated whether this is due to blocking of the neurohumoral response or the combination with a high-potency angiotensin receptor blocker.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Sandeep Singh and Sara-Joan Pinto-Sietsma contributed toward the conception and design of research. Christine Widrich, Martijn Nap, and Emile Schokker contributed toward material collection. Sandeep Singh, Aeilko H. Zwinderman, and Sara-Joan Pinto-Sietsma performed analysis and interpretation. Sandeep Singh and Sara-Joan Pinto-Sietsma drafted the manuscript. Sara-Joan Pinto-Sietsma, Aeilko H. Zwinderman, Christine Widrich, Martijn Nap, and Emile Schokker edited and revised the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author on reasonable request.

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REFERENCES

1. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-481.
2. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-1720.
3. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-1720.
4. Esler M, Esler. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? J Hypertens. 2020;38(5):781-782.
5. Fang L, Karakulakakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 2020;8(4):e21.
6. Díaz JH. Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19. J Travel Med. 2020;27:3.
7. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271-280.
8. Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-273.
9. Serfozo P, Wysocki J, Gulua G, et al. Ang II (angiotensin II) conversion to angiotensin-(1-7) in the circulation is POP (prolyl oligopeptidase)- dependent and ACE2 (angiotensin-converting enzyme 2)-independent. Hypertension. 2020;75(1):173-182.
10. Arendse LB, Danser AHJ, Poglitsch M, et al. Novel therapeutic approaches targeting the renin-angiotensin system and associated peptides in hypertension and heart failure. Pharmacol Rev. 2019;71(4):539-570.
11. Danser AHJ, Epstein M, Battie D. Renin-angiotensin system blockers and the COVID-19 pandemic: at present there is no evidence to abandon renin-angiotensin system blockers. Hypertension. 2020;75(6):1382-1385.
12. Wysocki J, Goodling A, Burgaya M, et al. Urine RAS components in mice and people with type 1 diabetes and chronic kidney disease. Am J Physiol Renal Physiol. 2017;313(2):F487-F494.
13. Bitker L, Burrell LM. Classic and nonclassic renin-angiotensin systems in the critically ill. Crit Care Clin. 2019;35(2):213-227.
14. Danser AHJ, Epstein M, Battie D. Renin-angiotensin system blockers and the COVID-19 pandemic: at present there is no evidence to abandon renin-angiotensin system blockers. Hypertension. 2020;75(6):1382-1385.
15. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation. 2005;111(20):2605-2610.
16. Wang X, Ye Y, Gong H, et al. The effects of different angiotensin II type 1 receptor blockers on the regulation of the ACE-AngII-AT1 and ACE2-Ang(1-7)-Mas axes in pressure overload-induced cardiac remodeling in male mice. J Mol Cell Cardiol. 2016;97:180-190.
17. Soler MJ, Ye M, Wysocki J, William J, Llovers J, Batlle D. Localization of ACE2 in the renal vasculature: amplification by angiotensin II type 1 receptor blockade using telmisartan. *Am J Physiol Renal Physiol*. 2009;296(2):F398–F405.

18. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med*. 2005;11(8):875–879.

19. Dijkman R, Jebbink MF, Deijs M, et al. Replication-dependent downregulation of cellular angiotensin-converting enzyme 2 protein expression by human coronavirus NL63. *J Gen Virol*. 2012;93(Pt 9):1924–1929.

20. Hoffmann M, Kleine-Weber H, Schroder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181(2):271–280.

21. Offringa A, Montijn R, Singh S, Paul M, Pinto YM, Pinto-Sietsma S-J. The mechanistic overview of SARS-CoV-2 using angiotensin-converting enzyme 2 to enter the cell for replication: possible treatment options related to the renin-angiotensin system. *Eur Heart J Cardiovasc Pharmacother*. 2020;6(5):317–325.

22. Kuster GM, Pfister O, Burkard T, et al. SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19? *Eur Heart J*. 2020;41(19):1801–1803.

23. Liu X, Long C, Xiong Q, et al. Association of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with risk of COVID-19, inflammation level, severity, and death in patients with COVID-19: A rapid systematic review and meta-analysis. *Clin Cardiol*. 2020;1–10. https://doi.org/10.1002/clc.23421

24. Khera R, Clark C, Lu Y, et al. Association of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers with the risk of hospitalization and death in hypertensive patients with coronavirus disease-19. *medRxiv: Prepr Ser Health*. 2020. https://doi.org/10.1101/2020.05.17.20104943

25. Morales DR, Conover MM, You SC, et al. Renin-angiotensin system blockers and susceptibility to COVID-19: a multinational open science cohort study. *medRxiv: Prepr Ser Health*. 2020. https://doi.org/10.1101/2020.06.11.20125849

26. Fosbøl EL, Butt JH, Østergaard L, et al. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. *J Am Med Assoc*. 2020;324:168.

27. Garg A, Rout A, Sharma A, Fiorello B, Kostis JB. Association of renin angiotensin system blockers with outcomes in patients with COVID-19: a systematic review and meta-analysis. *Mayo Clin Proc*. 2020;95(11):2559–2561. https://doi.org/10.1016/j.mayocp.2020.05.23.20111401

28. Barochiner J, Martinez R. Use of inhibitors of the renin angiotensin system and COVID-19 prognosis: a systematic review and meta-analysis. *J Clin Pharm Ther*. 2020;45(6):1244–1252. https://doi.org/10.1111/jcph.13534

29. Zhang P, Zhu L, Cai J, et al. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circ Res*. 2020;126(12):1671–1681.

30. Lam KW, Chow KW, Vo J, et al. Continued in-hospital ACE inhibitor and ARB use in hypertensive COVID-19 patients is associated with positive clinical outcomes. *J Infect Dis*. 2020;222:1256–1264.

31. Cannata F, Chiarito M, Reimers B, et al. Continuation versus discontinuation of ACE inhibitors or angiotensin II receptor blockers in COVID-19: effects on blood pressure control and mortality. *Eur Heart J Cardiovasc Pharmacother*. 2020;6(6):412–414. https://doi.org/10.1093/ehjcvp/pvaa056

32. 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.

33. de Abajo PJ, Rodriguez-Martin S, Lerma V, et al. Use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. *Lancet*. 2020;395:1705–1714.

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