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Antihypertensive and its relation to mortality by SARS-CoV-2 infection

Running title: COVID-19 and antihypertensive

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Abstract

Background: Role of antihypertensive, especially Renin-Angiotensin-Aldosterone System (RAAS) inhibitors are still debatable in COVID-19 related severity and outcome. Therefore, we search for a more global analysis of antihypertensive medication in relation to SAS-CoV-2 severity using prescription data worldwide.

Methods: Association between percentage use of different types of anti-hypertensive medications and mortality rates due to a SARS-CoV-2 infection during the first three weeks of the pandemic were analyzed using random effects linear regression models for 30 countries worldwide.

Result: Both a higher percentages of prescribed angiotensin receptor blockers (ARBs) [β, 95% CI; -0.02(-0.04- -0.0012); p=0.042] and calcium channel blockers (CCB) [β, 95% CI; -0.023 (-0.05- -0.0028); p=0.0304] were associated with a lower first 3-week SARS-

CoV-2 related death rate, whereas higher percentages of prescribed angiotensin converting enzyme inhibitors (ACEi) [β, 95% CI; 0.03 (0.0061-0.05); p=0.0103] was associated with a higher first 3-week death rate, even when adjusted for age and metformin use. There was no association of the amount of prescribed beta blockers (BB) and diuretics (Diu) and first 3-week death rate. When analyzing which combination of drugs are used by at least 50% of antihypertensive users, within the different countries, countries with the lowest first 3-week death rates all had at least an angiotensin receptor blocker as one of the most often prescribed antihypertensive medications ((ARBs)/ (CCB) (β, 95% CI; -0.02 (-0.03- -0.004); p=0.009), ARBs/ (BB) (β, 95% CI; -0.03 (-0.05- -0.006); p=0.01)). Finally, countries prescribing high potency ARB's, had lower first 3-week death rates than countries prescribing low potency ARB's.

Conclusion: In conclusion ARBs and CCB seems to have protective effect from dying with SARS-CoV-2 infection.

Keywords: CVOID-19; SARS-CoV-2; RAAS blockers; angiotensin-receptor blockers; angiotensin-converting enzyme inhibitor.

Introduction

The current pandemic of the SARS-CoV-2 coronavirus has infected millions of peoples worldwide(1, 2). Ongoing efforts globally, are pursued to find an effective treatment. Early epidemiological data suggests that individuals with chronic underlying comorbidities such as hypertension, diabetes, and coronary artery disease were at particular risk for a severe infection(3-6), although it is not clear whether this is due to

older age, and hereby associated impaired immune system, or the co-morbidities themselves which the elderly more often have. However, one of the existing hypothesis revolves around the widespread use of RAAS inhibitors, since 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 that use ACEi and ARBs, are presumed to have increased ACE2 expression levels and are therefore prone to more severe SARS-CoV-2 infection and because of that 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 increase in the pathological state (12, 13). Besides, it was suggested that RAAS blocking agents could reverse this shedding and could therefore increase the level of membrane bound ACE2 and therefore of infectious sites. Since 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 membrane-bound form, while for ARBs it is speculated that they might do (15-17). In contrast, it has also been suggested that ARBs could play a protective role. Namely, 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, since it is no longer

available. The, by the virus, increased angiotensin II levels, leads to cellular apoptosis, cytokine release, lung oedema, and eventual ARDS (6, 20-22).

The debate on how and if RAAS inhibitors influence SARS-CoV-2 infections has been subject to many clinical investigations. Recently published meta-analysis suggested no significant increased risk for infection by SARS-CoV-2 (23-26), nor 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 analyzes however is that both ACEi and ARBs are often combined in the analysis, while 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, since often antihypertensive medication will be withdrawn in patients with severe disease (30, 31). This confounding will cause bias because the withdrawal of favourable medication will falsely lead to the assumption that they 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 analysed global prescription data of 30 countries on antihypertensive medication and it's relation to mortality due to the SARS-CoV-2 virus.

Methodology

Medication prescription data on different types of anti-hypertensive 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 is entirely based on the locally reported core data elements of selected local audits. Data for publication in local audits is 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, since this will render the least influenced death rate data, since, in these first 3-weeks, the virus is new to all countries around the world and therefore, no standard adaptations to the virus within a country will have been taken place yet. Therefore, this will lead to the best outcome parameter to be used, to compare outcomes between countries. Second, since viral multiplication and spreading behave exponentially as well as death rates according to it. Therefore, 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. These slopes (death rate) were 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. Secondly, 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. Thirdly, 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 show mutually adjusted outcomes. This is important because we want to correct for the burden of co-morbidities 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 and can therefore be seen as a confounder. Since 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 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 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 it's relation with the first 3-week death rates we also analyzed our data taking into consideration the different pharmacokinetics and pharmacodynamics properties that different ARB's might have. For that matter, we analyzed whether countries prescribing more potent ARBs would have a lower first 3-week death rate as compared to countries prescribing less potent ARB's. 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 hours and a low receptor affinity and Telmisartan has a half-life of 20-24 hours and has the highest receptor affinity of all ARB's. Therefore, we grouped Telmisartan and Irbesartan as high

potency ARB's and the rest as low potency ARB's. 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.

Result

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 medication (Table 1). The use of the different types of antihypertensive medication was very different between countries (Table 1). The range for diuretics was between 36% for Spain versus 14% for Japan, for beta-blockers it was between 37% for Belgium versus 12% for Japan, for calcium-channel blockers it was between 46% for Japan versus 15% for South Africa, for ARBS it was between 51% for South Korea versus 12% for the UK and for ACEi it was between 35% for Hungry versus 1% for South Korea. When analyzing the type of antihypertensive medication and its relation to the first 3week death rate of a SARS-CoV-2 infection (Table 2), we observed that ARBs [β, 95% CI; -0.02(-0.04- -0.001); p=0.03] and CCB [β, 95% CI; -0.02 (-0.05- -0.002); p=0.03] were significantly associated with a lower first 3-week death rate while ACEi [β, 95% CI; 0.03 (0.006-0.05); p=0.01] were significantly associated with a higher first 3-week death rate of a SARS-CoV-2 infection (Figure 1-3a), even after correcting for median age and metformin use within a country (T**able 2)**. In addition, when analyzing 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=0.02] use was significantly associated with 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- -0.002); p=0.04] was independently associated with a lower first 3-week death rate.

Single antihypertensive drug analysis as well as mutually adjusting antihypertensive drug analysis is by no means a good representation of which antihypertensive is the most important driver of its relationship with the first 3-week death rate, since only a small portion of individuals will either use a single drug or all 5 of them. Therefore, we also analyzed which dual combination of medications at least 50% of the individuals on antihypertension medication was using 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 3(b)**. 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 power full tools in crude analysis. for that matter we analyzed whether countries prescribing a higher amount of more potent ARB's would have lower first 3-week death rates as compared to countries prescribing a higher amount of less potent ARB's. Interestingly, we were able to show that countries prescribing higher amounts of more potent ARB's had lower first 3-week death rates [β, 95% CI; -0.01 (-0.03- -0.0000); p=0.04]. Unfortunately, due to lack of power significance was lost [β, 95% CI; -0.01 (-0.03-0.003); p=0.12] after adjusting for the median age and metformin use.

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 ARB's. On the other hand, beta-blockers use was the only independent antihypertensive drug that was related to a lower first 3-week death rate. Whether this is due to blocking of the neuro-humoral response or the combination with a high potency ARB remains to be elucidated. In addition, countries with higher prescriptions of either an ACEi or a diuretics had a worse outcome 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 of 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 weeks of dying form a SARS-CoV-2 infection, taking also into account individuals that 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 included individuals that 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. (32) show the relationship between at-home medication on a SARS-CoV-2 positive test in 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 to individuals not using any medication, meaning that antihypertensive medication does nog prevent infection. In addition, others showed no significant increased risk of getting infected by the SARS-CoV-2 virus nor a more severe outcome, that is hospitalization, among individuals from the general population that used antihypertensive medication (24, 25)(33). From this 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 whether individuals using any of the antihypertensive medications have a worse outcome. Besides, individuals that use antihypertensive medication even RAAS inhibitors will still have 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 concerning one another, resulting in a better overall impression on the relationship of antihypertensive medication and their relationship with the severity of the disease.

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, although many have used it that way. On the other hand, 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 since many countries will not have taken measures and will test most cases, especially the ones with severe disease whom in the end died of it. Secondly, we also took into account out of hospital mortality when analyzing at home antihypertensive medication and death from a SARS-CoV-2 infection, while most other studies only looked at in-hospital mortality. Thirdly, we tried to substantiate our findings in 3 different ways. First, by analyzing the effect of dual combination which more than 50% of antihypertensive users are using 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. Thirdly, 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 drug

analysis, 2 different dual combination analysis and in a dose response effect analysis, underscores the strength of our study.

Since most countries only prescribe low potency angiotensin receptor blockers, with low affinity for the receptor, often dosed once a day while half-life is only max 6 hours, one can argue whether to expect sufficient angiotensin II type 1(AT1) receptor blockade to fully block the deleterious effects of the high angiotensin II levels. On the other hand, we are aware that our results regarding the potency of ARB use lacks power, since significance was lost after adjusting for the median age in an country and metformin use. Finally, since 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 medication 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 on the other hand, the decision for each underlying condition to choose any of the antihypertensive medication will not differ so much between countries, since 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 health care systems of different countries. On the other hand, if this would be the case, the three countries most often within the top 3 of the best health care systems (the United Kingdom, Australia, and the Netherlands) did not have the lowest death rates. On the other hand, to strengthen the analysis we corrected the data for the

median age within a country and metformin use. By correcting for the median age of a country and metformin use, the aging of and indirectly the health status of a country is taking into account, since it reflects the number of individuals that have co-morbidities and have 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 annulated when analyzing effects between countries.

Conclusion: In conclusion, countries that mostly prescribed ARB's had the lowest first 3-week death rates and BB was the only independently related to a lower first 3-week death rate. On the other hand, in countries in which less potent angiotensin receptor blockers are prescribed, the true beneficial effect of these medications might be obscured. Whether this is due to blocking of the neuro-humoral response or the combination with a high potency angiotensin receptor blocker remains to be elucidated.

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Conflict of Interest:

No conflict of interest

Data availability:

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

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Figure legends

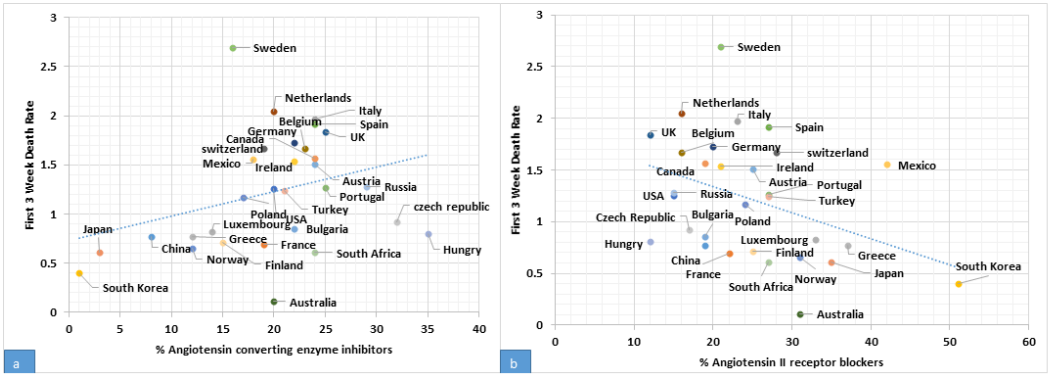

Figure 1 (a): Percentage use of Angiotensin converting enzyme inhibitors in a country with covid-19 related death rate [β, 95% CI; 0.03 (0.01-0.06); p=0.003]. (b) Percentage use of Angiotensin II receptor blockers (ARBs) use in a country with covid-19 related death rate ARBs [β, 95% CI; -0.02 (-0.04- -0.002); p=0.02].

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=0.003]. (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- -0.002); p=0.02].

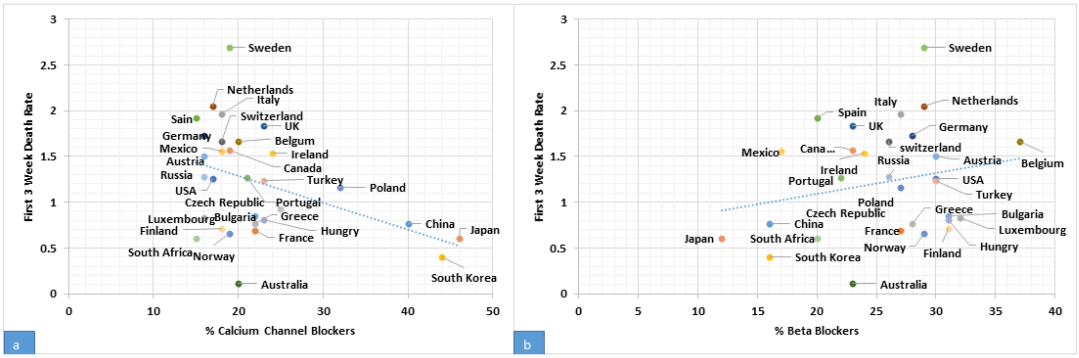

Figure 2 (a): Percentage use of calcium-channel blockers use in a country with covid-19 related death rate [β, 95% CI; -0.03 (-0.05- -0.009); p=0.004] . (b) Percentage use of beta blockers use in a country with covid-19 related death rate[β, 95% CI; 0.02 (-0.01-0.05); p=0.21] .

Figure 2 (a): Percentage use of calcium-channel blockers use in a country with covid-19 related first 3-week death rate [β, 95% CI; -0.03 (-0.05- -0.009); p=0.004]. (b) Percentage use of beta blockers use in a country with covid-19 related first 3-week death rate [β, 95% CI; 0.02 (-0.01-0.05); p=0.21].

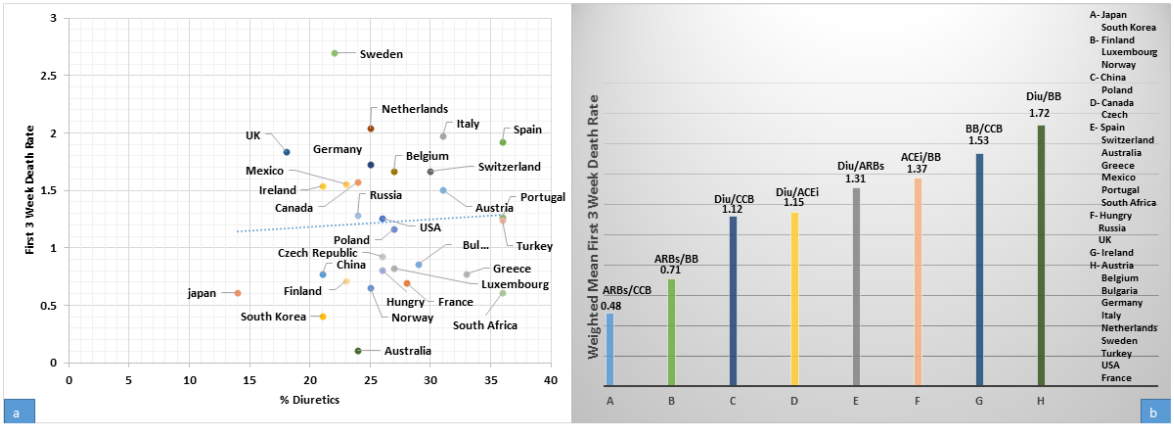

Figure 3 (a): Percentage use of diuretics use in a country with covid-19 related death rate [β, 95% CI; 0.02 (-0.02-0.05); p=0.39]. (b) weighted mean of death rate for two medication combination which was 50% or more of the total antihypertensive medication use.

Figure 3 (a): Percentage use of diuretics use in a country with covid-19 related first 3-week death rate [β, 95% CI; 0.02 (-0.02-0.05); p=0.39]. (b) weighted mean of first 3-week death rate for two medication combination which was 50% or more of the total antihypertensive medication use.

Table 1. Percentage use of antihypertensive medication in various countries

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

Hungry	35	12	26	31	23	67	127
South Africa	24	27	36	20	15	45	122
Total	19 %	21 %	25%	25%	24%	58%	
ACEi= angiotensin converting enzyme inhibitor; ARBs= angiotensin receptor blockers							

Table 2: Association of individual antihypertensive medication and metformin with Covid-19 related first 3-week death rate

	β (95% CI)	
	Unadjusted	Adjusted[#]
Angiotensin II receptor blockers	-0.02 (-0.04- -0.002)*	-0.02 (-0.04- -0.001)*
Angiotensin converting enzyme inhibitor	0.03 (0.01-0.06)*	0.03 (0.006-0.05)*
Beta blockers	0.02 (-0.01-0.05)	-0.001 (-0.04-0.04)
Calcium channel blockers	-0.03 (-0.05- -0.009)*	-0.02 (-0.05- -0.002)*
Diuretics	0.02 (-0.02-0.05)	0.01 (-0.02-0.05)
Metformin	0.02 (0.003-0.04)*	0.02 (0.002-0.04)*

#Adjusted anti hypertensive=Corrected for age and Metformin; Adjusted metformin=corrected for age*; p <0.05.

Table 3. Antihypertensive dual combinations and there 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)**	-	-	-	-
Hungry	-	-	-	-	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)	
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)**

ARBs= Angiotensin II receptor blockers; ACEi= Angiotensin-converting enzyme (ACE) inhibitors; CCB= Calcium channel blockers; BB= Beta blockers; 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)	
Drugs	Unadjusted	Adjusted#
ARBs/CCB	-0.02 (-0.03-0.007)*	-0.02 (-0.03-0.004)*
ARBs/BB	-0.02 (-0.04-0.006)	-0.03 (-0.05- -0.006)*
ARBs/Diuretics	-0.012 (-0.03-0.006)	-0.01 (-0.03-0.005)
ACEi/BB	0.02 (0.005-0.04)*	0.01 (-0.004-0.03)
ACEi/Diuretics	0.02 (0.003-0.03)*	0.02 (0.0000-0.03)*
BB/CCB	-0.03 (-0.06- -0.005)*	-0.03 (-0.06- -0.009)*
BB/Diuretics	0.01 (-0.007-0.03)	0.004 (-0.02-03)
CCB/Diuretics	-0.03 (-0.06- -0.007)*	-0.02 (-0.05- 0.002)

ARBs= Angiotensin II receptor blockers; ACEi= Angiotensin-converting enzyme (ACE) inhibitors; CCB= Calcium channel blockers; BB= Beta blockers; #Adjusted for age and metformin; *p <0.05.