Hypertension

COVID-19

Discontinuation of Antihypertensive Medications on the Outcome of Hospitalized Patients With Severe Acute Respiratory Syndrome-Coronavirus 2

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ABSTRACT: RAASi (renin-angiotensin-aldosterone system inhibitors) are suggested as possible treatment option in the early phase of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection. A meta-analysis investigating the possible detrimental effects of RAASi on the severity of (SARS-CoV-2) infection showed that ambulatory use of RAASi, by hospitalized patients, has a neutral effect. It is, however, conceivable that this observation is biased by the fact that antihypertensive medications, are often discontinued at or during admission in hospitalized patients with SARS-CoV-2. We, therefore, investigated the effect of discontinuation of antihypertensive medications, in hospitalized patients with SARS-CoV-2. We performed a retrospective observational study on 1584 hospitalized patients with SARS-CoV-2 from 10 participating hospitals in the Netherlands. Differences in the outcome (severity of disease or death) between the groups in which medications were either continued or discontinued during the course of hospitalization were assessed using logistic regression models. Discontinuation of angiotensin receptor blockers, ACE (angiotensin-converting enzyme) inhibitors and β-blockers, even when corrected for sex, age, and severity of symptoms during admission, resulted in a 2 to 4× higher risk of dying from SARS-CoV-2 infection (odds ratio [95% CI]); angiotensin receptor blockers 2.65 [1.17–6.04], ACE inhibitor (2.28 [1.15–4.54]), and β-blocker (3.60 [1.10–10.27]). In conclusion, discontinuation of at-home ACE inhibitor, angiotensin receptor blockers, or β-blocker in patients hospitalized for a SARS-CoV-2 infection was associated with an increased risk of dying, whereas discontinuation of calcium channel blockers and diuretics was not. **(*Hypertension*. 2021;78:165–173. DOI: 10.1161/HYPERTENSIONAHA.121.17328.)** • **Data Supplement**

Key Words: angiotensins ■ coronary artery disease ■ diuretics ■ obesity ■ pandemic

The current severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) pandemic has so far led to 2.96 million deaths worldwide (https://ourworldindata.org/covid-deaths, April 13, 2021). Epidemiological data suggests that people with underlying medical conditions like diabetes, hypertension, kidney, or coronary artery disease as well as obesity are more vulnerable to severe disease,[1,2] but this seems to be attenuated after adjusting for age.[3,4] Since the virus uses the membrane-bound ACE2 (angiotensin-converting enzyme 2), an enzyme involved in the renin-angiotensin-aldosterone system (RAAS), to enter and infect the host cells, many have commented on ACE inhibitors or angiotensin receptor blockers (ARB) to result in either a worse or a better outcome.[5,6] On the contrary, it has been suggested, that RAAS blocking agents might increase ACE2 levels and hereby increase the risk of a SARS-CoV-2 infection.[1,2] On the contrary, this has been refuted by others.[7] Interestingly, ARBs are suggested to be beneficial, since they block the deleterious

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For Sources of Funding and Disclosures, see page 172.

Novelty and Significance

What Is New?

- Our study shows that even when adjusting for criteria for severe illness, such as the modified early warning score score or oxygen level, discontinuing ACE (angiotensin-converting enzyme) inhibitor, angiotensin receptor blockers or β-blockers was associated with dying from a severe acute respiratory syndrome-coronavirus 2 infection in hospitalized patients.
- We used prescription level data from the general population as well to compare with data from hospitalized patients.

What Is Relevant?

- Apart from angiotensin receptor blockers and ACE inhibitor, we have also analyzed association of discontinuing 3 other class of at-home antihypertensive medications with outcome in hospitalized patients with severe acute respiratory syndrome-coronavirus 2.

Summary

This study shows that discontinuing renin-angiotensin-aldosterone system or β-blocking agents is associated with dying form severe acute respiratory syndrome-coronavirus 2 infection in hospitalized patients. Whether these medications might protect against a severe acute respiratory syndrome-coronavirus 2 infection cannot be concluded from this observational study.

Nonstandard Abbreviations and Acronyms

ACE2	angiotensin-converting enzyme 2
Ang II	angiotensin II
ARB	angiotensin receptor blocker
BB	β-blocker
CCB	calcium channel blocker
RAAS	renin-angiotensin-aldosterone system
SARS-CoV-2	severe acute respiratory syndrome-coronavirus 2

proinflammatory effects of increased angiotensin II levels, which emerge after viral infection.[8,9]

To be able to shed some light on these contradictory issues, many have investigated the effects of RAAS blocking agents on the severity of hospitalized patients with SARS-CoV-2. A most recently updated meta-analysis, that comprised 86 nonrandomized observational studies, showed that ACE inhibitor or ARBs was associated with a small but significant decrease in mortality, among hypertensive patients hospitalized for SARS-CoV-2.[10] Analysis on hospitalized patients is likely to be confounded, since in seriously ill patients antihypertensive and, therefore, RAAS blocking agents are often discontinued.[11,12] If this is the case, it will create a bias in which potentially beneficial medication is withdrawn, leading to a more unfavorable outcome and consequently a neutral net effect on at-home medication use in a SARS-CoV-2 infection. Indeed, recently, others showed that in-hospital withdrawal of ARBs or ACE inhibitor resulted in a higher risk of severe disease or death in patients with a SARS-CoV-2 infection.[11,13,14] Whether this was due to the fact that these patients already had severe disease at admission and whether this was controlled for in the analysis, was not reported. Furthermore, none of the mentioned studies addresses the issue of higher versus lower affinity ARBs. In the previously mentioned meta-analysis, 62% of the data came from Europe and the United States and by checking the prescription level data for individual ARB medications, we found that these countries mainly prescribe low-affinity ARBs.[10] This is another potential reason for the neutral association of ARBs with SARS-CoV-2 related mortality.

Besides, previously, we analyzed the prescription data of different types of antihypertensive medications among 30 countries worldwide and its relationship to the first 3-week mortality due to a SARS-CoV-2 infection. With this analysis, we were able to show that countries prescribing higher amounts of ARBs and especially higher amounts of high-affinity ARBs had lower mortality rates in the first 3 weeks.[15]

Therefore, we hypothesized that discontinuation of RAAS blocking agents in hospitalized patients with SARS-CoV-2, could have an association with worse outcome irrespective of disease severity at admission.

METHODOLOGY

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

Study Design and Data Collection

In this retrospective cohort study, data on SARS-CoV-2 related hospitalization was collected from 10 participating hospitals in the Netherlands. Baseline characteristics, medication use, comorbidities, and outcomes were extracted from the Electronic Health Records, by a Natural language processing and text mining-based tool validated in previous study.[16] For details see methods in the Data Supplement.

Study Population

Patients admitted to the hospital were included in the study if they were 18 years or older and were diagnosed with SARS-CoV-2. Data on comorbidities, such as hypertension, diabetes, coronary artery disease, and heart failure in the general population, were obtained from the Dutch bureau of statistics (StatLine database Dutch Bureau of Statistics 2018). To compare the use of antihypertensive medication between patients hospitalized with a SARS-CoV-2 infection and the general population personalized prescription data from IQVIA Netherlands was used (methods in the Data Supplement).

Definitions and Study Outcome

Patients were classified according to the severity of disease in 3 groups: mild disease, severe disease, or death. Patients with normal arterial oxygen partial pressure (pO2 ≥80 mm Hg) at admission and no admission to the intensive care unit or death during hospitalization were classified as having mild disease. Severe disease was defined as either a low pO2 (pO2 <80 mm Hg) at admission or intensive care unit admission during hospitalization. The final group consists of the patients who died of SARS-CoV-2. Patients using any of the 5 antihypertensive medication groups, irrespective of the underlying disease it was prescribed for, were classified as antihypertensive users. Data of the five most important antihypertensive medications, that is, ACE inhibitor, ARBs, β-blockers (BB), calcium channel blockers (CCB), and diuretics, either used at home or during hospitalization, were gathered. Information on when and for what reason medication was discontinued during hospitalization was not available. We also defined which ARB had a higher or lower receptor affinity, taking into account the differences in terms of receptor binding kinetics, pharmacodynamics as well as pharmacokinetic properties[17–19] (methods in the Data Supplement).

Statistical Analysis

All analyses were performed using SPSS version 26.0 (SPSS Inc, Chicago, IL). Results were reported as mean±SD for continuous variables and number and percentage (%) for categorical data, except when indicated otherwise. Baseline characteristics were compared using Fisher exact test. We conducted 3 analyses: first, we analyzed the proportions of antihypertensive medication use in all hospitalized patients on the severity of SARS-CoV-2 infection as compared with the general population. Second, we analyzed the impact of discontinuation of antihypertensive medication during hospitalization on the severity of SARS-CoV-2 infection. Finally, we analyzed the effect of discontinuing higher or lower affinity ARBs on severity of SARS-CoV-2 disease. The final model was corrected for sex, age, and modified early warning score. The model with outcome death was additionally adjusted for pO2 at admission (methods in the Data Supplement).

RESULTS

Study Population

Table 1 shows the baseline characteristics of admitted patients with SARS-CoV-2 as compared with the general population. A total of 2289 patients admitted for a SARS-CoV-2 infection were included in the database, for 1584 (69.20%) data was available on at-home and in-hospital antihypertensive medication use as well as all the desired outcome parameters. Of these 1584 patients, 914 (57.70%) used any of the antihypertensive medications at home. As expected, patients with a SARS-CoV-2 infection were older (68.77±13.52 versus 50.25±18.60; $P<0.05$), more often of male sex (59.2% versus 49.18%;

Table 1. Baseline Characteristics of All Patients Admitted With SARS-CoV-2 Infection as Compared With the General Population

Characteristic	General population, n=13 370 428*	Hospitalized patients with SARS-CoV-2, n=1584
Age, y, mean±SD	50.25±18.60	68.77±13.52†
Male gender, n (%)	6 575 155 (49.18)	937 (59.2)†
Antihypertensive medication, n (%)	…	914 (57.7)
No. of at-home antihypertensives, n (%)		
1	…	356 (38.94)
2	…	286 (31.29)
3	…	202 (22.10)
4 or 5	…	70 (7.65)
Emergency department admission only, n (%)	…	27 (1.70)
Comorbidities, n (%)		
Hypertension	2 727 567 (20.4)	627 (39.58)†
Diabetes	1 062 949 (8.0)	397 (25.06)†
History of CAD	1 272 419 (9.5)	219 (13.82)†
History of heart failure	209 470 (1.6)	158 (9.97)†
Outcome, n (%)		
Mild disease	…	418 (26.39)
Severe disease	…	791 (49.94)
Death	…	375 (23.67)
At-home antihypertensive medication, n (%)	n=1 880 205	n=914
Angiotensin receptor blockers	443 341 (23.58)	241 (26.36)
Low affinity	321 782 (72.58)	179 (74.27)
High affinity	121 559 (27.42)	62 (25.73)
ACE inhibitors	634 522 (33.74)	309 (33.80)
β blockers	953 127 (50.69)	524 (57.33)†
Calcium channel blockers	602 771 (32.05)	305 (33.36)
Diuretics	718 975 (38.23)	437 (47.81)†
Discontinued medication, *n* (%)		n=270
Angiotensin receptor blockers	…	76 (28.14)
ACE inhibitors	…	100 (37.04)
β blockers	…	33 (12.22)
Calcium channel blockers	…	66 (24.44)
Diuretics	…	99 (36.66)

ACE indicates angiotensin-converting enzyme; CAD, coronary artery disease; and SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2.

*Central bureau of statistics 2018.

†$P<0.05$.

$P<0.05$), and had significantly more often hypertension (39.58% versus 20.4%), diabetes (25.06% versus 8.0%), coronary artery disease (13.82% versus 9.5%), and heart failure (9.97% versus 1.6%) as compared with the general population (all $P<0.05$). Besides, patients admitted for a SARS-CoV-2 infection more often used β-blockers (57.33% versus 50.69%; $P<0.05$) or diuretics (47.81% versus 38.23%; $P<0.05$).

Table 2 shows the baseline characteristics of the study population according to disease severity. Of the 1584 patients admitted to the hospital, 418 (26.39%) had mild disease, 791 (49.94%) had severe disease, and 375 (23.67%) patients died. The patients who died were older (77.10±8.61 versus 65.66±12.77 versus 67.19±15.34), more often of male sex (67.43% versus 59.67% versus 51.19%), and had more comorbidities such as hypertension (49.33% versus 33.50% versus 42.58%), diabetes (33.60% versus 21.11% versus 24.64%), coronary artery disease (19.73% versus 10.74% versus 14.35%), and heart failure (13.86% versus 7.45% versus 11.24%) compared with the patients with severe or mild disease, respectively. Besides, patients who died used significantly more often ACE inhibitor (26.13% versus 15.80% versus 20.57; $P<0.05$) and CCBs (28.27% versus 16.02% versus 17.22%; $P<0.05$) compared with patients with severe disease and mild disease, respectively. Furthermore, patients who died used significantly more often β-blockers (40% versus 28.70%; $P<0.05$) and diuretics (33.07% versus 28.91%; $P<0.05$) compared with patients with severe disease. Patients who developed severe disease were more often men (59.67% versus 51.19%; $P<0.05$) and significantly less often used ARBs (13.78% versus 18.18%; $P<0.05$), ACE inhibitor (15.80% versus 20.57%; $P<0.05$), and β-blockers (28.70% versus 35.17%; $P<0.05$) compared with those who developed mild disease.

At-Home Antihypertensive and In-Hospital Prognosis

When analyzing only individuals with at-home antihypertensive medication, patients who died were older (77.76±8.02 versus 69.77±10.85 versus 72.80±11.77), more often men (65.12% versus 57.35% versus 52.02%), and had more comorbidities such as hypertension (57.75% versus 46.32% versus 55.24%), diabetes (38.37% versus 24.51% versus 26.61%), coronary artery disease (21.70% versus 13.72% versus 19.76%) compared with the patients with severe disease or mild disease, respectively (Table 3).

The number of patients in whom at least one antihypertensive medication was discontinued during

Table 2. Baseline Characteristics of All Patients Admitted With SARS-CoV-2 Infection With Mild or Severe Disease or Whom Died

Characteristic	Mild, n=418	Severe, n=791	Death, n=375
Age, y, mean±SD	67.19±15.34	65.66±12.77	77.10±8.61*†
Male gender, n (%)	214 (51.19)	472 (59.67)*	251 (67.43)*†
Antihypertensive medication, n (%)	248 (59.33)	408 (51.58)*	258 (69.21)*†
No of at-home antihypertensives, n (%)	248 (59.33)	408 (51.58)*	258 (68.80)*†
1	91 (36.69)	172 (42.15)	93 (36.04)
2	83 (33.47)	126 (30.88)	77 (29.84)
3	56 (22.58)	81 (19.85)	65 (25.19)
4 or 5	18 (7.25)	29 (7.10)	23 (8.91)
Emergency department admission only, n (%)	14 (3.35)	10 (1.26)*	3 (0.8)*
Comorbidities, n (%)			
Hypertension	178 (42.58)	265 (33.50)*	185 (49.33)†
Diabetes	103 (24.64)	167 (21.11)	126 (33.60)*†
History of CAD	60 (14.35)	85 (10.74)	74 (19.73)*†
History of heart failure	47 (11.24)	59 (7.45)*	52 (13.86)†
At-home antihypertensive medication, n (%)			
Angiotensin receptor blockers	76 (18.18)	109 (13.78)*	56 (14.93)
ACE inhibitors	86 (20.57)	125 (15.80)*	98 (26.13)*†
β blockers	147 (35.17)	227 (28.70)*	150 (40)†
Calcium channel blockers	72 (17.22)	127 (16.02)	106 (28.27)*†
Diuretics	116 (27.75)	197 (24.91)	124 (33.07)†

ACE indicates angiotensin-converting enzyme; CAD, coronary artery disease; and SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2.

*$P<0.05$ in comparison to mild disease.

†$P<0.05$ in comparison to severe disease.

Table 3. Baseline Characteristics of Patients on Antihypertensive Medication Admitted With SARS-CoV-2 Infection With Either Mild or Severe Disease or Whom Died

Characteristic	Mild, n=248	Severe, n=408	Death, n=258
Age, y, mean±SD	72.80±11.77	69.77±10.85*	77.76±8.02*†
Male gender, n (%)	129 (52.02)	234 (57.35)	168 (65.12)*
No. of at-home antihypertensives, n (%)			
1	91 (36.69)	172 (42.15)	93 (36.04)
2	83 (33.47)	126 (30.88)	77 (29.84)
3	56 (22.58)	81 (19.85)	65 (25.19)
4 or 5	18 (7.25)	29 (7.10)	23 (8.91)
Emergency department admission only, n (%)	6 (2.42)	6 (1.47)	0 (0)
Comorbidities, n (%)			
Hypertension	137 (55.24)	189 (46.32)*	149 (57.75)†
Diabetes	66 (26.61)	100 (24.51)	99 (38.37)*†
History of CAD	49 (19.76)	56 (13.72)*	56 (21.70)†
History of heart failure	35 (14.11)	46 (11.27)	41 (15.89)
At-home antihypertensive medication, n (%)			
Angiotensin receptor blockers	76 (30.65)	109 (26.72)	56 (21.70)*
ACE inhibitors	86 (34.68)	125 (30.63)	98 (37.98)
β blockers	147 (59.27)	227 (55.64)	150 (58.13)
Calcium channel blockers	72 (29.03)	127 (31.13)	106 (41.08)*†
Diuretics	116 (46.77)	197 (48.28)	124 (48.06)
Discontinued medication, n (%)			
Angiotensin receptor blockers	20 (26.32)	32 (29.36)	24 (42.85)
ACE inhibitors	24 (27.91)	30 (24.00)	46 (46.93)*†
β blockers	5 (3.40)	11 (4.85)	17 (11.33)*†
Calcium channel blockers	16 (22.22)	28 (22.05)	22 (20.75)
Diuretics	24 (20.69)	43 (21.83)	32 (25.80)

ACE indicates angiotensin-converting enzyme; CAD, coronary artery disease; and SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2.

*$P<0.05$ in comparison to mild disease.

†$P<0.05$ in comparison to severe disease.

hospitalization was 76 for ARBs (28.14%), 100 for ACE inhibitor (37.04%), 33 for BB (12.22%), 66 for CCB (24.44%), and 99 for diuretics (36.66%), as depicted in Table 1. Among the patients who died, discontinuation of ACE inhibitors (46.93% versus 24.0% versus 27.91%; $P<0.05$) and β-blockers (11.33% versus 4.85% versus 3.40%; $P<0.05$) was reported significantly more often compared with patients who developed severe disease and mild disease, respectively (Table 3).

When analyzing the risk of dying or developing severe disease in patients with a SARS-CoV-2 infection, we only observed that individuals using CCB had a higher risk of dying, independent of any of the adjustments including modified early warning score score (Table 4).

Discontinuation of Antihypertensive Medications During Hospitalization

When analyzing the effect of in-hospital discontinuation of antihypertensive medication on the severity of SARS-CoV-2 infection, we observed that discontinuation of ARBs, ACE inhibitor, and BB was associated with an increased risk of dying from a SARS-CoV-2 infection, even after adjusting for confounders such as age, sex, and modified early warning score at admission (β, ARB, 2.65 [95% CI, 1.17–6.04]); ACE inhibitor (β, 2.28 [95% CI, 1.15–4.54]); BB (β, 3.60 [95% CI, 1.10–10.27]; Table 5), where as discontinuation of CCBs or diuretics was not. Finally, to further substantiate our findings, we also analyzed the effect of discontinuing antihypertensive medication association with severity of a SARS-CoV-2 infection in a selected population of hypertensive patients only and found similar results (Table S1 in the Data Supplement).

High- Versus Low-Affinity ARBs

To further substantiate our observations, we also analyzed the distribution of higher or lower affinity ARBs on disease severity. We observed that with increasing severity of disease, a smaller number of individuals used high-affinity ARBs, which might suggest that

Table 4. Association of At-Home Antihypertensive Medications With Outcome in Patients on Antihypertensive Medication Hospitalized for SARS-CoV-2

Model	β (95% CI)				
At-home antihypertensive medication	Angiotensin receptor blockers	ACE inhibitors	β blockers	Calcium channel blockers	Diuretics
Mild disease	…	…	…	…	…
Severe disease					
Model I	0.83 (0.58–1.17)	0.83 (0.60–1.16)	0.86 (0.63–1.19)	1.11 (0.78–1.56)	1.06 (0.77–1.46)
Model II	0.84 (0.59–1.20)	0.78 (0.56–1.10)	0.94 (0.68–1.30)	1.08 (0.76–1.53)	1.15 (0.83–1.58)
Model III	0.87 (0.61–1.24)	0.74 (0.52–1.05)	0.89 (0.64–1.25)	1.10 (0.78–1.57)	1.12 (0.81–1.55)
Model IV	0.87 (0.60–1.26)	0.81 (0.56–1.15)	0.98 (0.68–1.40)	1.15 (0.77–1.72)	1.40 (0.94–2.08)
Model V	0.89 (0.62–1.27)	0.79 (0.56–1.12)	0.98 (0.70–1.36)	1.11 (0.78–1.58)	1.21 (0.86–1.69)
Death					
Model I	0.63 (0.42–0.94)*	1.15 (0.80–1.66)	0.95 (0.67–1.36)	1.71 (1.18–2.47)*	1.05 (0.74–1.49)
Model II	0.67 (0.44–1.02)	1.20 (0.82–1.75)	0.89 (0.61–1.29)	1.90 (1.29–2.80)*	0.94 (0.65–1.34)
Model III	0.68 (0.44–1.05)	1.13 (0.76–1.68)	0.85 (0.58–1.26)	1.93 (1.29–2.89)*	0.90 (0.62–1.32)
Model IV	0.61 (0.40–0.95)*	1.17 (0.79–1.74)	0.81 (0.53–1.21)	2.21 (1.34–3.30)*	0.84 (0.55–1.30)
Model V	0.65 (0.43–0.99)*	1.15 (0.78–1.69)	0.84 (0.58–1.24)	1.83 (1.23–2.72)*	0.89 (0.61–1.29)

Model I: univariate; model II: adjusted for age and sex; model III: model II+adjusted for MEWS; model IV: model II+adjusted for number of antihypertensive medication at home; model V: model II+adjusted for comorbidities (hypertension, diabetes, heart failure, and coronary artery disease). MEWS indicates modified early warning score; and SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2.

*$P<0.05$.

the affinity of ARBs is relevant in preventing disease severity. These findings were not statistically significant (Figure; Table S2).

DISCUSSION

In the present study, we show that discontinuation of ARBs, ACE inhibitor, and β-blockers during hospitalization for a SARS-CoV-2 infection is associated with a 2 to 4× increased risk of death, independent of the severity of disease at admission.

In animal models, it has been suggested, that ARBs might alleviate the deleterious effects of ever-increasing Ang II (angiotensin II) levels, due to the SARS-CoV-2 infection.[20,21] Since ACE2 is internalized when the SARS-CoV-2 virus binds to it, the enzyme no longer

Table 5. Association of Discontinuing At-Home Antihypertensive Medications With Outcome in Hospitalized Patients With SARS-CoV-2

Model	β (95% CI)				
Discontinued medication	Angiotensin receptor blockers	ACE inhibitors	β blockers	Calcium channel blockers	Diuretics
Mild disease	…	…	…	…	…
Severe disease					
Model I	1.16 (0.60–2.24)	0.82 (0.44–1.52)	1.45 (0.49–4.25)	0.99 (0.49–1.99)	1.07 (0.61–1.88)
Model II	1.15 (0.59–2.24)	0.82 (0.43–1.54)	1.23 (0.41–3.71)	0.94 (0.46–1.91)	1.03 (0.59–1.83)
Model III	1.16 (0.60–2.26)	0.83 (0.44–1.57)	1.25 (0.41–3.82)	0.95 (0.46–1.96)	1.11 (0.62–1.98)
Model IV	1.15 (0.59–2.24)	0.94 (0.48–1.83)	1.23 (0.40–3.73)	0.87 (0.42–1.83)	0.96 (0.54–1.72)
Model V	1.09 (0.55–2.18)	0.83 (0.44–1.58)	1.15 (0.38–3.52)	0.90 (0.44–1.86)	1.02 (0.57–1.81)
Death					
Model I	2.10 (1.01–4.38)*	2.29 (1.23–4.23)*	3.63 (1.30–10.12)*	0.92 (0.44–1.90)	1.33 (0.73–2.44)
Model II	2.57 (1.15–5.72)*	2.43 (1.25–4.70)*	3.64 (1.24–10.65)*	0.96 (0.44–2.09)	1.44 (0.77–2.70)
Model III	2.65 (1.17–6.04)*	2.28 (1.15–4.54)*	3.60 (1.10–10.27)*	0.91 (0.40–2.04)	1.51 (0.76–3.02)
Model IV	2.79 (1.21–6.44)*	2.43 (1.24–4.76)*	3.55 (1.21–10.45)*	1.03 (0.47–2.26)	1.58 (0.83–3.00)
Model V	2.38 (1.02–5.53)*	2.36 (1.20–4.63)*	3.83 (1.26–11.62)*	0.93 (0.42–2.09)	1.48 (0.78–2.82)

Model I: univariate; model II: adjusted for age and sex; model III: model II+adjusted for MEWS; model IV: model II+adjusted for number of antihypertensive medication at home; and model V: model II+adjusted for comorbidities (hypertension, diabetes, heart failure, and coronary artery disease). MEWS indicates modified early warning score; and SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2.

*$P<0.05$.

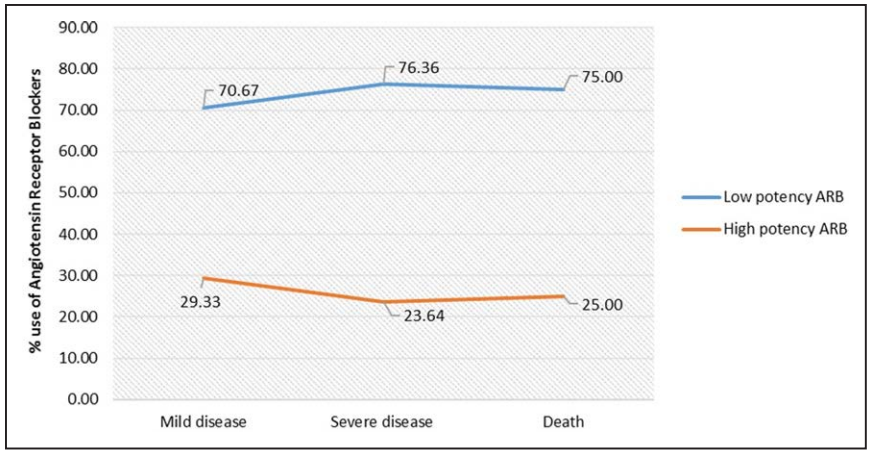

Figure. Distribution of high- versus low-affinity angiotensin receptor blockers (ARB) in individuals with mild or severe disease or whom died.

converts proinflammatory Ang II into anti-inflammatory Ang 1 to 7, leading to overstimulation of the Ang II type 1 receptor, inducing lung damage and respiratory distress syndrome. Therefore, since ARBs and ACE inhibitor block this pathway and maintain an equilibrium, discontinuation of these medications in patients with SARS-CoV-2 infection could lead to worsening of disease.[22] Besides, sympathetic overdrive due to an excessive increase in the level of Ang II could override the β1 adrenergic receptor blocked by daily use of β-blockers. The above mechanisms as well as the effect increasing Ang II has on superoxide production was previously described by us.[23]

During the initial phase of the pandemic, others have suggested that the use of ARBs and ACE inhibitor could lead to an increased susceptibility of a SARS-CoV-2 infection as ARBs and ACE inhibitor could upregulate ACE2 and facilitate the entry of the virus. If this would be the case, patients infected with the SARS-CoV-2 virus would more often use ARBs and ACE inhibitor compared with the general population, which has been shown not to be the case.[24,25] In addition, if the use of ARBs and ACE inhibitor would be associated with a more severe SARS-CoV-2 infection, represented by hospitalization, patients using ARBs and ACE inhibitor would be overrepresented among hospitalized SARS-CoV-2 patients as compared with the general population, which was not the case in the present study. Furthermore, previous studies were not designed to answer the question whether ARBs and ACE inhibitor lead to more severe SARS-CoV-2 disease in hospitalized patients, since they did not take into account the discontinuation of at-home medication during admission.[10]

Recently published studies that investigated the association between discontinuation of RAAS blocking agents and outcome in hospitalized SARS-CoV-2 patients, found similar results, namely that discontinuation of these medications during the course of hospitalization was associated with an increased risk of dying from SARS-CoV-2 infection,[11–13] whereas the continuation of these medications was associated with lower mortality.[14,26] On the contrary, a recent large randomized controlled trial on the discontinuation of RAAS inhibitors found no difference in the duration of hospital or death due to a SARS-CoV-2 infection but had a serious flaw in the study design. Namely, randomization was broken due to the fact that around 80 individuals were left out of the analysis, due to misconduct of one of the study sites. Interestingly, additional on treatment analysis showed a similar 2× higher risk of dying in the group randomized to discontinuation of ARB medication during hospitalization.[27]

Another important confounder to consider, is that a favorable outcome of ARBs, in case of a SARS-CoV-2 infection, can only be anticipated if the Ang II type 1 receptor is sufficiently blocked. The currently most prescribed ARBs, losartan and valsartan, have a low Ang II type 1 receptor affinity, a short half-life and are prescribed in a once daily dose. Therefore, they only modestly block the Ang II effects. Meaning that we cannot expect sufficient Ang II type 1 receptor blockade to affect the outcome of a SARS-CoV-2 infection. Since most of the published studies mainly prescribe low-affinity ARBs[10] and since we already showed that worldwide higher affinity ARBs are associated with lower first 3-week mortality,[15] we suggest that this should be better looked into. The current analysis only shows a slight decrease in the number of individuals on a high-affinity ARB, in the group that died, but the data was underpowered to show significance.

Strength and Limitations

One could speculate that discontinuation of ACE inhibitor, ARBs, and BB among patients who died of SARS-CoV-2, could be due to the fact that these patients were already on the verge of dying and for that reason antihypertensive medication was not deemed necessary and therefore discontinued. On the contrary, if this was the case, then this would also hold true for CCB and diuretics, which was not the case. Besides, information on when or for what reason medication was discontinued during hospitalization was lacking. Although

medications will often be discontinued because of more severe disease, we tried to control for that by correcting our data for the modified early warning score score, which did not change the results. Therefore, we speculate that higher risk of mortality is related to the discontinuation of RAAS and β-blockers themselves, although this analysis cannot confirm this because of its cross-sectional nature.

Another limitation might be that the analysis could be influenced by the fact that antihypertensive drugs are prescribed for different underlying conditions. We therefore, we adjusted the logistic regression analysis for comorbidities, which did not influence the results. In addition, we also analyzed hypertensive patients only and found similar results. Nevertheless, it is important to stress, that one should consider all antihypertensive medication users as a whole, irrespective of the underlying disease it is prescribed for, since its association with a SARS-CoV-2 infection will not differ. Whether the underlying disease and its reaction to a SARS-CoV-2 infection will differ, is still to be debated. Most of the underlying diseases, such as hypertension, diabetes, obesity, and cardiovascular disease overlaps within patients and probably have a common denominator, such as insulin resistance. However, we besides considering underlying comorbidities we also explored the association with the number of prescribed antihypertensives.

Another issue is the retrospective observational nature of the study, which means that the data is acquired in the past and one is dependent on the quality of this data. Therefore, we could not use the appropriate standard definition of SARS-CoV-2 severity but instead used the most crude and conservative definitions related to pO2 at admission. In addition, retrospective studies would not allow you to assess causality, therefore, we tried to substantiate our findings by assessing a kind of dose-response relationship by analyzing the effects of lower or higher affinity ARBs.

Conclusions

In conclusion, discontinuation of at-home ACE inhibitor, ARBs, or BB in patients hospitalized for a SARS-CoV-2 infection was associated with an increased risk of dying, whereas discontinuation of CCBs and diuretics was not.

Perspectives

In our multicentre study from the Netherlands, discontinuation of ACE inhibitor, ARBs, and BB in hospitalized patients with SARS-CoV-2 infection was associated with an increased risk of dying, irrespective of the severity of disease at admission. The observational study design, prevents us from concluding causality. However, this study provide association in the protective roles of ARBs, ACE inhibitor and β-blockers in hospitalized patients with SARS-CoV-2.

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DATA SUPPLEMENT:

Discontinuation of antihypertensive medications on the outcome of hospitalized SARS-CoV-2 patients

Short Title: antihypertensive discontinuation and SARS-CoV-2

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Supplement Methods

Study design and Data collection

In this retrospective cohort study, data on SARS-CoV-2 related hospitalization was collected from 10 participating hospitals in the Netherlands. Baseline characteristics, medication use, comorbidities and outcomes were extracted from the Electronic Health Records (EHR), by a Natural language processing and text mining-based tool validated in previous study [1]. EHR were searched using Clinical Data Collector (CDC; CTcue B.V., Amsterdam, The Netherlands) CDC is a Natural language processing (NLP) and text mining-based tool that gathers data from EHR using relevant search teams and creates a data set that has been utilized and validated in previously published studies [17]. The search queries were designed by two of the principal investigators of this study. Ethical approval was waived due to the seriousness of the pandemic the world was facing at the time of data collection.

Study population

Patients admitted to the hospital were included in the study if they were 18 years or older and were diagnosed with SARS-CoV-2. Data on co-morbidities such as hypertension, diabetes, coronary artery disease and heart failure in the general population were obtained from the Dutch bureau of statistics (StatLine database Dutch Bureau of Statistics 2018). To compare the use of antihypertensive medication between patients hospitalized with a SARS-CoV-2 infection and the general population personalized prescription data from IQVIA Netherlands was used . SARS-CoV-2 infection diagnosis was based on positive reverse-transcriptase (PCR) for SARS-CoV-2 (87.14%). If this was not available, a CORAD score ≥ 4 on chest computed tomography scan was used (8.17%) . Only in a minority of cases the diagnosis code for COVID-19 was used (4.67%). IQVIA (MIDAS) personalized sales database is a nationally representative, retrospective, prescription-based database, obtained from IQVIA's Real-World Data Longitudinal Prescription database (LRx, Amsterdam, The Netherlands). The database contains anonymous patient prescription records, including patient (e.g., age, gender), dispensing (e.g., pharmacy, prescription date), medication (e.g., name, dose, strength, therapy duration), and prescriber information. For this study, dispensed prescriptions of ARBs, ACEi beta blockers, calcium channel blockers and diuretics prescribed by cardiologists, general practitioners, internists and other prescribers were selected. In total, the database provides a coverage of approximately 70% of all prescriptions dispensed in The Netherlands, represented by both retail pharmacies and dispensing general practitioners. Data was available from the time period of January 2019 – December 2019.

Definitions and Study outcome

Patients were classified according to the severity of disease in three groups: mild disease, severe disease or death. Patients with normal arterial oxygen partial pressure ($pO2 \geq 80$ mmHg) at admission and no admission to the ICU or death during hospitalization, were classified as having mild disease. Severe disease was defined as either a low pO2 ($pO2 < 80$ mmHg) at admission or ICU admission during hospitalization. The final group consists of the patients that died of Sars-CoV-2. Unfortunately, our database did not provide in

many of the variables needed for this standardized definition according to the WHO classification of severity (https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf page 6). Therefore, we tried to define severity of disease in the most conservative way, with the variables that were at our disposal. We reasoned that the pO2 level at admission could serve as a logical proxy of severity of disease and this was available in around 97% of the patients in our cohort. Therefore patients with a normal pO2 level at admission were categorized as mild disease, although they could worsen to severe disease over the course of hospitalization, hereby misclassifying them as mild disease, which would only have weakened our results. On the other hand, these mild disease individuals were not allowed to be admitted to the ICU or die during the course of hospitalization. Besides, individuals that died or were admitted to the ICU, during the course of hospitalization, should clearly be regarded of as individuals with the most severe or severe disease, independent of their admission state. Meaning that individuals classified as severe disease due to the fact that they were admitted to the ICU during the course of hospitalization, were not allowed to die, so they would never classify as the most severe diseased.

Patients using any of the five antihypertensive medication groups, irrespective of the underlying disease it was prescribed for, were classified as "antihypertensive users". Data of the five most important antihypertensive medications, that is, ACEi, ARBs , beta blockers (BB), calcium channel blockers (CCB), and diuretics, either used at-home or during hospitalization were gathered. Information on when and for what reason medication was discontinued during hospitalization was not available. We also defined which ARB had a higher or lower receptor affinity, taking into account the differences in terms of receptor binding kinetics, pharmacodynamics as well as pharmacokinetic properties [18-20]. We classified telmisartan and irbesartan as high affinity ARBs and the rest as low affinity ARBs as they have very high liposolubility of around 500 Liters and 93 Liters respectively. Besides, telmisartan has the longest half-life of around 24 hours and dissociation half-lifes of 213 minutes (mins). For irbesartan, the next high affinity ARB, this was 20 hours and 7 mins [18]. In addition, these ARBs show insurmountable antagonism for AT1 receptor with the highest AT1 receptor affinity. In comparison losartan, valsartan, candesartan and olmesartan have a liposolubility of 17 Liters for each. Furthermore, losartan possesses a half-life of only 2 hours followed by 6 hours for valsartan and 9-12 hours candesartan. In addition, dissociation half-lives for losartan, and valsartan are only 67 and 70 mins while for candesartan and olmesartan are 133 and 166 mins, respectively [19, 20]. Furthermore, losartan also has a significant first-pass-effect, in which active (14%) and inactive metabolites are being formed by CyP2C9.

Missing data

Patients of whom data on antihypertensive medication use either at-home or in-hospital, as well as data on outcome, (ICU admission or death), were missing, were excluded from the database (n = 705). Missing data on baseline characteristics were imputed using multiple imputation method, with 5 imputed data sets with automatic imputation method. Data on pO2 was measured in n=1206 (96.71%) individuals on the day of admission or at presentation at the hospital. Data on pO2 and day on which pO2 was measured was also collected. Data on pO2 was missing for 335 (21.14%) individuals and for 337 (21.27%) individuals the day at which pO2 was measured

was missing. If pO2 values were not available, we assumed that patients had a mild clinical presentation and a normal peripheral oxygen saturation at the time of presentation. For these 335 individuals pO2 levels were considered to be normal, that is 80 mmHg or higher.

Statistical analysis

All analyses were performed using SPSS version 26.0 (SPSS Inc., Chicago, Illinois). Results were reported as mean ± standard deviation (SD) for continuous variables and number and percentage (%) for categorical data, except when indicated otherwise. Baseline characteristics were compared using Fisher's exact test. We conducted three analyses: first, we analyzed the proportions of antihypertensive medication use in all hospitalized patients on the severity of SARS-CoV-2 infection as compared to the general population. Second, we analyzed the impact of discontinuation of antihypertensive medication during hospitalization on the severity of SARS-CoV-2 infection. Finally, we analysed the effect of discontinuing higher or lower affinity ARBs on severity of SARS-CoV-2 disease. The final model was corrected for sex, age and Modified early warning score. The model with outcome death was additionally adjusted for pO2 at admission. For the first and second analysis we used two logistic regression models, on antihypertensive users alone. The first, to analyze the association between at-home antihypertensive medication use and severity of disease and the second to analyze discontinuation of antihypertensive medications during the course of hospitalization and severity of disease. For both models, for disease severity and death, mild disease was taken as the reference group"". Both models were corrected for the following possible confounders: "age" and "sex", the Modified Early Warning Score (MEWS), to represent severity of disease during hospitalization (Model III), the number of antihypertensive medications a patient was taking and the different co-morbidities (hypertension, diabetes, heart failure and coronary artery disease). Regression models were designed as: Model I: Univariate: Model II: Age and sex corrected; Model III: Age, sex and MEWS corrected: Model IV: Age, sex, and the number of antihypertensive medications a patient was using; Model V: Age, sex and corrected for comorbidities. A p-value < 0.05 was considered statistically significant.

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Supplement tables:

Table S1: Association of discontinuing at-home antihypertensive medications with outcome in patients on antihypertensive medication hospitalized for SARS-CoV-2

Model	**β (95% CI)**				
Discontinued medication	**Angiotensin receptor blockers**	**ACE inhibitors**	**Beta blockers**	**Calcium channel blockers**	**Diuretics**
Mild disease	-	-	-	-	-
Severe disease					
Model I	0.77 (0.31-1.93)	0.74 (0.30-1.82)	0.74 (0.13-4.19)	0.77 (0.26-2.23)	0.90 (0.43-1.88)
Model II	0.76 (0.30-1.91)	0.67 (0.26-1.73)	0.52 (0.08-3.26)	0.65 (0.21-1.94)	0.81 (0.38-1.72)
Model III	0.77 (0.31-1.95)	0.69 (0.26-1.88)	0.52 (0.08-3.42)	0.62 (0.20-1.91)	0.86 (0.40-1.86)
Model IV	0.65 (0.24-1.74)	0.67 (0.23-1.98)	0.48 (0.07-3.16)	0.67 (0.20-2.20)	0.75 (0.35-1.63)
Model V	0.72 (0.28-1.86)	0.71 (0.27-1.90)	0.44 (0.07-2.85)	0.65 (0.22-1.95)	0.76 (0.35-1.63)
Death					
Model I	2.29 (0.81-6.50)	2.02 (0.89-4.58)	3.06 (0.77-12.22)	1.19 (0.46-3.08)	0.85 (0.38-1.88)
Model II	3.30 (1.06-10.26)*	1.93 (0.81-4.58)	3.41 (0.79-14.69)	1.22 (0.46-3.27)	1.03 (0.44-2.39)
Model III	3.32 (1.06-10.42)*	1.89 (0.77-4.60)	3.47 (0.75-16.12)	1.14 (0.38-3.42)	1.06 (0.43-2.59)
Model IV	3.56 (1.11-11.41)*	1.94 (0.79-4.75)	3.16 (0.71-13.99)	1.27 (0.46-3.49)	1.06 (0.45-2.48)
Model V	3.46 (1.00-11.96)*	1.90 (0.79-4.55)	3.92 (0.84-18.17)	1.21 (0.44-3.34)	1.07 (0.46-2.53)

Model I Univariate; model II: adjusted for age and sex; model III: model II+ Adjusted for MEWS; Model IV: model II+ Adjusted for number of antihypertensive medication at home; Model V: Model II+ adjusted for comorbidities (hypertension, diabetes, heart failure and coronary artery disease); MEWS: Modified early warning score; *p<0.05

Table S2: High versus low affinity ARB distribution in SARS-CoV-2 hospitalized individuals with mild or severe disease and whom died

Characteristic	**Mild (75)**	**Severe (110)**	**Death (56)**
Low affinity ARB, *n (%)*	53 (70.67)	84 (76.36)	42 (75.0)
High affinity ARB, *n (%)*	22 (29.33)	26 (23.64)	14 (25.0)