ORIGINAL ARTICLE

No association between use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers prior to hospital admission and clinical course of COVID-19 in the COvid MEdicaTion (COMET) study

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Since the outbreak of SARS-CoV-2, also known as COVID-19, conflicting theories have circulated on the influence of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) on incidence and clinical course of COVID-19, but data are scarce. The COvid MEdicaTion (COMET) study is an observational, multinational study that focused on the clinical course of COVID-19 (i.e. hospital mortality and intensive care unit [ICU] admission), and included COVID-19 patients who were registered at the emergency department or admitted to clinical wards of 63 participating hospitals. Pharmacists, clinical pharmacologists or treating physicians collected data on medication prescribed prior to admission. The association between the medication and composite clinical endpoint, including mortality and ICU admission, was analysed by multivariable logistic regression models to adjust for potential confounders. A total of 4870 patients were enrolled. ACEi were used by 847 (17.4%) patients and ARB by 761 (15.6%) patients. No significant association was seen with ACEi and the composite endpoint (adjusted odds ratio [OR] 0.94; 95% confidence interval [CI] 0.79 to 1.12), mortality (OR 1.03; 95%CI 0.84 to 1.27) or ICU admission (OR 0.96; 95%CI 0.78 to 1.19) after adjustment for covariates. Similarly, no association was observed between ARB and the composite endpoint (OR 1.09; 95%CI 0.90 to 1.30), mortality (OR 1.12; OR 0.90 to 1.39) or ICU admission (OR 1.21; 95%CI 0.98 to 1.49). In conclusion, we found no evidence of a harmful or beneficial effect of ACEi or ARB use prior to hospital admission on ICU admission or hospital mortality.

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1 | INTRODUCTION

The severe acute respiratory syndrome (SARS)-coronavirus 2 (CoV-2) is responsible for coronavirus disease 2019 (COVID-19). SARS-CoV-2 invades human cells by binding a viral spike protein to angiotensin converting enzyme (ACE) 2, similar to SARS-CoV-1 which caused an earlier outbreak of SARS in 2002.[1–4] Renin–angiotensin–aldosterone system (RAAS) activation ensures conversion of angiotensin I to angiotensin II by ACE1. Activating the type I angiotensin II (AT1) receptor causes vasoconstriction, inflammation and fibrosis, whereas conversion of angiotensin I and II by ACE2 leads to a pathway involving angiotensin-(1–9) and angiotensin-(1–7), which is thought to counter these detrimental effects (Figure 1A). The binding of SARS-CoV-2 and ACE2 leads to local downregulation of ACE2.[5] In turn, angiotensin II accumulates resulting in increased vascular permeability and an acute respiratory distress syndrome-like syndrome. In addition to its role in RAAS modulation, ACE2 is also involved in degrading several other substrates, such as apelin and bradykinin. Recently, its role in degrading bradykinin has been suggested to play a causal role in the development of severe acute respiratory distress syndrome.[6] Previous studies showed that during lung injury, ACE1, angiotensin II, and the AT1 receptor function as lung injury-promoting factors, whereas ACE2 protects against lung injury.[5,7] Since RAAS inhibitors (RAASi), such as ACE(1) inhibitors (ACEi) or angiotensin II receptor blockers (ARB), have been described to have an effect on ACE2 expression (i.e. upregulation in various organs), these drugs may increase the risk of infectivity of SARS-CoV-2 resulting in a higher incidence of COVID-19 in patients using RAASi (Figure 1B).[8] The theoretical increased risk of infectivity has been strengthened by literature showing that conditions in which RAASi are used, such as hypertension, diabetes mellitus and cardiovascular diseases, correlate with COVID-19-related mortality.[8–11] Paradoxically, beneficial effects have also been suggested, since an increase in ACE2, if truly present, might protect against inflammation and lung injury as described earlier (Figure 1B).[12–14] In the absence of evidence, randomized clinical trials have been initiated in which ACEi and ARB have been either discontinued or prescribed.[15–18] The COMET study aims to evaluate the effect of ACEi and ARB use prior to hospital admission on COVID-19-related outcomes (e.g. mortality and ICU admission).

2 | METHODS AND ANALYSIS

2.1 | Study design and participants

The COvid MEdicaTion (COMET) study, is a European, multinational, multicentre, retrospective study. The rationale and design have

What is already known about this subject

- Several studies have shown that the use of renin–angiotensin–aldosterone system inhibitors (RAASi) was not associated with a more serious course or higher mortality of COVID-19 patients compared to no use of RAASi.

What this study adds

- A large multicentre, international cohort that further confirms the results shown in previously published studies.
- In addition to mortality, there is no association between the use of preadmission RAASi and intensive care unit admission in COVID-19 patients.

previously been described in detail.[19] In summary, patients were included by pharmacists, clinical pharmacologists, or treating physicians from 63 hospitals in 10 countries. To prevent major selection bias, a minimum number of patients was set to participate in the study (i.e. 50 patients per centre or all patients if <50 patients were available). All participating investigators were requested to consecutively include either those patients who were SARS-CoV-2 positive registered at the Emergency Department (42% of participating hospitals) or on the clinical wards (58% of participating centres). The major criterion for a patient to be included in the study was COVID-19 positive by either a positive SARS-CoV-2 polymerase chain reaction (PCR) or a high clinical likelihood based on bilateral pulmonary infiltrates not explained otherwise after consensus by the local COVID-19 expert team, based on clinical, biochemical and radiological criteria. The timeframe of inclusion of consecutive patients was at the discretion of the participating hospital and inclusion was performed during a median of 25 days (interquartile range [IQR] 15–45).

2.2 | Data collection

The timeframe for data collection was limited as it took place during the first wave of COVID-19 infections. Data collection focused on prescribed medication prior to admission, patient and admission characteristics, and clinical outcomes (e.g. hospital mortality and ICU admission). The current analysis focused on the use of RAASi (ACEi or ARB) prior to admission and clinical outcomes. The following variables were collected: year of birth, sex,
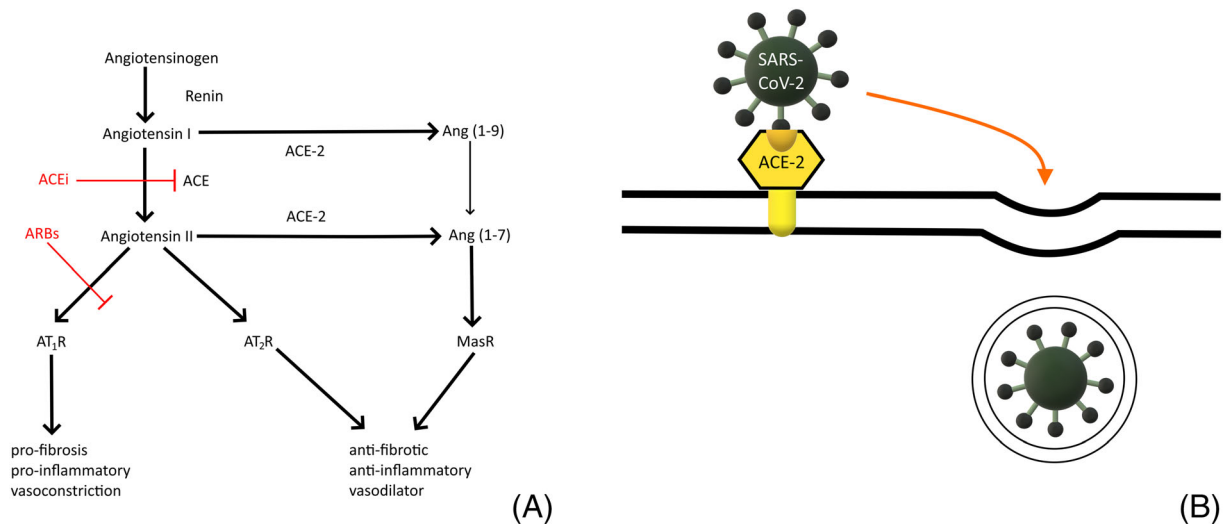
FIGURE 1 Schematic illustration of the renin–angiotensin–aldosterone system including the role of ACE2 and link with SARS-CoV-2 infection. (A) ACE2 converts angiotensin II to Ang (1–7) and angiotensin I to Ang (1–9). Ang (1–7) and Ang (1–9) have an organic-protective effect and counterbalance the negative effects of binding AT_1R by angiotensin II. (B) Binding of SARS-CoV-2 on ACE2 internalize the virus into the cell. ACE2 may be upregulated by renin–angiotensin–aldosterone system inhibitor, leading to the hypothesis that the infectivity of SARS-CoV-2 increases. However, due to the beneficial effects shown in (A), this increase in ACE2 might also be beneficial due to protection against inflammation and lung injury in conditions known for low ACE2 expression, such as diabetes and hypertension. Abbreviations: ACE, angiotensin converting enzyme; ACEi, ACE inhibitor; Ang, angiotensin; ARB, angiotensin receptor blocker; AT_1R, type 1 angiotensin II receptor, AT_2R; type 2 angiotensin II receptor; MasR, Mas receptor

prescribed medication by ATC code, dosing regimen, hospital mortality and ICU admission. As the entry of comorbid disease is time consuming and often incomplete, data on type of drugs served as a proxy for disease; hypertension, atherosclerotic cardiovascular disease (i.e. coronary artery disease, cerebrovascular disease, or peripheral artery occlusive disease)and diabetes mellitus. These conditions were considered present in patients when any blood pressure-lowering drugs, antiplatelet drugs, or glucose-lowering drugs or insulins were used, respectively.

Medication in single pill combinations were coded into the individual drug classes (e.g. if a patient used a combination of both an ACEi and a beta blockers, they were included as using an ACEi and a β-blocker).

In reference to the Bradford Hill criteria of causality,[20] an exploratory analysis was added to assess dose response relationship on the clinical course. Each daily dose of ACEi and ARB was proportionally converted to a standard dose. The standard dose is an equipotent daily dose within a drug class and was based on the usual maintenance dose of each drug recommended in reference pharmacopoeias. The standard dose has been suggested to describe equipotency better than the World Health Organization daily defined dose.[21] For example, lisinopril 20 mg was considered equivalent to 2 standard doses ACEi.

Data were collected in an online database (Clinical Rules reporter, version 1.6.3, Digitalis Rx, Amsterdam, the Netherlands). A study number was assigned to each participant. The coding file was only available to the local investigator. Each local investigator collected pseudonymized data. The institutional review committee of the

main site, Erasmus MC in the Netherlands, approved the study (MEC-2020-0277), as well each institutional review board of the participating hospitals approved the use of data, as described in our protocol study.[19] All data were treated according to the privacy regulations applicable for European countries and conducted in accordance with the Declaration of Helsinki.[22]

2.3 | Study endpoints

The study endpoints were a composite of clinical course of the COVID-19 patients including mortality and ICU admission, and both mortality and ICU admission as individual endpoints. Both mortality and ICU admission were in-hospital endpoints and scored according to the patient records.

2.4 | Statistical analysis

Descriptive statistics were used to depict the characteristics of patients in the total study sample, and stratified for patients without RAASi, ACEi use and ARB use. All characteristics were described as counts (%) and medians [IQR]. Patients without RAASi were used as the reference category. For the study endpoints, a multivariable binary logistic regression model was used to analyse the data. Results were presented as odds ratios (OR) with corresponding 95%confidence interval (95%CI). First, crude, unadjusted estimates were obtained (Model I). These were then

adjusted for age and sex (Model II), and finally for the concomitant blood pressure-lowering drugs other than RAASi, antiplatelet drugs and glucose-lowering drugs. (Model III). In addition, an exploratory model with adjustment for a propensity score (PS) of RAASi, ACEi or ARB use was developed (Model IV). The use of propensity scores was employed as a method for dealing with confounding factors.[23] The propensity score was defined as an individual's probability of being treated with the drug of interest given the variables of that individual. Thus, the use of a probability that a subject would have been treated allows adjustment of the estimated treatment effect, creating *quasirandomized* trial and reducing confounding by indication.[24] The PS was derived from a logistic regression model with either RAASi, ACEi or ARB as dependent variables, and clinical factors as potential determinants. The individual models have been displayed in the manuscript to identify the effect of correcting for the additional potential confounding factors. Effect modification was assessed for age and sex by adding a multiplicative variable. The data showed no multiplicative effect modification for RAASi, ACEi or ARB.

A potential effect of RAAS modulation on clinical endpoints may be offset by comorbidity such as hypertension. To explore the latter, additional analyses were performed with calcium-channel blockers (CCB). Patients without CCB were used as the reference category. The association with these drugs and clinical endpoint were added as CCB do not target RAAS.

There was missing data for mortality in 152 patients (3.1%) and for ICU admission in 156 patients (3.2%). Imputation of missing data in some variables such as body mass index or clinical endpoints was not applied due to potential collinearity and to the limited number of available variables.

A 2-tailed probability value of <.05 was used as the criterion for statistical significance. All analyses were performed using SPSS, version 25.0 on Windows (SPSS inc., Chicago, IL, USA).

3 | RESULTS

3.1 | Demographics and characteristics

A total of 4870 patients with COVID-19 were included. Table 1 describes the baseline characteristics. The median age was 68 [IQR 57–78] and 62.5% of the patients were male. Prior to admission, a RAASi was used by 1592 patients (32.7%), an ACEi by 847 (17.4%) patients and an ARB by 761 (15.6%) patients. In total 1206 (24.8%) patients were admitted to the ICU, and 975 (21.0%) patients died.

Table 2 describes the difference in baseline characteristics between patients without RAASi and patients with an ACEi or ARB prior to admission. Patients with RAASi are generally older (Age$_{median}$ ACEi 73 y [IQR 64–80], Age$_{median}$ ARB 73 y [IQR 66–80] compared to no RAASi use (Age$_{median}$ no RAASi 65 [IQR 54–76]), used more other blood pressure-lowering drugs (ACEi 76.5%, ARB 80.2% *vs.* no RAASi

TABLE 1 Baseline characteristics

	Total (n = 4870)
Age (y)	68 [57–78]
<65	2020 (41.5)
65–75	1236 (25.4)
>75	1614 (33.1)
Male sex	3046 (62.5)
Concomitant medication	
Blood pressure-lowering medication	2560 (52.6)
RAASi	1592 (32.7)
Angiotensin-converting enzyme inhibitors	847 (17.4)
Angiotensin receptor blocker	761 (15.6)
Blood pressure-lowering medication (excluding RAASi)	2213 (45.4)
Calcium-channel blocker	883 (18.1)
Diuretic	905 (18.6)
Potassium-sparing diuretic	159 (3.3)
Beta-blocker	1219 (25.0)
Antiplatelet therapy	1025 (21.0)
Glucose lowering medication	983 (21.2)
Number of unique drugs	5 [2–8]
Countries	
Austria	13 (0.3)
Belgium	85 (1.7)
Switzerland	178 (3.7)
Germany	71 (1.5)
Denmark	62 (1.3)
France	204 (4.2)
UK	208 (4.3)
Italy	754 (15.5)
The Netherlands	2967 (61.9)
Portugal	148 (3.0)
Spain	180 (3.7)
Endpoints	
Composite clinical endpoint	1873 (38.5)
Mortality	975 (21.0)
Intensive care unit admission	1206 (24.8)

Displayed values are medium [interquartile range] or *n* (%).
RAASi, renin–angiotensin–aldosterone system inhibitors.

29.5%) and used overall more drugs (drugs$_{median}$ ACEi and ARB both 7 [IQR 5–10] *vs.* drugs$_{median}$ no RAASi 3 [IQR 1–6].

3.2 | Clinical outcomes and used medication

The association between RAASi and the study endpoints is displayed in Table 3. After adjustment for available confounders (Model III), no

TABLE 2 Characteristics per exposure

	No RAASi (n = 3278)	ACEi (n = 847)	ARB (n = 761)
Age (y)	65 [54–76]	73 [64–80]	73 [66–80]
<65	1627 (49.6)	220 (26.0)	177 (23.3)
65–75	750 (22.9)	243 (28.7)	247 (32.5)
>75	901 (27.5)	384 (45.3)	337 (44.3)
Male sex	2023 (61.7)	587 (69.3)	447 (58.7)
Concomitant medication			
Blood pressure-lowering medication (excluding RAASi)	968 (29.5)	648 (76.5)	610 (80.2)
Calcium-channel blocker	361 (11.0)	259 (30.6)	267 (35.1)
Diuretic	383 (11.7)	270 (31.9)	256 (33.6)
Potassium-sparing diuretic	64 (2.0)	49 (5.8)	46 (6.0)
Beta-blocker	572 (17.4)	353 (41.7)	299 (39.3)
Antiplatelet therapy	467 (14.2)	317 (37.4)	243 (31.9)
Glucose lowering drugs	457 (13.9)	275 (32.5)	259 (34.0)
Number of unique drugs	3 [1–6]	7 [5–10]	7 [5–10]
Endpoints			
Composite clinical endpoint	1200 (36.6)	346 (40.9)	333 (43.8)
Mortality	556 (17.0)	218 (25.7)	205 (26.9)
Intensive care unit admission	828 (25.3)	187 (22.1)	194 (25.5)

Displayed values are medium [interquartile range] or n (%).
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; RAASi, renin–angiotensin–aldosterone system inhibitor.

TABLE 3 Association between RAAS inhibition and clinical outcomes

Study endpoint	No RAASi (n = 3278)	RAASi (n = 1592) OR (95%CI)	ACEi (n = 847) OR (95%CI)	ARB (n = 761) OR (95%CI)
Composite clinical endpoint (mortality and/or ICU admission) (n = 1873)				
I	REF	1.28 (1.13–1.45)	1.21 (1.04–1.42)	1.35 (1.15–1.59)
II		1.10 (0.97–1.25)	1.02 (0.86–1.20)	1.18 (1.00–1.40)
III		1.01 (0.87–1.16)	0.94 (0.79–1.12)	1.09 (0.90–1.30)
IV		1.01 (0.88–1.17)	0.95 (0.80–1.13)	1.10 (0.92–1.32)
Mortality (n = 975)				
I	REF	1.77 (1.53–2.05)	1.72 (1.43–2.06)	1.83 (1.52–2.20)
II		1.22 (1.04–1.43)	1.16 (0.95–1.41)	1.29 (1.05–1.57)
III		1.07 (0.90–1.27)	1.03 (0.84–1.27)	1.12 (0.90–1.39)
IV		1.08 (0.92–1.28)	1.03 (0.84–1.27)	1.14 (0.93–1.41)
ICU admission (n = 1206)				
I	REF	0.93 (0.80–1.06)	0.85 (0.70–1.01)	1.01 (0.84–1.22)
II		1.03 (0.89–1.20)	0.92 (0.76–1.12)	1.15 (0.95–1.39)
III		1.06 (0.90–1.26)	0.96 (0.78–1.19)	1.21 (0.98–1.49)
IV		1.06 (0.90–1.25)	0.96 (0.79–1.18)	1.20 (0.98–1.48)

Model: I, crude; II, adjusted for sex, age category (<65 y, 65 to 75 y, >75 y); III, II + additional adjustment for concomitant drugs (blood pressure-lowering drugs other than RAASi, antiplatelet drugs, glucose lowering drugs); IV, adjusted for the propensity score, composed of sex, age category, concomitant drugs.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; RAASi, renin–angiotensin–aldosterone system inhibitor.

statistically significant association of RAASi use on the composite clinical endpoint (OR$_{RAASi}$: 1.01; 95%CI: 0.87 to 1.16), mortality (OR$_{RAASi}$: 1.07; 95%CI: 0.90 to 1.27) or ICU admission (OR$_{RAASi}$: 1.06; 95%CI: 0.90 to 1.26) was present when compared to no RAASi use prior to admission. Similar results were seen for ACEi and ARB's after adjustment for available confounders (Model III) on the composite clinical endpoint (OR$_{ACEi}$: 0.94; 95%CI: 0.79 to 1.12 and OR$_{ARB}$: 1.09; 95%CI: 0.90 to 1.30), mortality (OR$_{ACEi}$: 1.03; 95%CI: 0.84 to 1.27 and OR$_{ARB}$: 1.12; 95%CI: 0.90 to 1.39) or ICU admission (OR$_{ACEi}$: 0.96; 95%CI: 0.78 to 1.19 and OR$_{ARB}$: 1.21, 95%CI: 0.98 to 1.49) when compared to no RAASi use prior to admission. Similar to Model III, no statistically significant association was seen for RAASi, ACEi or ARB and the composite clinical endpoint, mortality and ICU admission when compared to no RAASi prior to admission after adjusting for the propensity score (model IV).

The exploratory analyses with CCBs showed similar results for mortality (model III OR$_{CCB}$: 1.12; 95%CI: 0.92 to 1.35). However, a statistically significant association was seen between CCB use and ICU admission (OR$_{CCB}$ 1.28; 95% CI: 1.07 to 1.54) when compared to no CCB use prior to admission (Table S1).

3.3 | Clinical outcomes and standard dose of medication

The association between the standard dose of medication and clinical outcome is displayed in Table 4. Similar to the (binary) use of RAASi, ACEi and ARB, there was no statistically significant association between the dose of RAASi, ACEi or ARB and the composite clinical endpoint, mortality or ICU admission.

4 | DISCUSSION

This multinational, multicentre, retrospective cohort study aimed to investigate the associations between the use of RAASi, ACEi and ARB prior to admission, and hospital mortality and ICU admission in a large sample of COVID-19 patients. The results indicated that the use of RAASi prior to hospital admission had neither a harmful, nor beneficial effect on mortality or ICU admission. Additionally, no differential effect was observed when using an ACEi or ARB prior to admission on clinical outcomes.

Since the outbreak of COVID-19, concerns have emerged about the effect of different types of medication on clinical course and mortality of COVID-19, with a particular focus on ACEi and ARB. Recently, the first studies addressing this subject have been published, all with different study designs.[25-30] Previous studies assessed both the effect of RAASi on the incidence of COVID-19[25,26,30] and the effect of the use of RAASi prior to admission on clinical outcomes of COVID-19.[27-29] These studies found no relationship of RAASi on either the incidence or COVID-19 related morbidity or mortality. One of the first retrospective studies by Mehra et al.[31] included 8910 patients from 169 hospitals in 11 countries and examined the relationships between many variables and in-hospital mortality without a pre-specified hypothesis increasing the probability of chance associations. Remarkably, this study was withdrawn due to concerns about study design and data, because all the authors were not granted access to the raw data and the raw data could not be made available to a third-party auditor.[32] As a result, the primary data sources underlying this article were unable to be validated.[33] This emphasizes the importance of replication studies, preferably with different study designs since every study design has its own bias.

TABLE 4 Association between standard dose of RAAS inhibition and clinical outcomes

Study endpoint	No RAASi (n = 3278)	RAASi (n = 1592) OR (95%CI)	ACEi (n = 847) OR (95%CI)	ARB (n = 761) OR (95%CI)
Composite clinical endpoint (mortality and/or ICU admission) (n = 1873)				
I	REF	1.05 (1.02–1.08)	1.05 (1.01–1.09)	1.05 (1.00–1.09)
II		1.02 (0.99–1.05)	1.02 (0.98–1.06)	1.01 (0.97–1.06)
III		1.01 (0.98–1.04)	1.01 (0.97–1.05)	1.00 (0.95–1.04)
Mortality (n = 975)				
I	REF	1.09 (1.05–1.12)	1.09 (1.04–1.13)	1.11 (1.06–1.16)
II		1.02 (0.99–1.06)	1.02 (0.97–1.06)	1.04 (0.99–1.09)
III		1.00 (0.97–1.04)	1.00 (0.95–1.05)	1.01 (0.96–1.06)
ICU admission (n = 1206)				
I	REF	0.98 (0.95–1.01)	0.99 (0.94–1.03)	0.97 (0.92–1.02)
II		1.00 (0.96–1.03)	1.01 (0.96–1.05)	0.99 (0.93–1.04)
III		1.00 (0.96–1.04)	1.01 (0.96–1.06)	0.99 (0.93–1.04)

*OR per 1 standard dosing increase (e.g. lisinopril 10–20 mg).
Model: I, crude; II, adjusted for sex, age category (<65 y, 65 to 75 y, >75 y); III, II + additional adjustment for concomitant drugs (blood pressure-lowering drugs other than RAASi, antiplatelet drugs, glucose lowering drugs).
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; RAASi, renin–angiotensin–aldosterone system inhibitor.

In the studies of Mancia et al.[25] and Reynolds et al.,[26] data were collected from a general database (in Mancia et al. up to date up to December 2019) and electronic health records respectively to assess the incidence of COVID-19 in RAASi users. In contrast, the study of Abajo et al.[30] used a case–control design. A strength of the COMET study design is that hospital pharmacists, clinical pharmacologists and treating physicians obtained and verified real-time medication data, resulting in critically reviewed, up-to-date data.

Zhang et al.[27] and Li et al.[28] assessed the association between RAASi use and all-cause mortality and severe diseases outcomes respectively. They did not perform a differential analysis on the effect of ACEi or ARB on the COVID-19-related morbidity and mortality. The present study examined both the effect of ACEi and ARBs separately as well as RAASi in general on the clinical course and mortality of COVID-19. Furthermore, the effect of CCB on the clinical course and mortality of COVID-19 was assessed. This served as a confirmation, since CCBs have a blood pressure lowering effect, but do not target the RAAS. Additionally, a dose–response analysis of ACEi and ARBs in relation to clinical course and outcome was performed, had an association been discovered this would have been used to assess causality.

A statistically significant effect for the use of CCBs prior to admission and trend for the use of ARB was observed on admission to ICU. This might be due to confounding or multiple testing. However, the increased risk of ICU admission could also be related to the underlying hypertensive condition. Although RAASi are mostly prescribed for their blood pressure-lowering effects, RAASi is the therapy of choice in other morbidities, such as congestive heart failure. However, the low percentage of users of potassium-sparing diuretics suggests that the percentage with clinically relevant congestive heart failure was low and this might not have significantly affected the correlation between RAASi and clinical course of COVID-19.

In contrast to more regionally centred studies, the COMET study included patients from 63 hospitals from 10 European countries, including both academic and nonacademic hospitals. This makes the data collected broadly representative and generalizable.

Finally, the protocol was published for scientific transparency.[19]

A potential limitation of the current study, similarly to the earlier studies, was the potential for confounding due to the observational design. Confounding by indication is important in intervention-related studies. To correct for this, a PS was calculated and the association between RAAS inhibition and clinical outcomes was assessed using an exploratory PS model. A PS was created and several variables were adjusted for; however, due to the limited number of collected variables, the PS may have limited value. The minimization of collected parameters ensured quick data entry and made participating in this study accessible, but the limited number of parameters precluded extensive correction for potential confounders. Nonetheless, due to detailed medication data collected, major comorbidities could be inferred and included in the multivariate and PS analyses. Secondly participants in our study were hospitalized patients. Patients with relatively mild disease who were not admitted were not included. The inclusion of patients was consecutive, thereby limiting major selection bias. However, this design limits the generalizability of the results to patients in primary health care.

The high incidence of RAASi is in line with the high frequency of RAASi use in the Netherlands, this can be explained by the fact that the Dutch centres were large contributors to this study. Similar percentages are seen in other studies. Mancia et al.[25] reported 23.9% ACEi users and 22.2% ARB users in COVID-19 positive patients. Additionally, Conversano et al.[29] reported a 32% use of ACE/ARB in survivors who tested positive for COVID-19. The large proportion of elderly patients with comorbidities also contributes to the high incidence of RAASi in COVID-19 patients, which is supported by our data. The data collection regarding medication in the current study focused on data prior to hospital admission. No information on medication continuation or discontinuation after testing positive for COVID-19 was available. If RAASi was discontinued during hospitalization, it is unlikely to produce different outcomes concerning the effect of ACE2 on our endpoints. As seen in other RAAS parameters, up- and downregulation of ACE2 might take time and would not have an immediate effect. Furthermore, clinical guidelines and statements recommended continuation of RAASi.[34–36] Nonetheless, continued RAASi during hospitalization could be an aim of a follow-up study. Furthermore, we have no insight into adherence to treatment. All data presented are prescribed medication. However, this applies to almost all studies in this area and nonadherence would probably result in nondifferential misclassification.

In conclusion, the COMET study showed that RAASi use prior to hospital admission was not associated with an increase in COVID-19 related mortality or ICU admission. The results indicated that the preadmission use of RAASi has neither a harmful nor beneficial effect on hospital mortality or ICU admission. The data do not suggest that the relationship between hypertension and severity of COVID-19 can be explained by the use of ACEi or ARB prior to hospital admission and their regulation of ACE2.

COMPETING INTERESTS

The authors are solely and equally responsible for the design and conduct of this study, all study analyses, and the drafting and editing of the paper and its final contents.

CONTRIBUTORS

R.S.G.S., F.E.F.H., M.L., J.V. and H.v.d.K. contributed to study design, data collection, data analysis, writing and revision of the article. B.P.A. v.d.L. contributed to study design, data collection and revision of the article. E.B. contributed to study design, data analysis and revision of the article. S.D.B. contributed to writing and revision of the article. All

other authors in the appendix are contributed to data collection and revision of the article.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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