Effect of combined renin angiotensin aldosterone inhibitors and diuretic treatment among patients hospitalized with SARS-CoV-2 Infection COVID-19

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Abstract

Background: Antecedent use of renin angiotensin aldosterone inhibitors (RAASi) appears crucial to prevent clinical deterioration and protect against cardiovascular and/or thrombotic complications of Coronavirus Disease (COVID-19), for indicated patients. Doubts have been raised about continuing treatment throughout infection, and nothing is known regarding its effect with concomitant medications. Hence, the purpose of this paper is to evaluate the differential effect of RAASi continuation in patients hospitalized with COVID-19 according to diuretic use.

Methods: We used the Coracle (epidemiology, clinical characteristics, and therapy in real life patients affected by Sars-Cov-2) multi-center registry, which contains data of hospitalized patients with COVID-19 from 4 regions of Italy. We performed analyses on adult (50+ years) records with admission on/after February 22, 2020 with a known mortality or discharge status as of April 1, 2020. We constructed a multivariable Firth logistic regression model to complete our objective.

Results: There were 286 patients in this analysis. Overall, 100 (35.0%) patients continued RAASi and 186 (65%) discontinued. There were 98 patients who were treated with a diuretic; 51 (52%) of those continued RAASi. The in-hospital mortality rates among patients treated with a diuretic and continued vs. discontinued RAASi were 7.8% vs 25.5% ($p = 0.0179$). There were 188 patients who were not treated with a diuretic; 49 (26.1%) of those continued RAASi. The in-hospital mortality rates among patients who were not treated with a diuretic and continued vs. discontinued RAASi were 16.3% vs 9.4% ($p = 0.1827$). After accounting for age, congestive heart failure, and coronary heart disease/ischemic heart disease, continuing RAASi decreased the risk of mortality by approximately 72% ($OR = 0.28$, 95% $CI = 0.08 - 0.94$, $p = 0.0391$) for patients treated with diuretics, but did not alter the risk in patients who were not treated with diuretics.

Conclusion: Diuretic use in hospitalized patients with COVID-19 who were on RAASi prior to admission was associated with increased risk of in-hospital mortality. Whether this combined therapy increases risk or is the reflection of a more severe presentation deserves further investigation. Continuing RAASi therapy in patients concomitantly treated with diuretics was associated with reduced in-hospital mortality.

Introduction

Since the coronavirus disease (COVID-19) pandemic engulfed the world in 2020, it has been established that its complications are greatly exacerbated in patients affected by cardiovascular (CV) disease (CVD). [1,2] Patients with high CV risk burden are more likely to develop a severe clinical presentation and experience an increased mortality risk. Traditional risk factors such as hypertension, diabetes, obesity, and metabolic disorders are considered predictive features for both CV and respiratory complications. [3,4] Therefore, the most common types of CVD (ischemic heart disease, chronic heart failure) are associated with increased risk for adverse events. Indeed, a substantial number of patients hospitalized for COVID-19 present with CV complications related to the underlying infection or due to acute

destabilization of their chronic disease. [5-7] Indeed, RAASi is the landmark treatment for patients with evidence of established CVD, as well as for those with high CV risk. However, it has been hypothesized that use of RAASi may negatively impact outcomes of patients with COVID-19 by influencing the expression of the angiotensin converting enzyme 2 (ACE2) receptor. The protein viral spike S located on the external virus membrane together with protein spike priming by the transmembrane protease serine 2, use the ACE to enter the human cell and infect the host.[8] Because the ACE2 receptor is not confined to the CV system, but is also expressed in epithelial cells of the respiratory system, many queries have been raised about the opportunity to withdraw this therapy in infected patients. [9] Of note, the potential virus facilitation due to ACE activation is counterbalanced by the protective CV effects of RAASi.[10-14] The use of RAASi appears crucial to prevent clinical deterioration and possibly protect the CV system from CV and/or thrombotic complications of COVID-19, for patients with the appropriate indications. [15,16] Despite a common agreement about the neutral-to-protective role of RAASi prior to infection, doubts have been raised about continuing treatment throughout infection, since it may worsen kidney function, plasma osmolality, and/or sodium and water exchange when associated with dehydration or diffuse inflammatory burden. Two recent studies reported nonsignificant differences in adverse event rates in patients who continued vs. discontinued RAASi treatment, supporting the notion to continue RAASi therapy in those with appropriate indications. [17,18] However, there are two primary questions that remain unanswered from these studies: 1) is RAASi therapy associated with outcomes in patients with COVID-19, independently of CVD?; 2) is this association uniform across concomitant medications? To investigate these aspects, we retrospectively studied the effect of RAASi in combination with diuretics (either thiazide or loop), and examined whether the combination therapy may have similar effects among different types of CVD.

Methods

Data

The data used for this study have been previously described.[19] In short, we utilized the Coracle (epidemiology, clinical characteristics, and therapy in real life patients affected by Sars-Cov-2) multi-center registry, which contains data of hospitalized patients with COVID-19 from 4 regions of Italy. We performed analyses on adult records from the registry with an admission on or after February 22, 2020 with a known mortality or discharge status as of April 1, 2020. We restricted this analysis to patients aged 50 years or more to be consistent with prior work. Further, because our primary interest was to evaluate the possibility of a differential effect of RAASi continuation on in-hospital mortality between those treated with diuretics (either thiazide or loop) vs. those not treated with diuretics, we additionally excluded patients who were not treated with an ACE inhibitor and/or ARB prior to hospitalization, as well as those who were missing information regarding diuretic treatment. This work was approved by the ethical committee of Turin (Coracle registry: epidemiology clinical characteristics and therapy in real life patients affected by SARS-CoV-2).

Statistical Analysis

Categorical variables are reported as frequencies and percentages. Differences in characteristics between patients who continued vs. discontinued RAASi were assessed via Chi-Square or Fisher's Exact test. Analyses were performed within subgroups of patients treated with diuretics and patients not treated with diuretics. We constructed a multivariable logistic regression model including a term for RAASi continuation, diuretic use, and an interaction term to answer our primary objective. There were too few events to fully explore adjusted models using traditional logistic regression, so we utilized Firth logistic regression to build a model adjusting for age and CVD (coronary artery disease/ischemic heart disease and congestive heart failure). We also considered subgroup analyses according to type of RAASi (ACEi and angiotensin receptor blocker [ARB]). Analyses were performed using SAS version 9.4 (Cary, NC).

Results

We reviewed 956 patient records; 175 (18.3%) were excluded due to age < 50 years, 477 (49.9%) records were excluded due to lack of RAASi treatment prior to hospitalization, and 18 (1.9%) records were excluded due to unknown use of diuretics. Hence, 286 patients were included in this analysis. Overall, 100 (35.0%) patients continued RAASi and 186 (65%) discontinued RAASi. There were no significant differences in patient characteristics between those who continued vs. discontinued treatment (Table 1). There were 98 patients who were treated with a diuretic; 51 (52%) of those patients continued RAASi and 47 (48%) discontinued. The in-hospital mortality rates among patients treated with a diuretic and continued vs. discontinued RAASi were 7.8% vs 25.5% ($p = 0.0179$). There were 188 patients who were not treated with a diuretic; 49 (26.1%) of those continued RAASi and 139 (73.9%) discontinued. The in-hospital mortality rates among patients who were not treated with a diuretic and continued vs. discontinued RAASi were 16.3% vs 9.4% ($p = 0.1827$).

Overall, patients treated with diuretics were at an increased risk for in-hospital mortality (Table 2). Conversely, when considering all patients, (dis)continuing RAASi was not associated with in-hospital mortality. However, we found evidence to support a differential effect of RAASi continuation on in-hospital mortality, according to diuretic treatment (interaction $p=0.0098$). Specifically, continuing RAASi in patients who were not treated with diuretics did not have a significant association with in-hospital mortality (OR = 1.89, 95% CI = 0.73 - 4.88); however, continuing RAASi in patients who were treated with diuretics decreased the risk of in-hospital mortality by approximately 75% (OR = 0.25, 95% CI = 0.07 – 0.84). After accounting for age, which conferred an increased risk of in-hospital mortality of approximately 9% per year of life (OR = 1.09, 95% CI = 1.05 – 1.14, $p < 0.0001$), as well as congestive heart failure and coronary heart disease/ischemic heart disease, neither of which were associated with the risk of mortality, continuing RAASi decreased the risk of mortality by approximately 72% (OR = 0.28, 95% CI = 0.08 – 0.94, $p = 0.0391$) for patients treated with diuretics, but did not alter the risk in patients who were not treated with diuretics (Table 2). The Hosmer-Lemeshow statistic did not indicate any problems with the model fit.

Upon admission, 160 (55.9%) patients were using an ACEi and 126 (44.1%) were using an ARB. In subgroup analyses, we failed to find an association between RAASi (dis)continuation and in-hospital

mortality among ACEi users, regardless of diuretic use (Table 3). However, there was evidence to support a differential role of RAASi continuation on in-hospital mortality among ARB users according to diuretic use. Specifically, the mortality rates for ARB continuation vs. discontinuation among patients treated with a diuretic were 3.9% vs. 35% ($p=0.0142$), whereas the rates were 17.7% vs. 7.9% ($p=0.3568$) among patients who were not treated with a diuretic.

Discussion

In this analysis of 286 patients hospitalized with COVID-19, early in early phase of the pandemic, we found that patients taking combination RAASi and diuretic for the indication of Hypertension were at higher risk of in-hospital mortality than patients taking RAASi alone. We also found that continuing RAASi therapy was highly beneficial, in terms of in-hospital mortality, for patients who were concomitantly treated with a diuretic. We did not find an association between RAASi (dis)continuation and in-hospital mortality for patients who were not treated with a diuretic. These trends remained true after accounting for age, which was also associated with increased risk of mortality, as well as coronary artery disease and congestive heart failure. We found that RAASi continuation was most important for patients with COVID-19 treated with both an ARB and a diuretic. These findings suggest that RAASi combined with diuretic use may have been a proxy for left ventricular diastolic or systolic dysfunction; thus, these drugs exerted a beneficial effect throughout the COVID-19 hospitalization course, which is invariably influenced by degrees of respiratory failure.

Others have suggested that RAASi treatment may be protective in patients with COVID-19. [10,12,13] Most studies focused on these drugs in the context of hypertension and not in other CV settings such as IHD or CHF. Among those with HF, the compiled results of many studies suggest that continuation of RAASi and other components of goal-directed medical therapy is consistently associated with reduced mortality and hospitalization. [20] This principle appears to extend to patients hospitalized with COVID-19 at high risk for acute cardiorenal syndromes.[21,22] Recently, the BRACE CORONA trial showed no association between RAASi continuation and the primary outcome of death following hospital discharge for patients with COVID-19. [17] Further, a separate study demonstrated that discontinuation of RAASi therapy for patients hospitalized with COVID-19 was associated with increased risk of mortality following discharge. [18] Because patients with severe hypertension and those with other CVD are often treated with a combination of RAASi and diuretics, we investigated the differential effect of (dis)continuing this combination therapy on in-hospital mortality. Our work had two primary findings 1) patients who were treated with diuretics had a higher rate of in-hospital mortality compared to those who were not treated with a diuretic (16.3% vs. 11.1%); 2) we confirmed an overall neutral effect on in-hospital mortality for patients continuing versus discontinuing RAASi, except for patients who were also treated with a diuretic. The risk of in-hospital mortality was significantly increased for patients treated with a diuretic who discontinued RAASi therapy compared to those who continued RAASi therapy (25.5% vs. 7.8%); this finding was largely driven by ARB-users. These observations may support the hypothesis that in COVID-19 an enhancement of RAAS activity is harmful and correlates with the degradation of respiratory

function as well as the arterial vascular tone] In this view, the use of diuretics amplifying the activity of RAAS can lead worse outcome.

The roles of RAASi observed in various settings may be explained by the different baseline conditions in terms of age, sex, ethnicity, extra-cardiac comorbidities and frailty. Indeed, the treatment may configure a negative effect in older patients with more advanced systemic diseases and vulnerable general conditions. Therefore, ACE expression varies in relation to race and sex, explaining some discrepancies observed in young people and in black patients, in whom prior ARB use was associated with augmented viral susceptibility and infection severity.[24,25]

There are clinical scenarios in which patients may need to discontinue therapy. Patients with more hemodynamic impairment, lower blood pressure, and dehydration may benefit from discontinuing RAASi. [26] Notably, A double-edged mechanism related to clinical presentation and underlying CVD may be posed. In this context, it is important to know the clinical status related to the underlying CVD and baseline condition prior to infection. [9,27] In the Swedish meta-analysis including 138,700 patients, the protective effect of RAASi was observed for all types of CVD studied. Unfortunately, that study investigated only antecedent use of RAASi; the effect of continuation was not evaluated.[28] In another study comparing CV therapies head-to-head, Reynolds and colleagues did not find relevant differences between any of the five major drug classes. [29] Behind these data, some observations about the role of the ACE system in viral spread may be warranted. The virus could enter directly inside the epithelial cell of the respiratory system via the ACE receptor, inducing an inflammatory cascade via bradykinin escape. [30,31] The subsequent increase in prostaglandins and cyclooxygenases leads to interleukins overproduction. ACE catalyzes the conversion between angiotensin I to angiotensin II, resulting in a potent vasoconstrictive effect, whereas ACE2 converts angiotensin II to angiotensin 1-7, causing significant vasodilatory, anti-inflammatory, and anti-fibrotic effects. [32,33] The consequent ACE2 upregulation mediated by ACE-inhibitors leads to beneficial pulmonary and vascular effects, improving endothelial and epithelial cell metabolism, and antagonizing thrombotic cascade. [16,34] Current mechanisms are likely less pronounced by ARB, in which ACE blockade occurs only at the angiotensin tissue (AT2) receptor level with incomplete protection against ACE system modification in COVID-19. [35] Overall, our findings confirm a relevant role of RAASi in the context of COVID-19 and show the importance of considering the basal clinical condition, severity of infection, and concomitant treatments that may influence drug discontinuation and outcomes. [36]

Limitations

This a retrospective observational analysis with relatively small number of patients meeting inclusion criteria; thus, the findings are limited by the small sample size. Further, due to the small event count, we required specialized statistical methods to produce tractable estimates and confidence intervals for the multivariable adjusted model. Approximately 98% of the patients in this study had hypertension, so the findings may not be widely generalizable. Additionally, we did not record information regarding prior hospitalizations and/or severity of extracardiac diseases affecting these patients. Similarly, we lacked

information on RAASi dose, duration, and tolerability with respect blood pressure and kidney function. The observational period was strictly limited to the hospital setting; no data were available post-discharge. Our findings cannot be extended to ambulatory patients with less severe symptoms. Finally, these data reflect patients hospitalized during the first wave of the pandemic in Italy and may not reflect characteristics of patients hospitalized more recently since evidence of viral mutations.

Conclusion

Diuretic use in hospitalized patients with COVID-19 who were on RAASi prior to admission was associated with increased risk of in-hospital mortality. Whether this combined therapy increases risk or is the reflection of a more severe presentation deserves further investigation. While (dis)continuing RAASi therapy for hypertension was not associated with the risk of in-hospital mortality, continuing RAASi therapy in patients who were concomitantly treated with diuretics was associated with reduced in-hospital mortality.

Declarations

Authors contribution list:

ALBERTO PALAZZUOLI conception of the work ideation and writing paper

KRISTEN TUCSON Statistical analysis and creation new software

MARCO VIVENZI data collection final approval

FABRIZIO D'ASCENZO critical review and stat analysis

GAETANO M DE FERRARI critical review

SILVIA MONTICONE data collection and writing support

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GUIDO TAVAZZI acquisition analysis final approval

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FRANCESCO FEDELE critical review

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Compliance with Ethical Standards No sources of funding, no potential conflicts of interest (financial or non-financial) were provided during the study, written informed consent were obtained by all patients and data were anonymized.

Disclosures: The study was done by the CORACLE registry that is an observational registry no profit collecting data from various Italian Hospitals and Sites

Availability of data and material: The presented data are recorded into an excel file including all participating centers; because the study is an observational registry this is a spontaneous dataset can be provided if reviewer would verify the statistic analysis.

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Tables

Table 1. Characteristics of patients hospitalized with COVID-19 according to RAASi continuation and diuretic use

	Diuretics Utilized			Diuretics Not Utilized		
	RAASi Continued (n=51)	RAASi Discontinued (n=47)	p-value	RAASi Continued (n=49)	RAASi Discontinued (n=139)	p-value
Age (years)	73.48±9.22	76.12±8.27	0.1398	72.05±11.75	70.22±9.94	0.2914
Gender (male)	25 (49%)	24 (51.1%)	0.8398	36 (73.5%)	95 (68.3%)	0.5022
Hypertension	49 (96.1%)	45 (95.7%)	1.0000	49 (100%)	136 (97.8%)	0.5688
Obstructive lung disease	4 (7.8%)	8 (17%)	0.1661	4 (8.2%)	16 (11.5%)	0.5134
Diabetes mellitus	18 (35.3%)	9 (19.1%)	0.0642	10 (20.4%)	33 (23.7%)	0.6329
Smoking status			0.9794			0.8420
Yes	4 (7.8%)	4 (8.5%)		5 (10.2%)	16 (11.5%)	
No	41 (80.4%)	38 (80.9%)		40 (81.6%)	111 (79.9%)	
Former	6 (11.8%)	5 (10.6%)		3 (6.1%)	12 (8.6%)	
Missing	0 (0%)	0 (0%)		1 (2%)	0 (0%)	
Chronic heart failure	13 (25.5%)	13 (27.7%)	0.8080	3 (6.1%)	4 (2.9%)	0.3023
Coronary artery disease	19 (37.3%)	12 (25.5%)	0.2125	7 (14.3%)	13 (9.4%)	0.3355
Beta blocker	20 (39.2%)	17 (36.2%)	0.7560	8 (16.3%)	39 (28.1%)	0.1030
Calcium channel antagonist	16 (31.4%)	11 (23.4%)	0.3777	18 (36.7%)	37 (26.6%)	0.1808
Thiazide diuretic	40 (78.4%)	25 (53.2%)	0.0083	0 (0%)	0 (0%)	-
Loop diuretic	20 (39.2%)	31 (66%)	0.0081	0 (0%)	0 (0%)	-
Invasive ventilation	6 (11.8%)	5 (10.6%)	0.8599	7 (14.3%)	21 (15.1%)	0.9429
High flow ventilation without intubation	23 (45.1%)	21 (44.7%)	0.9669	21 (42.9%)	46 (33.1%)	0.2070
Oxygen low flow	20 (39.2%)	17 (36.2%)	0.7560	21 (42.9%)	61 (43.9%)	0.9258

Table 2. Odds of in-hospital mortality according to RAASi and Diuretic treatments

Effect, unadjusted model	Odds Ratio	95% Confidence Interval Bounds		P-value
Diuretics (yes vs. no), RAASi discontinued	3.32	1.39	7.93	0.0068
Diuretics (yes vs. no), RAASi continued	0.44	0.12	1.56	0.2008
Continue vs discontinue RAASi, no diuretics	1.89	0.73	4.88	0.1880
Continue vs discontinue RAASi, diuretic-treated	0.25	0.07	0.84	0.0244
Effect, adjusted model				
Diuretics (yes vs. no), RAASi discontinued	2.82	1.12	7.1	0.0282
Diuretics (yes vs. no), RAASi continued	0.49	0.14	1.76	0.2722
Continue vs discontinue RAASi, no diuretics	1.62	0.6	4.37	0.3451
Continue vs discontinue RAASi, diuretic-treated	0.28	0.08	0.94	0.0391
Age (per year increase)	1.09	1.05	1.14	<.0001
Coronary artery disease (yes vs. no)	1.48	0.59	3.72	0.4104
Congestive heart failure (yes vs. no)	0.36	0.1	1.32	0.1248

RAASi = renin-angiotensin-aldosterone system inhibitor

Unadjusted model: overall effect of RAASi continuation p = 0.1880, overall effect of diuretic use p = 0.0068, interaction term p = 0.0098.

Adjusted model: overall effect of RAASi continuation p = 0.3451, overall effect of diuretic use p = 0.0282, interaction term p = 0.0279.

Table 3 In-hospital mortality rates according to RAASi type, continuation, and diuretic use

	Diuretics			No Diuretics		
	RAASi Continued	RAASi Discontinued	P-value	RAASi Continued	RAASi Discontinued	P-value
ACEi	3 (12.0%)	5 (18.5%)	0.7050	5 (15.6%)	8 (10.5%)	0.5213
ARB	1 (3.9%)	7 (35.0%)	0.0142	3 (17.7%)	5 (7.9%)	0.3568
RAASi = renin-angiotensin-aldosterone system inhibitor; ACEi = angiotensin converting enzyme inhibitor; ARB = aldosterone receptor blocker						
N (ACEi and diuretic) = 52; N (ACEi and no diuretic) = 108						
N (ARB and diuretic) = 46; N (ARB and no diuretic) = 80						
All p-values calculated using Fisher's Exact Test						

Figures

Figure 1

Differences in hospital mortality for patients who continued vs discontinued RAASi treatment according to additional use of diuretics