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Usefulness of Combined Renin-Angiotensin System Inhibitors and Diuretic Treatment In Patients Hospitalized with COVID-19

Alberto Palazzuoli, MD, PhD[a,*], Kristen M. Tecson, PhD[b,c], Marco Vicenzi, MD[d], Fabrizio D'Ascenzo, MD, PhD[e], Gaetano Maria De Ferrari, MD[e], Silvia Monticone, MD[f], Gioel G. Secco[g], Guido Tavazzi, MD[h], Giovanni Forleo, MD[i], Paolo Severino, MD[j], Francesco Fedele, MD[j], Francesco De Rosa, MD[k], and Peter A. McCullough, MD, MPH[l]

Antecedent use of renin-angiotensin system inhibitors (RASi) prevents clinical deterioration and protects against cardiovascular/thrombotic complications of COVID-19, for indicated patients. Uncertainty exists regarding treatment continuation throughout infection and doing so with concomitant medications. Hence, the purpose of this study is to evaluate the differential effect of RASi continuation in patients hospitalized with COVID-19 according to diuretic use. We used the Coracle registry, which contains data of hospitalized patients with COVID-19 from 4 regions of Italy. We used Firth logistic regression for adult (>50 years) cases with admission on/after February 22, 2020, with a known discharge status as of April 1, 2020. There were 286 patients in this analysis; 100 patients (35.0%) continued RASi and 186 (65%) discontinued. There were 98 patients treated with a diuretic; 51 (52%) of those continued RASi. The in-hospital mortality rates in patients treated with a diuretic and continued versus discontinued RASi were 8% versus 26% (p = 0.0179). There were 188 patients not treated with a diuretic; 49 (26%) of those continued RASi. The in-hospital mortality rates in patients not treated with a diuretic and continued versus discontinued RASi were 16% versus 9% (p = 0.1827). After accounting for age, cardiovascular disease, and laboratory values, continuing RASi decreased the risk of mortality by approximately 77% (odds ratio 0.23, 95% confidence interval 0.06 to 0.95, p = 0.0419) for patients treated with diuretics, but did not alter the risk in patients treated with RASi alone. Continuing RASi in patients concomitantly treated with diuretics was associated with reduced in-hospital mortality. **(Am J Cardiol 2022;167:133−138)**

Presentation severity and complications of Coronavirus diseases 2019 (COVID-19) are greatly exacerbated in patients who have cardiovascular disease (CVD), most commonly ischemic heart disease and heart failure.[1,2] Many patients hospitalized for COVID-19 present with cardiovascular complications related to acute destabilization of chronic disease.[3−5] Use of a renin-angiotensin inhibitor (RASi) is the landmark treatment for patients with high cardiovascular risk or established CVD. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) uses the angiotensin-converting enzyme 2 (ACE2) receptor to enter the human cell; because the ACE2 receptor's expression occurs in epithelial cells of the respiratory system and is influenced by RASi, concerns about this therapy emerged early in the pandemic.[6,7] Despite eventual agreement about the neutral-to-protective role of RASi before infection, uncertainty lingered about continuing treatment throughout infection.[8−10] Hence, we sought to explore differential associations between in-hospital COVID-19 mortality rates and RASi continuation according to combination diuretic treatment and CVD.

The data used for this study have been previously described.[11] In short, we used the Coracle 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 admission on or after February 22, 2020, with a known discharge status as of April 1, 2020. We restricted this analysis to patients aged 50 years or

[a]Cardiovascular Diseases Unit, Department of Medical Sciences, AOUS Le Scotte Hospital University of Siena, Siena, Italy; [b]Baylor Heart and Vascular Institute, Baylor Scott & White Research Institute, Dallas, Texas; [c]Texas A&M University College of Medicine Health Science Center, Dallas, Texas; [d]Cardiovascular Diseases Unit, Department of Internal Medicine, University of Milan, Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico Milan, Italy; [e]Cardiology, Department of Medical Sciences University of Turin, Le Molinette Hospital Turin, Italy; [f]Internal Internal Medicine ASST Nord Milano E. Bassini Hospital Cisanello Balsamo, Italy; [g]Interventional Cardiology and Cardiac Surgery Unit Azienda Ospedaliera SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy; [h]Intensive Care University of Pavia, Fondazione IRCCS policlinico San Matteo, Pavia Italy; [i]Section of Electrophysiology and Cardiac Pacing, Azienda Ospedaliera Polo Universitario L Sacco, Milano Italy; [j]Department of Clinical Internal Anesthesiological and Cardiovascular Sciences, La Sapienza University Roma Italy; [k]Infectious Diseases Department of Medical Sciences, University of Torino, Città della Salute e della Scienza, Torino Italy; and [l]Cardiorenal Society of America, Phoenix, AZ. Manuscript received August 31, 2021; revised manuscript received and accepted December 7, 2021.

See page 137 for disclosure information.

*Corresponding author: Tel: +39577585363, +39577585461; fax: +39577233480.

E-mail address: palazzuoli2@unisi.it (A. Palazzuoli).

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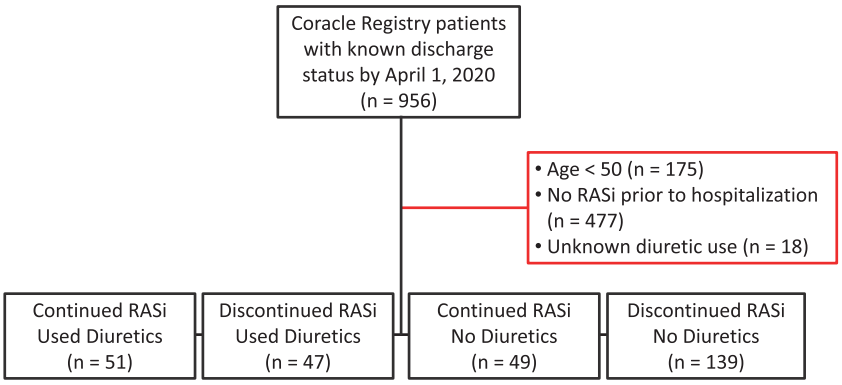

Figure 1. Study flow diagram.

more to be consistent with previous work. Further, because our primary interest was to evaluate the possibility of a differential effect of RASi (either ACE inhibitor or angiotensin receptor blocker [ARB]) continuation on in-hospital mortality between those treated with diuretics (either thiazide or loop) versus those not treated with diuretics, we additionally excluded patients who were not treated with an ACE inhibitor and/or ARB before hospitalization, as well as those who were missing information regarding diuretic treatment. We did not include spironolactone or eplerenone in this analysis. Informed consent was obtained before including anonymized data from patients in the registry. This work was approved by the ethical committee of Turin and extended to participating centers (Coracle registry: epidemiology clinical characteristics and therapy in real-life patients affected by SARS-CoV-2).

Categorical variables are reported as frequencies and percentages. Differences in characteristics between patients who continued versus discontinued RASi were assessed by way of 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 RASi 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 used Firth logistic regression to build a model adjusting for age, CVD (coronary artery disease/ischemic heart disease and congestive heart failure [CHF]), and laboratory values found to be associated with RASi discontinuation (that is, serum creatinine, urea, potassium). We also considered subgroup analyses according to the type of RASi (ACEi and ARB). Analyses were performed using SAS, version 9.4. (SAS Institute Inc., Cary, North Carolina).

We reviewed 956 patient records; 175 (18%) were excluded because of age <50 years, 477 (50%) records were excluded because of lack of RASi treatment before hospitalization, and 18 (2%) records were excluded because of unknown use of diuretics. Hence, 286 patients were included in this analysis (Figure 1). Overall, 100 patients (35%) continued RASi and 186 (65%) discontinued. There were no significant differences in patient characteristics between those who continued versus discontinued treatment, except for laboratory values (Table 1). Of the 186 patients who discontinued RASi, 60 (32%) did so for acute kidney injury, 20 (11%) for hyperkalemia, 80 (43%) for hypotension, 19 (10%) for other illnesses (e.g., digestive disorder, cognitive status), 5 (3%) for a combination of factors, and 2 (1%) for unknown reasons. A total of 98 patients were treated with a diuretic, 51 (52%) of those patients continued RASi, and 47 (48%) discontinued. The in-hospital mortality rates in patients treated with a diuretic and continued versus discontinued RASi were 8% versus 26% (p = 0.0179). The median time from admission to RASi discontinuation for those who were treated with a diuretic was $4^{2,5}$ days; such patients had a median length of stay of $7^{3,12}$ days. Patients treated with a diuretic who continued RASi had a median length of stay of $10^{6,13}$ days. A total of 188 patients were not treated with a diuretic; 49 (26%) of those continued RASi and 139 (74%) discontinued. The in-hospital mortality rates in patients who were not treated with a diuretic and continued versus discontinued RASi were 16% versus 9% (p = 0.1827). The median time from admission to RASi discontinuation for those who were not treated with a diuretic was $3^{2,5}$ days; such patients had a median length of stay of $9^{6,14}$ days. Patients who were not treated with a diuretic had a median length of stay of $7.5^{5,14}$ days.

Overall, patients concomitantly treated with diuretics were at an increased risk for in-hospital mortality (Table 2). Conversely, when considering all patients, (dis)continuing RASi was not associated with in-hospital mortality. However, we found evidence to support a differential effect of RASi continuation on in-hospital mortality, according to diuretic treatment (interaction p = 0.0098). Specifically, continuing RASi in patients who were not treated with diuretics did not have a significant association with in-hospital mortality; however, continuing RASi in patients concomitantly treated with diuretics was associated with a decreased risk of in-hospital mortality by approximately 75% (OR 0.25, 95% CI 0.07 to 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 1.04 to 1.13, p <0.0001), as well as congestive heart failure, coronary heart disease/ischemic heart disease, and laboratory values (serum creatinine, urea, potassium), none of which were associated with the risk of mortality, continuing RASi was associated with a decreased risk of mortality by approximately 77% (OR 0.23, 95% CI 0.06 to 0.95, p = 0.0419) for patients treated with diuretics, but did not alter the risk in patients who were treated with RASi alone

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

	Diuretics Utilized			Diuretics Not Utilized		
	RASi Continued (n = 51)	RASi Discontinued (n = 47)	p Value	RASi Continued (n = 49)	RASiDiscontinued (n = 139)	p Value
Age (years)	73±9	76.12±8.27	0.1398	72±12	70±10	0.2914
Men	25 (49%)	24 (51%)	0.8398	36 (74%)	95 (68%)	0.5022
Hypertension	49 (96%)	45 (96%)	1.0000	49 (100%)	136 (98%)	0.5688
Obstructive lung disease	4 (8%)	8 (17%)	0.1661	4 (8%)	16 (12%)	0.5134
Diabetes mellitus	18 (35%)	9 (19%)	0.0642	10 (20%)	33 (24%)	0.6329
Smoker			0.9794			0.8420
Yes	4 (8%)	4 (9%)		5 (10%)	16 (12%)	
No	41 (80%)	38 (81%)		40 (82%)	111 (80%)	
Former	6 (12%)	5 (11%)		3 (6%)	12 (9%)	
Missing	0	0		1 (2%)	0	
Serum creatinine	1.1 [0.9, 1.4]	2.5 [1.6, 2.9]	<0.0001	1.05 [0.9, 1.2]	1.4 [1.3, 1.8]	<0.0001
Potassium	4.5 [4.3, 4.7]	4.8 [4.3, 5.2]	0.0217	4.5 [4.2, 4.6]	4.2 [3.7, 4.7]	0.0171
Urea	41 [36, 46]	68 [53, 79]	<0.0001	40 [37, 45.5]	47 [41, 62]	<0.0001
Chronic heart failure	13 (26%)	13 (28%)	0.8080	3 (6%)	4 (3%)	0.3023
Coronary artery disease	19 (37%)	12 (26%)	0.2125	7 (14%)	13 (9%)	0.3355
Beta blocker	20 (39%)	17 (36%)	0.7560	8 (16%)	39 (28%)	0.1030
Calcium channel antagonist	16 (31%)	11 (23%)	0.3777	18 (37%)	37 (27%)	0.1808
Thiazide diuretic	40 (78%)	25 (53%)	0.0083	0	0	
Loop diuretic	20 (39%)	31 (66%)	0.0081	0	0	
Invasive ventilation	6 (12%)	5 (11%)	0.8599	7 (14%)	21 (15%)	0.9429
High flow ventilation without intubation	23 (45%)	21 (45%)	0.9669	21 (43%)	46 (33%)	0.2070
Oxygen low flow	20 (39%)	17 (36%)	0.7560	21 (43%)	61 (44%)	0.9258

(Figure 2, Table 2). The Hosmer-Lemeshow statistic did not indicate any problems with the model fit.

Upon admission, 160 (56%) patients were using an ACEi and 126 (44%) were using an ARB. In subgroup analyses, we failed to find an association between RASi (dis)continuation and in-hospital mortality in ACEi users, regardless of diuretic use (Table 3). However, there was evidence to support a differential role of RASi continuation on in-hospital mortality in ARB users according to diuretic use. Specifically, the mortality rates for ARB continuation versus discontinuation in patients treated with a diuretic were 4% versus 35% (p = 0.0142), whereas the rates were 18%

Table 2
Odds of in-hospital mortality according to RASi and diuretic treatments

Variable (Unadjusted Model)	Odds Ratio	95% Confidence Interval Bounds		p Value
Diuretic use vs non-use				
In patients who discontinued RASi	3.32	1.39	7.93	0.0068
In patients who continued RASi	0.44	0.12	1.56	0.2008
RASi continuation versus discontinuation				
In patients without diuretics	1.89	0.73	4.88	0.188
In patients treated with diuretics	0.25	0.07	0.84	0.0244
Variable (adjusted model)				
Diuretic use vs non-use				
In patients who discontinued RASi	3.13	1.07	9.17	0.0375
In patients who continued RASi	0.5	0.14	1.8	0.2885
RASi continuation vs discontinuation				
In patients without diuretics	1.45	0.51	4.09	0.4886
In patients with diuretics	0.23	0.06	0.95	0.0419
Age (per year increase)	1.09	1.04	1.13	<0.0001
Coronary artery disease (yes vs no)	1.46	0.58	3.68	0.4221
Congestive heart failure (yes vs no)	0.38	0.1	1.38	0.1415
Urea	1.01	0.96	1.07	0.6944
Potassium	0.7	0.24	2.07	0.5228
Serum creatinine	0.9	0.49	1.67	0.7451

Adjusted model: overall effect of RASi continuation p = 0.4886, overall effect of diuretic use p = 0.0375, interaction term p = 0.0285.
Unadjusted model: overall effect of RASi continuation p = 0.1880, overall effect of diuretic use p = 0.0068, interaction term p = 0.0098.
RASi = renin-angiotensin system inhibitor.

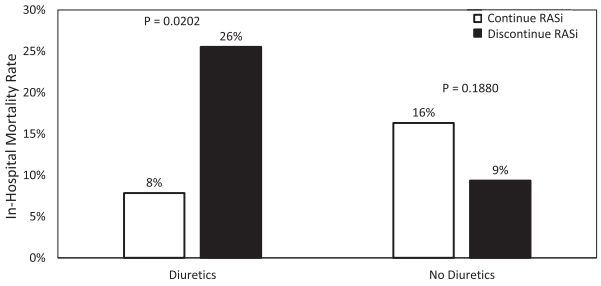

Figure 2. Differences in hospital mortality for patients who continued versus discontinued renin-angiotensin inhibitor (RASi) treatment according to concomitant use of diuretics.

versus 8% (p = 0.3568) in patients who were not treated with a diuretic.

In this analysis of 286 patients hospitalized with COVID-19 in the early phase of the pandemic, we found that patients taking combination RASi and diuretic were at higher risk of in-hospital mortality than patients taking RASi alone. We also found that discontinuing RASi therapy was associated with greater in-hospital mortality for patients who were concomitantly treated with a diuretic; an observation driven by ARB users. We did not find an association between RASi (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, and coronary artery disease, and CHF. Although diuretic treatment was more prevalent in HF patients, the diagnosis was based on clinical history in the health record. It was not confirmed by specific examinations during the current hospitalization; the in-hospital treatment was based on domiciliary therapy.

Others have suggested that RASi treatment may be protective in patients with COVID-19.[8−10] However, most studies did not consider treatment beyond the context of hypertension. In those with HF, continuing goal-directed medical therapy is associated with reduced mortality and hospitalization, a principle that appears to extend to patients hospitalized with COVID-19 at high risk for acute cardiorenal syndromes.[13−15] Recently, the Blockers of Angiotensin Receptor and Angiotensin-Converting Enzyme inhibitors suspension in hospitalized patients with coronavirus infection (BRACE CORONA) trial showed no association between RASi (dis)continuation and the primary outcome of death following hospital discharge for patients with COVID-19.[12] Further, 2 large studies demonstrated that discontinuation of RASi therapy for patients hospitalized with COVID-19 was associated with increased risk of mortality following discharge.[16,17]

The role of RASi observed in different settings may be explained by the baseline conditions in terms of age, gender, ethnicity, extracardiac comorbidities, and frailty. Indeed, the treatment may configure a negative effect on older patients with more advanced systemic diseases and vulnerable general conditions. ACE expression varies concerning race and gender, explaining some discrepancies observed in young people and Black patients, in whom previous ARB use was associated with augmented viral susceptibility and infection severity.[18−20]

There are clinical scenarios in which patients may need to discontinue RASi. Patients with severe hemodynamic impairment, lower blood pressure, and dehydration may benefit from discontinuing RASi.[21] 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, inflammation, and baseline condition before infection.[22] In the Swedish meta-analysis including more than 1 million patients, a protective effect of RASi was observed for all types of CVD studied. Unfortunately, that study investigated only antecedent use of RASi; the effect of continuation was not evaluated.[23] Overall, our findings reveal the importance of considering the basal clinical condition, severity of the infection, and concomitant treatments that may influence drug discontinuation and outcomes.

This is a retrospective observational analysis with a relatively small number of patients meeting inclusion criteria; thus, the findings are limited by the small sample size. Further, because of the small event count, we required specialized statistical methods to produce tractable estimates and confidence intervals for the multivariable-adjusted model. Additionally, we did not record information regarding before hospitalizations and/or severity of extracardiac diseases affecting these patients. Similarly, we lacked information on RASi dose and whether doses were altered for those who continued therapy. We did not analyze the effects of aldosterone antagonists and our results are limited to RASi administration. Because of these limitations and the observational nature of this work, we are unable to conclude causality; discontinuation may simply be a proxy for an adverse health state. The observational period was strictly limited to the hospital setting; no data were available after 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

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

	Diuretics			No Diuretics		
	RASi Continued	RASi Discontinued	p Value	RASi Continued	RASi Discontinued	p Value
ACEi	3/25 (12%)	5/27 (19%)	0.7050	5/32 (16%)	8/76 (11%)	0.5213
ARB	1/26 (4%)	7/20 (35%)	0.0142	3/17 (18%)	5/63 (7.9%)	0.3568

N (ARB) = 126; N (ARB and diuretic) = 46; N (ARB and no diuretic) = 80; RASi = renin-angiotensin system inhibitor; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; n (ACEi) = 160; n (ACEi and diuretic). = 52; n (ACEi and no diuretic) = 108.

All p values were calculated using Fisher's exact test.

hospitalized more recently since evidence of viral mutations.

In conclusion, diuretic use in hospitalized patients with COVID-19 who were on RASi before admission was associated with an increased risk of in-hospital mortality. Whether this combined therapy increases risk or is the reflection of a more severe presentation deserves further investigation. Although discontinuing RASi therapy for hypertension was not associated with in-hospital mortality, discontinuing RASi therapy in patients who were concomitantly treated with diuretics was associated with a greater risk of in-hospital mortality. Because our results showed that ACEi/ARB discontinuation in diuretic-users was associated with increased mortality, it may be beneficial to analyze the effect of reducing, not discontinuing, RASi in such patients.

Disclosures

The authors have no conflicts of interest to declare.

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