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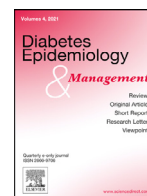
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Original article

Renin-angiotensin system inhibitors and mortality among diabetic patients with STEMI undergoing mechanical reperfusion during the COVID-19 pandemic



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ABSTRACT

Background: During the coronavirus disease 2019 (COVID-19) pandemic, concerns have been arisen on the use of renin-angiotensin system inhibitors (RASi) due to the potentially increased expression of Angiotensin-converting-enzyme (ACE)2 and patient's susceptibility to SARS-CoV2 infection. Diabetes mellitus have been recognized favoring the coronavirus infection with consequent increase mortality in COVID-19. No data have been so far reported in diabetic patients suffering from ST-elevation myocardial infarction (STEMI), a very high-risk population deserving of RASi treatment.

Methods: The ISACS-STEMI COVID-19 registry retrospectively assessed STEMI patients treated with primary percutaneous coronary intervention (PPCI) in March/June 2019 and 2020 in 109 European high-volume primary PCI centers. This subanalysis assessed the prognostic impact of chronic RASi therapy at admission on mortality and SARS-CoV2 infection among diabetic patients.

Results: Our population is represented by 3812 diabetic STEMI patients undergoing mechanical reperfusion, 2038 in 2019 and 1774 in 2020. Among 3761 patients with available data on chronic RASi therapy, between those ones with and without treatment there were several differences in baseline characteristics, (similar in both periods) but no difference in the prevalence of SARS-CoV2 infection (1.6% vs 1.3%, respectively, $p = 0.786$). Considering in-hospital medication, RASi therapy was overall associated with a significantly lower in-hospital mortality (3.3% vs 15.8%, $p < 0.0001$), consistently both in 2019 and in 2020.

Conclusions: This is first study to investigate the impact of RASi therapy on prognosis and SARS-CoV2 infection of diabetic patients experiencing STEMI and undergoing PPCI during the COVID-19 pandemic. Both pre-admission chronic RASi therapy and in-hospital RASi did not negatively affected patients' survival during the hospitalization, neither increased the risk of SARS-CoV2 infection.

Trial registration number: NCT 04412655

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Background

The global pandemic of coronavirus disease 2019 (COVID-19) has dramatically impacted on healthcare system worldwide, and its effects are still ongoing. As of 30th June 2021, more than 185 million cases of COVID-19 have been reported in more than 185 countries and territories, resulting in near 4 million deaths, especially in Europe, the United States, India and Latin America.

Increasing interests have been focused on a potential harmful role of angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), jointly named renin-angiotensin system inhibitors (RASi). These drugs were assumed playing a role in the SARS-CoV2 infect action, favoring the virus cell entry through upregulation of angiotensin-converting enzyme 2 (ACE2) [1–3]. The enhanced expression of ACE2 during RASi treatment, which was suspected to increase the patient's susceptibility to COVID-19, have pulled up several concerns, especially in high risk population as diabetics, that consistently benefit from RASi treatment, especially in light of their high cardiovascular risk profile that significantly impact on long-term survival [4,5]. As stated by international societies guidelines [6], RASi are strongly suggested as first line treatment for hypertension in patients with diabetes mellitus particularly in those with evidence of end-organ damage, like albuminuria and left ventricular hypertrophy [6–8]. Considering the high prevalence of hypertension among diabetics, > 60% [9], a specific attention has been reserved to these patients, already showing independently enhanced risk of COVID-19 adverse consequences, that could get even worse [10].

Not univocal messages were provided by international professional societies, especially in the first months of the pandemic, regarding recommendation for patients under treatment with a RASi, even if the general agreement was to continue the ongoing therapy until final evidences from sufficiently powered studies [11–13].

No specific increased risks of COVID-19 or related adverse events for RASi were detected in general population [14–17]. However, no definite data have been so far reported in diabetics patients suffering from ST-elevation myocardial infarction (STEMI), a very high-risk population with extensive use of RASi.

The International Study on Acute Coronary Syndromes – ST Elevation Myocardial Infarction (ISACS-STEMI) COVID-19 was established in response to the emerging outbreak of COVID-19 to provide a worldwide snapshot and estimates of the true impact of the COVID-19 pandemic on the treatment and outcome of STEMI patients treated by PPCI [18,19]. The aim of the present investigation was to inquire whether chronic use of RASi at the time of admission and their use during the hospitalization impacted on susceptibility to COVID-19 and on mortality risk among diabetic patients with STEMI undergoing primary angioplasty.

Methods

Study design and population

Our study population is represented by patients enrolled in the ISACS-STEMI COVID-19 (NCT 04412655), a retrospective multicenter registry including STEMI patients enrolled by 109 high-volume primary percutaneous coronary intervention (PCI) centers from Europe, Latin America, South-East Asia and North-Africa. This study was conducted to compare STEMI patients treated from March 1st until June 30th of 2019 with those admitted within the same period of 2020.

We collected demographic, clinical, procedural data, data on total ischemia time, door-to-balloon time, referral to primary PCI facility, PCI procedural data, in-hospital mortality. The study was approved by the Ethical Committee of AOU Maggiore della Carità. Novara. Detailed data have previously been provided [18,19].

Statistics

Data analysis was performed by using SPSS Statistics Software 23.0 (IBM SPSS Inc., Chicago, Illinois). Quantitative variables were described using median and interquartile range. Absolute frequencies and percentages were used for qualitative variables. ANOVA or Mann-Whitney and chi-square test were used for continuous and categorical variables, respectively. Normal distribution of continuous variables was tested by the Kolmogorov-Smirnov test.

A propensity score analysis was performed in order to overcome the potential bias related to differences in baseline characteristics. For each patient, a propensity score indicating the likelihood of having chronic RASI or in-hospital RASI administration was calculated by use of forward logistic regression analysis that identified variables independently associated with RASI prescription.

The discriminatory capacity of the propensity score was assessed by the area under the ROC curve (*c*-statistic) as an index of model performance. On the basis of the propensity score, the population was divided in four groups (from the lowest to the highest probability to have RASI prescribed) by the use of quartiles. The impact of RASI on mortality and SARS-CoV2 positivity was evaluated for each quartile, separately.

Furthermore, multivariable logistic regression analyses were performed to identify the association of RASI with in-hospital mortality and SARS-CoV2 infection after adjustment for baseline confounding factors between the two groups, including the propensity score. All significant variable (set at a *P*-value < 0.1) were entered in block into the model.

A *p* < 0.05 was considered statistically significant. The data coordinating center was established at the Eastern Piedmont University, Novara, Italy.

Results

Of the 16,077 STEMI patients undergoing mechanical reperfusion included in the study, 3812 (23.7%) were diabetic, in whom complete demographic, clinical, procedural, and outcome data were available as well as information regarding in-hospital RASI therapy. Patients with informative data on RASI treatment at admission were 3761 (98.7%). Higher RASI discontinuation rate after hospital admission was observed in 2019 compared to 2020 (46.2% in 2019 vs 39.0% in 2020, *p* = 0.001).

Table 1

Baseline demographic and clinical characteristics according to chronic RASI therapy at admission.

	OVERALL POPULATION (N = 3761)			YEAR 2019 (N = 2014)			YEAR 2020 (N = 1747)		
	RASI (n = 2049)	No RASI (n = 1712)	P value	RASI (n = 1072)	No RASI (n = 942)	P value	RASI (n = 977)	No RASI 2020 (n = 770)	P value
Age (median, IQR)									
Age > 75 year – n. (%)	525 (25.6)	344 (20.1)	<0.001	289 (27.0)	196 (20.8)	0.001	236 (24.2)	148 (19.2)	0.013
Male gender – n. (%)	1382 (67.4)	1269 (74.1)	<0.001	734 (68.5)	709 (75.3)	0.001	648 (66.3)	560 (72.7)	0.004
Hypertension- n (%)	1853 (90.4)	889 (51.9)	<0.001	955 (89.1)	504 (53.5)	<0.001	898 (91.9)	385 (50.0)	<0.001
Hypercholesterolemia - n (%)	1174 (57.3)	774 (45.2)	<0.001	601 (56.1)	422 (44.8)	<0.001	573 (58.6)	352 (45.7)	<0.001
Active Smoker – n (%)	921 (44.9)	837 (48.9)	0.016	468 (43.7)	455 (48.3)	0.037	453 (46.4)	382 (49.6)	0.178
Family History of CAD - n (%)	365 (17.8)	276 (16.1)	0.169	205 (19.1)	151 (16.0)	0.069	160 (16.4)	125 (16.2)	0.936
Previous STEMI- n (%)	337 (16.4)	151 (8.8)	<0.001	166 (15.5)	84 (8.9)	<0.001	171 (17.5)	67 (8.7)	<0.001
Previous PCI – n (%)	495 (24.2)	201 (11.7)	<0.001	244 (22.8)	108 (11.5)	<0.001	251 (25.7)	93 (12.1)	<0.001
Previous CABG - n (%)	78 (3.8)	38 (2.2)	0.005	38 (3.5)	24 (2.5)	0.196	40 (4.1)	14 (1.8)	0.006
Referral to Primary PCI Hospital									
Ambulance (from community) – n (%)	880 (42.9)	753 (44.0)	0.303	462 (43.1)	408 (43.3)	0.149	418 (42.8)	345 (44.8)	0.699
Time delays									
Ischemia time, median [25 - 75th]									
Total Ischemia time > 12 h – n (%)	240 (11.7)	266 (15.5)	0.001	105 (9.8)	137 (14.5)	0.001	135 (13.8)	129 (16.8)	0.089
Door-to-balloon time, median [25 - 75th]									
Door-to-balloon time >30 min (%) – n (%)	1280 (62.5)	1106 (64.6)	0.176	650 (60.6)	622 (66.0)	0.012	630 (64.5)	484 (62.9)	0.483
Clinical Presentation									
Anterior STEMI – n (%)	956 (46.7)	860 (50.2)	0.029	505 (47.1)	465 (49.4)	0.312	451 (46.2)	395 (51.3)	0.033
Out-of-hospital cardiac arrest – n (%)	89 (4.3)	80 (4.7)	0.627	49 (4.6)	41 (4.4)	0.813	40 (4.1)	39 (5.1)	0.332
Cardiogenic shock – n (%)	179 (8.7)	170 (9.9)	0.209	86 (8.0)	93 (9.9)	0.145	93 (9.5)	77 (10.0)	0.736
Rescue PCI for failed thrombolysis – n (%)	194 (9.5)	110 (6.4)	0.001	103 (9.6)	60 (6.4)	0.008	91 (9.3)	50 (6.5)	0.032

*Mann-Whitney test.

CAD = Coronary Artery Disease; STEMI = ST-segment Elevation Myocardial Infarction; PCI = Percutaneous Coronary Intervention; CABG = Coronary Artery Bypass Graft.

Table 2
Baseline demographic and clinical characteristics according to in-hospital RASI therapy.

	OVERALL POPULATION (N = 3812)			YEAR 2019 (N = 2038)			YEAR 2020 (N = 1774)		
	RASI (n = 2049)	No RASI (n = 1763)	P value	RASI (n = 1034)	No RASI (n = 1004)	P value	RASI (n = 1015)	No RASI (n = 759)	P value
Age (median, IQR)									
Age > 75 year – n. (%)	434 (21.2)	446 (25.3)	0.003	230 (22.2)	260 (25.9)	0.054	204 (20.1)	186 (24.5)	0.027
Male gender – n. (%)	1504 (73.4)	1182 (67.0)	<0.004	773 (74.8)	685 (68.2)	0.001	731 (72.0)	497 (65.5)	0.003
Hypertension- n (%)	1509 (73.6)	1268 (71.9)	0.233	742 (71.8)	733 (73.0)	0.529	767 (75.6)	535 (70.5)	0.017
Hypercholesterolemia - n (%)	1129 (55.1)	849 (48.2)	<0.001	550 (53.2)	486 (48.4)	0.031	579 (57.0)	363 (47.8)	<0.001
Active Smoker – n (%)	1026 (50.1)	768 (43.6)	<0.001	505 (48.8)	436 (43.4)	0.014	521 (51.3)	332 (43.7)	0.002
Family History of CAD - n (%)	416 (20.3)	248 (14.1)	<0.001	223 (21.6)	144 (14.3)	<0.001	193 (19.0)	104 (13.7)	0.003
Previous STEMI- n (%)	296 (14.4)	200 (11.3)	0.005	145 (14.0)	108 (10.8)	0.025	151 (14.9)	92 (12.1)	0.095
Previous PCI – n (%)	408 (19.9)	297 (16.8)	0.015	189 (18.3)	166 (16.5)	0.299	219 (21.6)	131 (17.3)	0.024
Previous CABG - n (%)	67 (3.3)	52 (2.9)	0.571	37 (3.6)	27 (2.7)	0.250	30 (3.0)	25 (3.3)	0.684
<i>Referral to Primary PCI Hospital</i>									
Ambulance (from community) – n (%)	1011 (49.3)	659 (37.4)	<0.001	508 (49.1)	379 (37.7)	<0.001	503 (49.6)	280 (36.9)	<0.001
<i>Time delays</i>									
Ischemia time, median [25 - 75th]									
Total Ischemia time > 12 h – n (%)	267 (13.0)	248 (14.1)	0.351	124 (12.0)	122 (12.2)	0.912	143 (14.1)	126 (16.6)	0.144
Door-to-balloon time, median [25 - 75th]									
Door-to-balloon time > 30 min - n (%)	1227 (59.9)	1167 (66.2)	<0.001	611 (59.1)	664 (66.1)	0.001	616 (60.7)	503 (66.3)	0.016
<i>Clinical Presentation</i>									
Anterior STEMI– n (%)	978 (47.7)	854 (48.4)	0.662	501 (48.5)	477 (47.5)	0.670	477 (47.0)	377 (49.7)	0.264
Out-of-hospital cardiac arrest – n (%)	69 (3.4)	100 (5.7)	0.001	32 (3.1)	58 (5.8)	0.003	37 (3.6)	42 (5.5)	0.056
Cardiogenic shock– n (%)	123 (6.0)	226 (12.8)	<0.001	53 (5.1)	126 (12.5)	<0.001	70 (6.9)	100 (13.2)	<0.001
Rescue PCI for failed thrombolysis – n (%)	143 (7.0)	161 (9.1)	0.014	79 (7.6)	84 (8.4)	0.546	64 (6.3)	77 (10.1)	0.003

*Mann-Whitney test.

CAD = Coronary Artery Disease; STEMI = ST-segment Elevation Myocardial Infarction; PCI = Percutaneous Coronary Intervention; CABG = Coronary Artery Bypass Graft;.

(adjusted OR [95% CI] = 0.61[0.47–0.79], $p < 0.001$) and 30-day mortality (adjusted HR [95% CI] = 0.78[0.62–0.97], $p = 0.028$).

In-hospital treatment with RASI showed significant benefits in-hospital and 30-day mortality that was consistent in both 2019 and 2020 (Fig. 2). The benefits were confirmed in almost all the quartiles of the propensity score (Fig. 2S) and confirmed after the adjustment for all the confounding baseline and procedural characteristics (Age > 75 years, Gender, Hypercholesterolemia, Previous PCI, Rescue PCI, instant thrombolysis, Radial access, target vessel, multivessel disease, thrombectomy, DES, use of mechanical support devices, bivalirudin, postprocedural TIMI flow, DAPT), including the propensity score, for in-hospital (adjusted OR [95% CI] = 0.21[0.22–0.30], $p < 0.001$) and 30-day mortality (adjusted HR [95% CI] = 0.3 [0.23–0.38], $p < 0.001$).

Both chronic treatment and in hospital therapy with RASI did not affect the SARS-CoV2 positivity ($n = 26$) (Fig. 3).

Discussion

The main finding of the present study is that among diabetic patients experiencing STEMI and treated with mechanical reperfusion during the COVID-19 pandemic, chronic RASI therapy at admission showed a lower rate of death not raising the statistical significance in 2020, whereas in-hospital treatment with RASI resulted in a significantly lower mortality in both pandemic and pre-pandemic period. Both chronic treatment and in-hospital therapy with RASI did not affect the SARS-CoV2 positivity.

Diabetes mellitus is a condition enhancing patients' cardiovascular risk profile due to damages on both microvascular and macrovascular sides [20–22]. Prolonged glucose homeostasis impairment leads to endothelial dysfunction, atherosclerosis progression and pro-thrombotic environmental, recognizing diabetics as patients at higher risk for cardiovascular events. RASI constitute a cornerstone of treatment in various cardiovascular diseases providing robust

evidences in reducing death and morbidity [23–26]. Their benefits were confirmed also among diabetics, indeed RASI are considered first treatment option in several condition, including hypertension [27].

However, previous animal studies have reported worries on RAS modulation, suggesting that ACE2 expression might play a negative prognostic role in COVID-19 patients: the ACE2 enzyme is a cell membrane protein, that is used by the SARS-CoV2 virus to enter cells [9,28]. Given that experimental studies showed that angiotensin receptor blockers (ARBs) and an ACE inhibitors (ACEIs) could increase ACE2 expression in cardiovascular and renal systems [29,30], favouring the conversion of angiotensin II to angiotensin (1–7) [31], concerns have been raised on potential detrimental consequences driven by ARBs and ACEIs treatment on SARS-CoV2 infection and the severity of the COVID-19 [32].

Clinical evidences on the of ACEIs/ARBs in patients with COVID-19 has been controversial in part due to early reports from China, showing higher mortality in hypertensive patients admitted for COVID-19 [33–37]. Those analysis were hampered by small cohort and main confounding factors such as older age and cardiovascular disease, were collinear with hypertension. Further and larger studies have found no harmful effects or even beneficial effects from RASI therapy [14–17]. In a large population-based case-control study in the Lombardy region of Italy performed by Mancia et al. [13], a total of 6272 case patients with confirmed SARS-CoV2 infection were matched with more than 30,000 patients according to age, sex and municipality of residence. RASI were detected more frequently used in COVID-19 patients compared to controls, but no significant increased risk of SARS-CoV2 infection was found for chronic RASI treatment.

Diabetes mellitus confers per se a higher risk of mortality and adverse events in patients with cardiovascular disease [27]. Also in COVID-19 an increased death rate was independently associated with diabetes mellitus and metabolic diseases [38–40]: a retrospective analysis from Bode et al. including 1122 patients showed a 4-fold

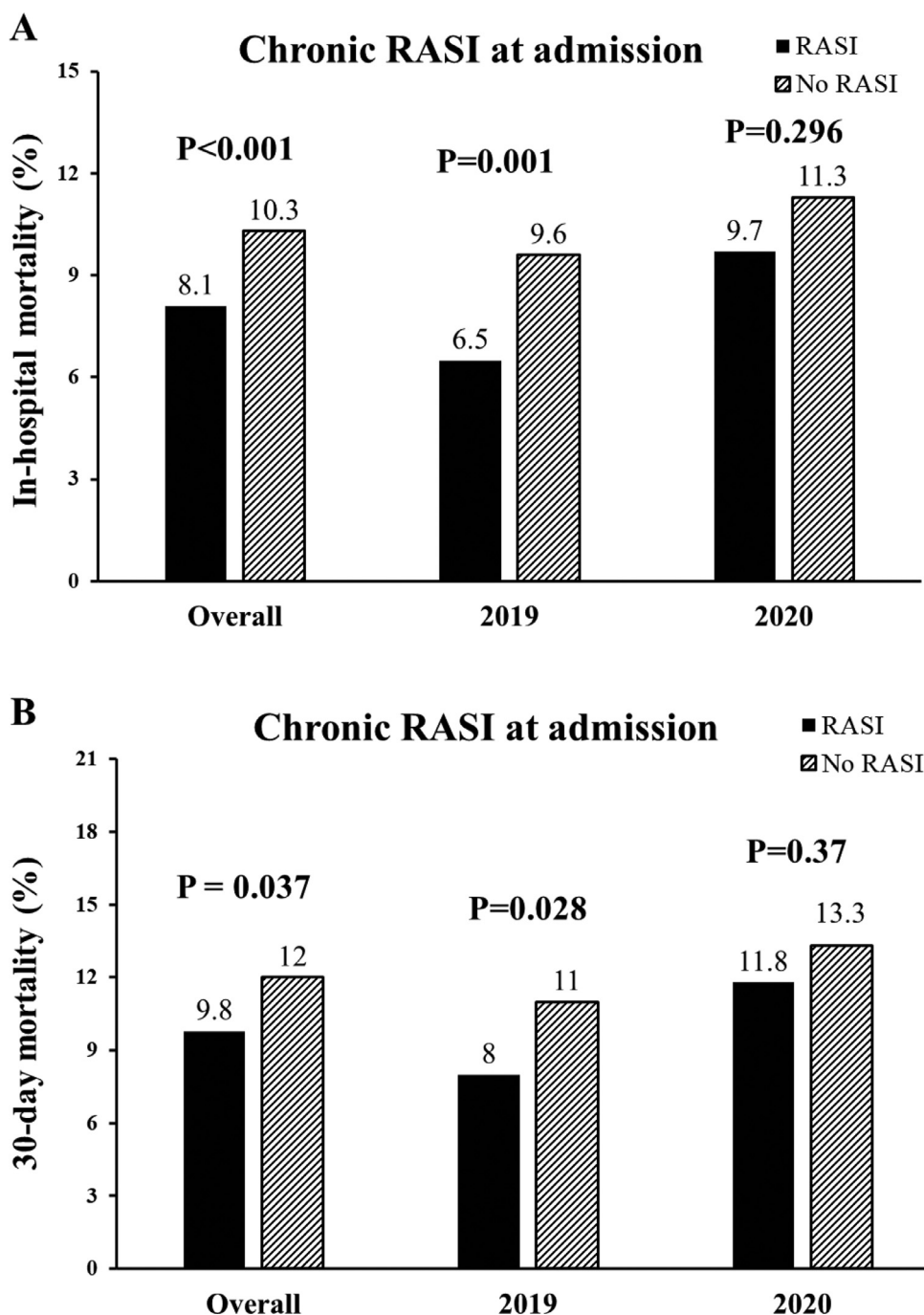


Fig. 1. Bar graphs show in-hospital (panel A) and 30-day (panel B) mortality in overall population, in 2019 and 2020 patients according to chronic RASI therapy at admission.

increased mortality among diabetics compared to non-diabetics, with a further enhanced risk of death in case of uncontrolled hyperglycemia [41]. Main mechanisms, which diabetes mellitus and high glucose promote SARS-CoV2 replication through, are strictly related to enhanced production of reactive oxygen species and pro-inflammatory cytokines [42]. Similarly, are the findings from Zhu et al. that showed significant clinical benefits correlated with improved glycaemic control during COVID-19 hospitalization.

Therefore, inquiring the interplay between renin-angiotensin system and diabetes mellitus during COVID-19 results essential to evaluate patients' prognosis. In fact, the diabetic status favors SARS-CoV2 infection and could be influenced by RASI therapy [43]. The relationship between increased ACE2 expression during RASI treatment and pro-inflammatory environment in diabetics is not completely

established, with few studies that addressed their resulting balance. Aghaaliakbari et al. retrospectively investigated the effect of ACEIs and diabetes in COVID-19 patients: among 153 diabetics, ACEIs treatment was found significantly increasing the risk of mortality [44]. Conversely, Ramos-Rincón et al. reported in diabetics with more than 80 years old a potential protective role of chronic treatment with ARB [45]. In a randomized trial testing the continuation versus discontinuation of RASI, authors showed that they can be safely continued in patients admitted for COVID-19, consistently in diabetic and non-diabetics [46].

However, so far no data have been reported in diabetic patients with STEMI, representing a population with a very high adverse event risk and (guideline-recommended) RASI use in the majority of patients [47]. Our report is the first study focused on STEMI patients

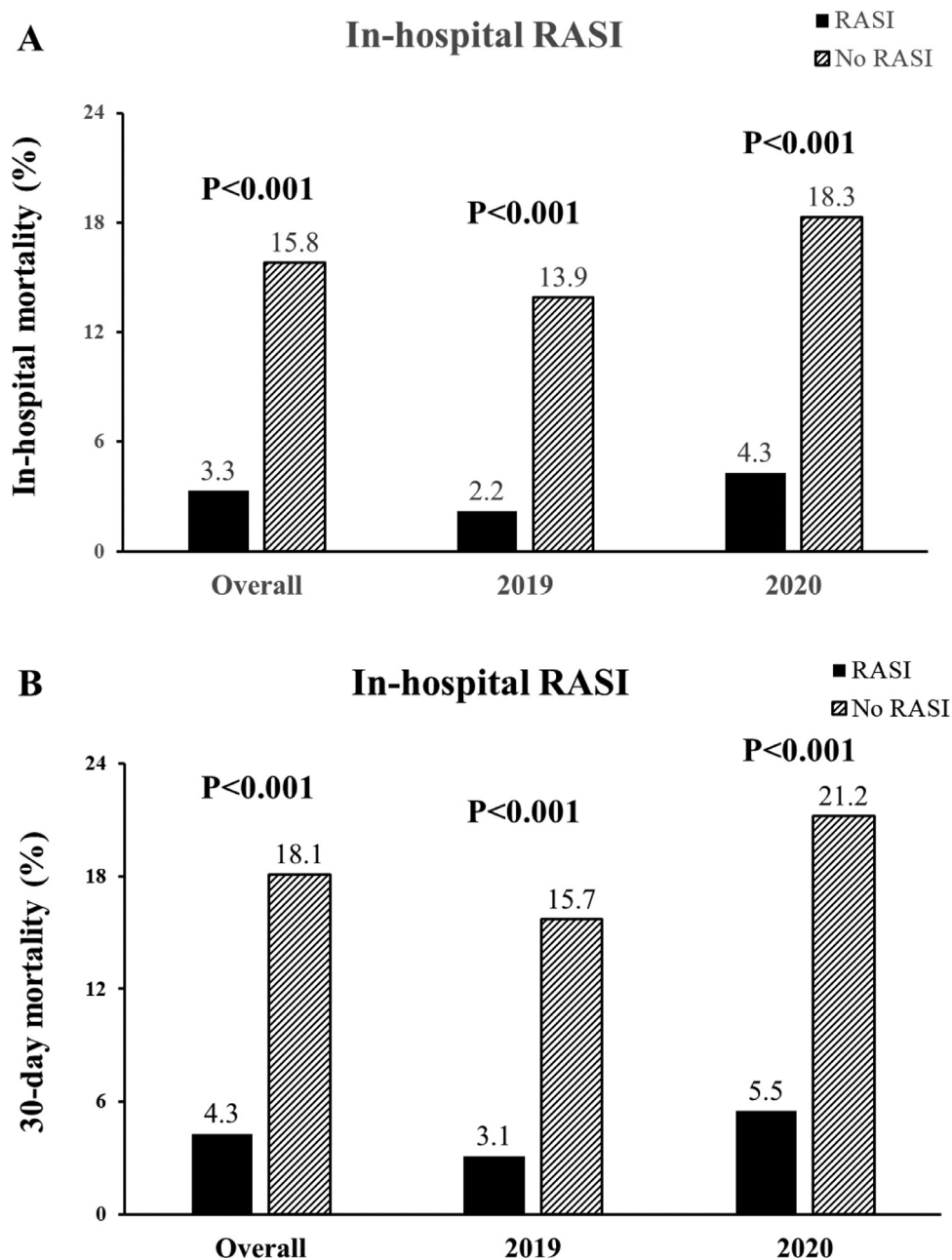


Fig. 2. Bar graphs show in-hospital (panel A) and 30-day (panel B) mortality in overall population, in 2019 and 2020 patients according to in-hospital RASI therapy.

with diabetes undergoing mechanical reperfusion, including more than 3800 diabetics undergoing mechanical reperfusion. We found that chronic RASI at admission did not affect the prevalence of SARS-CoV2 infection and showed a lower rate of death not raising the statistical significance in 2020. Furthermore, in-hospital RASI treatment was associated with a significantly lower mortality, consistently in 2019 and 2020, without affecting the prevalence of SARS-CoV2 infection. Therefore, confirming our previous report in a general population [48], the present study confirms the overall mortality benefits of RASI among diabetic patients with STEMI. Moreover, it does not suggest a link between RASI therapy and COVID-19 susceptibility or subsequent worse outcomes among these patients.

Professional societies have issued position statements that ACEIs/ARBs should not be discontinued that this study supports [49]. Support of continuing RASI therapy was yielded by the recent randomized BRACE-CORONA Trial, 659 patients with chronic RASI therapy at admission and confirmed diagnosis of COVID-19 were randomly

assigned to a temporary 30-day suspension or continuation of RASI therapy. No differences were observed for 30-day mortality (2.8% vs 2.7%) between the two groups [50].

Further randomized trials focused on diabetic patients are needed to clarify the protective or harmful effects of RASI treatment during COVID-19. Benefits provided by RASI seems confirmed in diabetics experiencing STEMI treated with mechanical reperfusion, without increasing the risk for COVID-19 and in-hospital mortality.

Limitations

This study is limited by its retrospective, non-randomized design. As may be expected, diabetics on RASI therapy differed from the other patients in comorbidities, firstly hypertension prevalence, however the results on mortality were not affected by baseline differences.

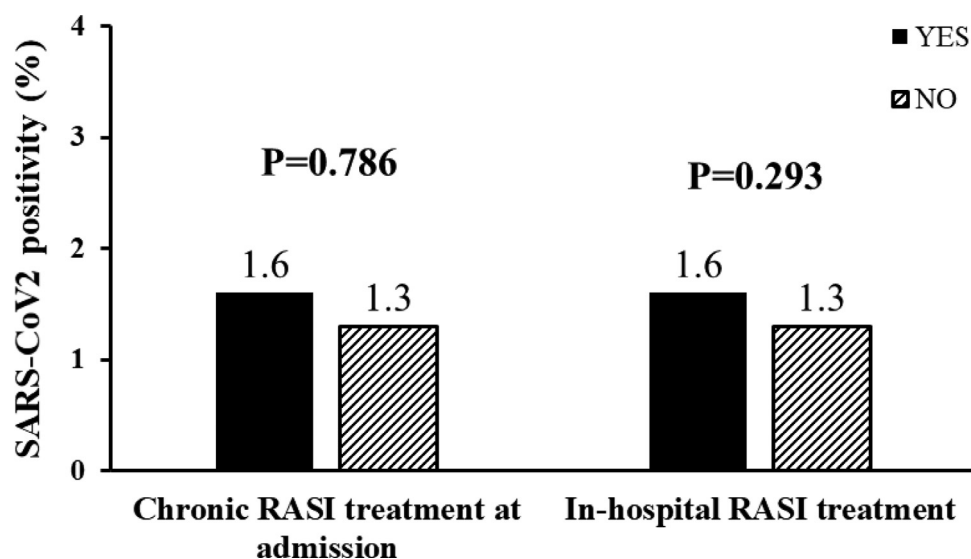


Fig. 3. Bar graphs show the prevalence of SARS-CoV2 infection in patients treated in 2020 according to chronic RASI therapy at admission (left side) and in-hospital RASI (right side).

Moreover, our research was conducted during a pandemic emergency, which was a challenge and expected to encounter some missing data. Nevertheless, considering all adversities, the proportion of patients with missing data regarding in-hospital RASI therapy was tolerable.

The choice of interrupt RASI treatment at admission as well as its introduction during the hospitalization was made by physicians and at their own discretion: that, together with the uncertainty of RASI harm on SARS-CoV2 infection risk, could have impacted patients' outcome, even if no increased mortality was found in analyses of both chronic and in-hospital treatments.

As we did not collect information on the type and dosage of RASI, we cannot perform a further in-depth assessment of prognostic implications. Finally, although our database comprised almost 3800 diabetic STEMI patients with known in-hospital pharmacological therapy, procedural features and clinical outcome following mechanical reperfusion procedure, the evaluation of the prognostic impact of RASI treatment among SARS-CoV2-positive patients was limited due to the low prevalence of the infection.

Conclusions

This is the first study investigating the prognostic impact of RASI therapy in patients with diabetes mellitus experiencing STEMI treated with mechanical reperfusion during COVID-19 pandemic. Our main finding is that RASI therapy was associated with an overall significant reduction in mortality, without any negative effect on SARS-CoV2 infection. Therefore, waiting for future dedicated and randomized trials, during the pandemic RASI should not be suspended or omitted among these high-risk patients suffering from STEMI and undergoing mechanical reperfusion.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.deman.2021.100022](https://doi.org/10.1016/j.deman.2021.100022).

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