Ramipril and COVID-19 in a High Risk Population – Insights from the Randomized RASTAVI trial

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Abstract.
Background: The coronavirus disease 2019 (COVID-19) is caused by SARS-CoV2 that interfaces with the renin-angiotensin-aldosterone system (RAAS) through angiotensin-converting enzyme 2 (ACE-2). This interaction has been proposed as a potential risk factor in patients treated with RAAS-inhibitors.
Objectives: To analyze if RAAS-inhibitors modify the risk for COVID-19.
Methods: RASTAVI (NCT03201185) is an ongoing randomized clinical trial randomly allocating Ramipril or control after successful transcatheter aortic valve replacement at 14 centers is Spain. We performed a non-pre-specified interim analysis to evaluate its impact on COVID-19 risk in this vulnerable population.
Results: As in April 1st 2020, 102 patients (50 Ramipril and 52 controls) were included in the trial. Mean age was 82.3±6.1 years, 56.9% males. Median time of Ramipril treatment was 6 months [IQR:2.9-11.4]. Eleven patients (10.8%) have been diagnosed with COVID-19 (6 in control group and 5 receiving Ramipril, HR=1.150 [95%CI: 0.351-3.768]). The risk of COVID-19 was increased in older patients (p=0.019), those with atrial fibrillation (p=0.066), lower hematocrit (p=0.084), and more comorbidities according to Society of thoracic surgeons score (p=0.065). Admission and oxygen supply was required in 4.9% (2 patients in the Ramipril and 3 in control), and 4 of them died (two in each randomized group). A higher body mass index was the only factor increasing the mortality rate (p=0.039).
Conclusions: In a high risk population of old patients with cardiovascular disease, randomization to Ramipril had no impact in the incidence or severity of COVID-19. This analysis supports the maintenance of RAAS-inhibitor treatment during COVID-19 crisis.

Clinical Trial: NCT03201185

Keywords: COVID-19; SARS-CoV2; Renin-angiotensin; TAVR.

CONDENSED ABSTRACT.
The use of RAAS-inhibitors in patients suffering COVID-19 or at risk is controversial. A total of 102 patients with cardiovascular disease were randomized in the RASTAVI trial to Ramipril (n=50) or control (n=52). Of them, 11 patients (10.8%) developed COVID-19 up to April/2020 (five from Ramipril group and six from control group), and four died (two from each group). COVID-19 occurred more often in older patients and higher body-mass index was related to greater mortality. However, the use of Ramipril did not affect the risk of infection or the prognosis. Hence, the use of RAAS-inhibitors during COVID-19 pandemic seems safe.

ABBREVIATIONS.
ACE: Angiotensin-converting enzyme.
CMR: Cardiac magnetic resonance.
COVID-19: Coronavirus disease 2019.
IQR: Interquartile range.
MERS-CoV: Middle East respiratory syndrome coronavirus.
NYHA: New York Heart Association.
PCR: Polymerase chain reaction.
RAAS: Renin-angiotensin-aldosterone system.
SARS-CoV2: Severe acute respiratory syndrome coronavirus-2.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak is caused by a new coronavirus (1-4), the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) (5-9). According to several authors, the virus internalizes the cell by binding its trimeric spike protein to the human receptor angiotensin-converting enzyme 2 (ACE2) (10-12). Renin-angiotensin-aldosterone (RAAS) inhibition upregulates ACE2, which casts doubts on whether the administration of these drugs could predispose to or worsen the course of the disease (13-15). With this background, some authors advice the discontinuation of RAAS blockers either with prophylactic purposes or, in infected patients, to avoid the evolution to SARS (16). On the other hand, high ACE2 levels have been shown to protect the lung in SARS (17), and small series suggest an absence of a deleterious effect in hypertensive patients taking RAAS-inhibitors (18) with a decrease in the peak viral load and the inflammatory markers in patients under these medications. Moreover, the well-known cardiorenal effects of RAAS blockade in cardiovascular disease should not be dismissed, particularly in COVID-19 patients, in whom cardiovascular comorbidities favor a severe course of the disease.

An ongoing clinical trial, the RAAS blockade after TAVI (RASTAVI) Study (http://www. ClinicalTrials.gov NCT03201185) is a randomized 1:1 open-label study evolving 14 Spanish centers. To remark, Spain presents one of the highest rates of confirmed COVID-19 cases and of deaths per million in the world. The RASTAVI trial is investigating the effect of adding Ramipril to the standard care in patients successfully treated with percutaneous aortic valve in terms of ventricular remodeling as assessed by cardiac magnetic resonance (CMR) and in the major clinical outcomes (19,20).

By 5th May 2020, 3.525,116 people all over the world have been infected by SARS-CoV2 (21) whereas thousands of patients worldwide are taking RAAS-inhibitors daily. In this scenario, we aimed to describe for the first time the impact of COVID -19 pandemic in high-risk patients from the RASTAVI trial randomly assigned to receive Ramipril or standard care.

METHODS

Study population.

The RASTAVI Study is a national, multicenter, open-label and randomized 1:1 trial aiming to determine the effect of Ramipril on cardiac events, functional capacity and cardiac remodeling on patients with aortic stenosis successfully treated with transcatheter aortic valve replacement (TAVR). The first patient was included in 2018 March 26th, and the study will continue recruiting until end 2021. Patients are randomized, after signing informed consent, between 1 and 5 days after TAVR procedure to receive either standard care or an initial dose of Ramipril (2.5 mg daily). Titration of the Ramipril is performed at each monitorization visit aiming full dose (10 mg daily) if tolerated. Patients included in the control group if their blood pressure is beyond recommended parameters (140/90 mm Hg) receive any medication to control it, except for RAAS-inhibitors (19).

Until 1st April 2020, 109 patients have been included in the study. The aim of this non pre-specified interim analysis is to investigate how SARS-CoV2 infection has affected this high-risk population and get further insight on the effect of RAAS-inhibitors on the susceptibility to the disease. For this purpose, all patients underwent updated follow up through phone calls and consulting electronic clinical reports. This follow up was monitored and performed under the ethics committee approval (see **Supplemental file 1**).

COVID-19 diagnosis.

All patients from the study were contacted by phone and a questionnaire was performed to determine the presence of symptoms (fever, cough, dyspnea, syncope, myalgia, or others) in the last 5 months, or contact with confirmed cases of the disease. Also, any admission in the last months was recorded as per protocol, and the clinical reports as well as any laboratory exam were gathered. Confirmation of the infection was performed through real time reverse transcription polymerase chain reaction (RT-PCR) of nasopharyngeal sample and the test was performed as clinically indicated.

Statistical analysis.

Categorical variables are reported as number (percent) and continuous variables as mean (standard deviation) or median (25th to 75th interquartile range), depending on variable distribution. Comparisons between those developing COVID-19 and those who did not were performed in order to determine predisposing factors..

A Cox regression analysis was performed for investigating the effect of Ramipril administration upon the time symptoms of COVID-19 were developed in the study patients. Ramipril was the only factor included in the analysis to avoid overfitting. Also, factors associated with mortality were estimated for patients with SARS-CoV2 infection comparing the characteristics of those who died and those who survived the disease. Pearson $\chi 2$ test and Fisher´s exact test were performed in comparisons between groups with qualitative variables, and Student´s t-test or Mann-Whitney test in continuous variables. All tests were 2 sided at the 0.05 significance level. Statistical analysis was performed with IBM SPSS Statistics version 25 (IBM, Armonk, New York).

RESULTS

After careful assessment of the patients randomized in the study (**Central Illustration**) a total of 102 patients (50 Ramipril and 52 controls) were included in this interim analysis. Of them, 11 patients (10.8%) presenting clinical symptoms compatible with COVID-19 underwent SARS-CoV-2 RT-PCR of nasopharyngeal sample with positive result, five of them from Ramipril group and six from the control group (p=0.802). No other patients developed symptoms but seven of them had the SARS-CoV-2 test performed due to risk contacts and presented negative result.

Baseline characteristics.

Main baseline characteristics from the 102 patients according to development of COVID-19 are summarized in **Table 1**. Mean age was 82.3±6.1 years and 56.9% were males. In those randomized to the drug, median time under treatment with Ramipril was 6 months [IQR:2.9-11.4], with all the included cases receiving the therapy at least for 1 month. Time from 1st January 2020 to onset of COVID-19 symptoms is presented in **Figure 1**. The prior administration of Ramipril presented a hazard ratio of 1.150 [95% confidence interval: 0.351-3.768] for the development of COVID-19. Patients developing COVID-19 were significantly older 86 [84-88] vs. 83 [78-86] years, p=0.019, and presented a trend to higher rate of prior atrial fibrillation and anemia. No significant differences existed regarding the rate of main cardiovascular risk factors between patients suffering from COVID-19 and those free of the infection, including hypertension, diabetes mellitus, and dyslipidemia. Globally, there were no differences in major comorbidities including coronary artery disease, moderate or severe chronic obstructive pulmonary disease, and chronic kidney disease. However, there was a trend to worse baseline risk according to the Society of Thoracic Surgeons score (3.90 [2.64 to 6.60] vs. 3.06 [1.82 to 4.02]; p=0.065).

Main features of COVID-19 patients.

Amongst COVID-19 patients (n = 11), fever was the most frequent symptom (63.5%), followed by cough (54.5%), dyspnea (27.3%) and myalgia (9.1%). Five patients presented severe respiratory disease that required admission to a healthcare institution and specific treatment (lopinavir/ritonavir, hydroxychloroquine, azithromycin, and corticoids) as opposed to only symptomatic treatment in those who did not require hospitalization. Four of these five hospitalized patients (36.4% of the COVID-19 cases) died as a consequence of bilateral pneumonia with severe acute respiratory distress. The specific characteristics of each one of the four patients who died are described in detail in **Table 2**. No differences were found according to the drug randomization, with two of the cases under RAAS-inhibitors treatment and two under standard care. All of them presented persistent heart failure despite successful treatment of their valvular disease. The only factor related to higher mortality in patients suffering from COVID19 was a greater median body mass index 30.7 (interquartile range: 28.8-30.9) compared to 25.2 (interquartile range: 23.9-26.3), p=0.039 (**Figure 2**).

DISCUSSION

In the beginning of the COVID-19 pandemic certain publications called for the discontinuation of RAAS-inhibitors, both to potentially – we must not miss the hypothetical nuance – prevent the disease and to improve the prognosis in patients already suffering or with suspected COVID-19 (16, 22-25). This call for caution has prevailed in the medical community and the media despite the rise of discordant voices defending alternative hypothesis (26) and has led the American College of Cardiology to request for urgent research to clarify this aspect (27). Hypertension has been described as one of the most common coexisting conditions in patients admitted in hospital due to COVID-19 (28), probably as a result of its higher prevalence in older

patients. Often, this cardiovascular condition is treated with RAAS-inhibitors, which explains the great clinical relevance of clarifying the potential role of these drugs in COVID-19 pandemic.

The main findings of our study suggest that: 1/ Age, but not hypertension, seems to be the only factor significantly associated with risk for developing the COVID-19 in this comorbid population. 2/ More than 10% of the patients developed the COVID-19 and one-third of them died, but the use of RAAS-inhibitors was neither associated with risk for the clinically symptomatic infection nor with poorer outcomes in the course of the disease. 3/ Patients who died due to the infection presented a higher body mass index as unique and characteristic feature. Obesity is a frequent condition among COVID-19 in-hospital patients (29), present in up to 42% of those admitted to the hospital (30), but its influence in the prognosis has not been well described yet. However, the experience with other virus like H_1N_1 influenza suggest that patients with obesity (31), even of young age, may evolve toward severe alveolitis with respiratory failure and death (32). Therefore, this is not a minor finding and warrants future analysis.

The outbreak of COVID-19.

By late 2019, six coronavirus species have been described to cause human disease. Four of them – 229E, OC43, NL63 and HKU1 – are responsible of light or mild respiratory disease (1). The two other species can cause severe disease and were the causal agents of severe acute respiratory syndrome outbreaks in 2002 – SARS-CoV (2,3) – and in 2012 – Middle East respiratory syndrome coronavirus (MERS-CoV) (4)–. In early December 2019 in Wuhan (China), first cases of pneumonia due to an unidentified microbial agent were described (5,6). RT-PCR of lower respiratory tract samples allowed sequencing the genome of a novel RNA-virus with 79.6 % of similarities with SARS-CoV, hence named SARS-CoV2 (7,8). Person-to-person transmission was rapidly described (9).

Interplay of SARS-Co2 and ACE2.

The SARS-CoV2 presents a spike protein to facilitate get into target cells. It links to ACE2 and is internalized after priming by the transmembrane protease, serine 2 (TMPRSS2) (7,10-12)(**Figure 3**). ACE2 membrane-bound is part of a 3-enzymes system to convert angiotensin II to angiotensin-(1-7), with oppose properties to angiotensin II in order to balance human body (**Figure 3A**). ACE2 is considerable similar to ACE, which converts angiotensin-I to angiotensin-II (28,33), and this second, nor ACE2, is the target of ACE inhibitors. ACE2 is 2% in a soluble form –not valid for SARS-CoV2 binding-, after cleavage by a desintegrin and metalloprotease 17 (ADAM17). Angiotensin I upregulates ADAM17, thus increasing soluble ACE2 levels (13,14) (**Figure 3B**). Furthermore, ADAM17 also mediates the release of membrane bound precursors of pro-inflammatory cytokines (TNFα, IFN-γ, and IL-4) into the circulation. These cytokines, downregulate ACE2 cell surface expression reducing SARS-CoV2 capability of damage (15) (**Figure 3C**). The hypothesis that RAAS-inhibitors might increase the susceptibility of patients taking them to COVID-19 pandemic and proposing its discontinuation were based in this pathophysiologic explanation (16). On the other hand, Meng et al (18) found lower interleukin-6 and peak viral load in peripheral blood, and increased CD3 and CD8 T cells in patients with hypertension treated with RAAS-inhibitors. Despite this contradictory evidence, the most recent clinical data suggest that the upregulation of inflammatory cytokines by angiotensin-II, harmful to the outcomes of COVID-19 patients, can be decreased thank to the reduced formation of angiotensin-II caused by RAAS-inhibitors, thus explaining the better clinical outcomes detected by leading-edge research groups (18,26,30).

Clinical impact of management of RAAS-inhibitors during COVID-19 pandemic.

The recommendation of discontinuation from RAAS-inhibitors was initially accepted by part of the medical community as a prophylactic measurement aiming to potentially reduce the risk of a severe respiratory disease. However, in this discussion one important issue was forgotten; loss-of-function experiments using ACE2 knockout mice have demonstrated increased susceptibility to myocardial infarction, hypertension and myocardial hypertrophy, microvascular complications, inflammation, fibrosis, diastolic and systolic dysfunction and oxidative stress (19). Translated into humans, avoiding these drugs, where indicated, may increase major cardiovascular events causing more damage than the potential increased susceptibility to SARS-CoV2.

Therefore, in view of the overwhelming evidence of mortality reduction in cardiovascular disease and the lack of impact found in our research, we believe that recommend RAAS-inhibitors should be maintained or even initiated in patients with new onset heart failure, hypertension, or myocardial infarction according to current guidelines as tolerated, irrespective of SARS-CoV2 disease outbreak. The frequently updated information on the disease suggests that, not only mortality due to COVID-19 has increased, but also other comorbidities are experiencing a rise in their mortality rates. Cardiovascular events are still the greatest cause of mortality in our society and inadequate handling of secondary prevention can have a catastrophic impact in the health status of the population (26,29,34). However, as pointed out by Vaduganathan et al (26), the effects on ACE2 should not be assumed to be uniform across RAAS-inhibitors or even in response to therapies within a given drug class. For this reason we need to remark that the current research only provided accurate evidence for Ramipril and not for other drugs of this group.

The main limitations of the present study include its retrospective nature and the limited number of cases with confirmed COVID-19 infection. Detection of immunization should be undertaken as soon as confinement allows testing all patients in the trial in order to verify the real incidence of COVID-19 in this population, otherwise the real incidence of the disease remains unknown. Reporting this information in a near future is warranted but, still, reporting the impact of Ramipril on prognosis of symptomatic infection is clinically relevant. The relatively short length of the follow-up precludes from further conclusions regarding the long-term, but a continuous monitoring of patients at risk from the RASTAVI study will be performed.

CONCLUSIONS

More than 10% of this high risk patients developed the COVID-19 and one-third of them died. Older patients with higher body mass index presented higher risk of infection and mortality, respectively. However, the use of Ramipril did not increase the risk of infection or impaired the prognosis. Hence, the use of RAAS-inhibitors during COVID-19 pandemic seems safe.

PERSPECTIVES.

Competency in Medical Knowledge: ACE2 is the receptor for SARS-CoV-2 cell-entrance, the virus responsible for the COVID -19 pandemic and it is part of the RAAS system. Little is known about the impact of using ACE-inhibitors on susceptibility to this virus and severity of the disease due to cross effects of ACE2 and ACE, target of RAAS-inhibitors.

Competency in Patient Care: The use of Ramipril did not increase the risk of infection or impaired its prognosis. Hence, the use of RAAS-inhibitors during COVID-19 pandemic seems safe.

Translational Outlook 1: Although this is a relatively small study, it is the first randomized trial that investigated the impact of RAAS-inhibitors on COVID-19 and suggests a lack of risks.

Translational Outlook 2: Given the benefits of these drugs in the prognosis of cardiovascular comorbidities, RAAS-inhibitors should probably be maintained in this context.

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Figure legend

Figure 1. COVID-19 symptoms onset from 1st January 2020. Development of symptoms from 1st January 2020 according to the administration of Ramipril or standard care. COVID-19: Coronavirus disease 2019.

Figure 2. Impact of body mass index in mortality. Body mass index (Kg/m2) in patients with COVID-19 according to mortality. The box shows the interquartile range and the T-bars represent the highest and lowest values (the range). The horizontal line in the middle is the median. COVID-19: Coronavirus disease 2019.

Figure 3. Interplay of renin-angiotensin-aldosterone system and SARS-CoV2. Hypothetic model of renin-angiotensin-aldosterone system activation and SARS-CoV2 cell entry. **A**. ACE2 converts Ang I to Ang-(1-9) and Ang II to Ang-(1-7). When ACEI are present, they prevent the conversion of Ang I to Ang II. ARB act at AT_1R. **B**. When a ADAM17 binds ACE2, results in the occurrence of soluble(s) ACE2, which can no longer mediate SARS-CoV-2 entry and which might even prevent such entry by keeping the virus in solution. **C**. SARS-CoV2 - S links to ACE2 and is internalized after priming by the TMPRSS2. ACE2: Angiotensin-converting enzyme 2. ACEI: ACE inhibitors. ADAM17: disintegrin and metalloprotease 17. Ang II: angiotensin II. ARB: Angiotensin-receptor blockers. AT_1R: Angiotensin II type 1 receptor. SARS-CoV2: Severe acute respiratory syndrome by coronavirus-2. SARS-CoV2 – S: Severe acute respiratory syndrome type 2 - spike. TMPRSS2: transmembrane protease serine 2.

Central illustration: Patient flowchart. Schematic flowchart of the patients included in the RASTAVI trial and the interim analysis showing their rate of SARS-CoV2 infection and the mortality. RASTAVI: Renin-angiotensin system inhibitors following transcatheter aortic valve implantation. SARS-CoV2: Severe acute respiratory syndrome by coronavirus-2.

Table 1. Baseline Characteristics of the RASTAVI Study Population according to COVID-19 diagnosis.

	COVID-19 positive (n=11)	COVID-19 negative (n= 91)	*p* -value

Age (years)	86.0 (84.0-88.0)	83.0 (78.0-86.0)	**0.019**
Body mass index /Kg/m^2)	26.3 (24.9-28.7)	27.1 (24.6-30.5)	0.580
Gender (women)	5 (45.5%)	53 (52.8%)	0.524
Hypertension	6 (54.5%)	49 (53.8%)	0.965
Diabetes	2 (20.0%)	19 (21.3%)	0.999
Dyslipidemia	6 (54.5%)	60 (65.9%)	0.512
Prior atrial fibrillation	6 (54.5%)	22 (24.2%)	**0.066**
Coronary artery disease	2 (18.2%)	24 (26.7%)	0.724
Prior myocardial infarction	0 (0.0%)	6 (6.6%)	0.635
Prior PCI	2 (18.2%)	18 (19.8%)	0.999
CKD (eGFR <60 ml/min)	4 (36.4%)	29 (31.9%)	0.744
Moderate or severe COPD	1 (9.1%)	5 (5.6%)	0.663
Peripheral vascular disease	2 (18.2%)	9 (9.9%)	0.338
Prior Stroke/TIA	1 (9.1%)	12 (13.2%)	0.999
Prior blood test parameters:			
Hematocrit (%)	31 (28.6-33.4)	33.1 (31-36.6)	**0.084**
Creatinine (mg(dL)	0.90 (0.80-1.15)	0.80 (0.70-1.10)	0.470
NTproBNP (pg/mL)	1284 (918-1894)	1140 (522-2724)	0.719
Prior treatment:			
Oral anticoagulation	6 (54.5%)	28 (31.1%)	0.175
Statins	6 (54.4%)	61 (67.8%)	0.501
Oral hypoglycemic drug	1 (9.1%)	15 (16.7%)	0.999
Barthel index	92.5 (75.0-100.0)	95.0 (90.0-100.0)	0.584
NYHA class ≥ 2	11 (100%)	78 (85.7%)	0.351
EuroSCORE II, %	5.02 (3.90-5.95)	3.89 (3.20-5.26)	0.112
STS - PROM, %	3.90 (2.64-6.60)	3.06 (1.82 - 4.02)	**0.065**
Echocardiographic findings:			
LVEF, % (Simpson's method)	60.0 (50.0-65.0)	61.5 (56.0-66.0)	0.472
Residual aortic regurgitation ≥ 3	0	4 (4.4%)	0.478
Residual peak aortic gradient (mmHg)	18 (10.5-21)	7 (4.5-9)	0.276
Aortic velocity-time integral	17 (16-19)	22 (19.5-28.5)	**0.071**
Septal with (mm)	13 (11.5-15.5)	13 (12-15)	0.947

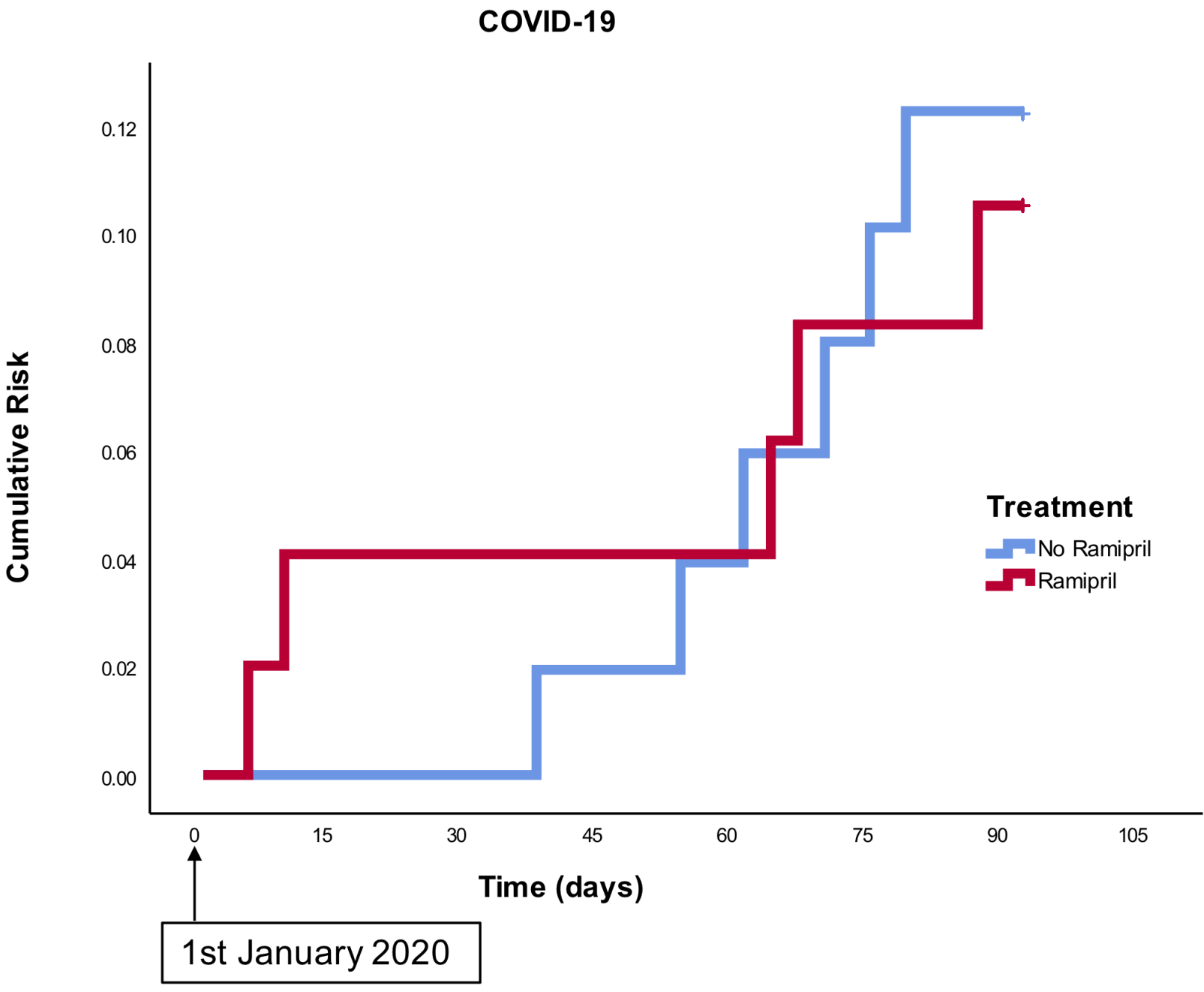
Values are n (%), mean ± SD or median (interquartile range).
CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; LVEF: Left ventricular ejection fraction; PCI: Percutaneous coronary intervention; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; TIA: Transient ischemic attack.

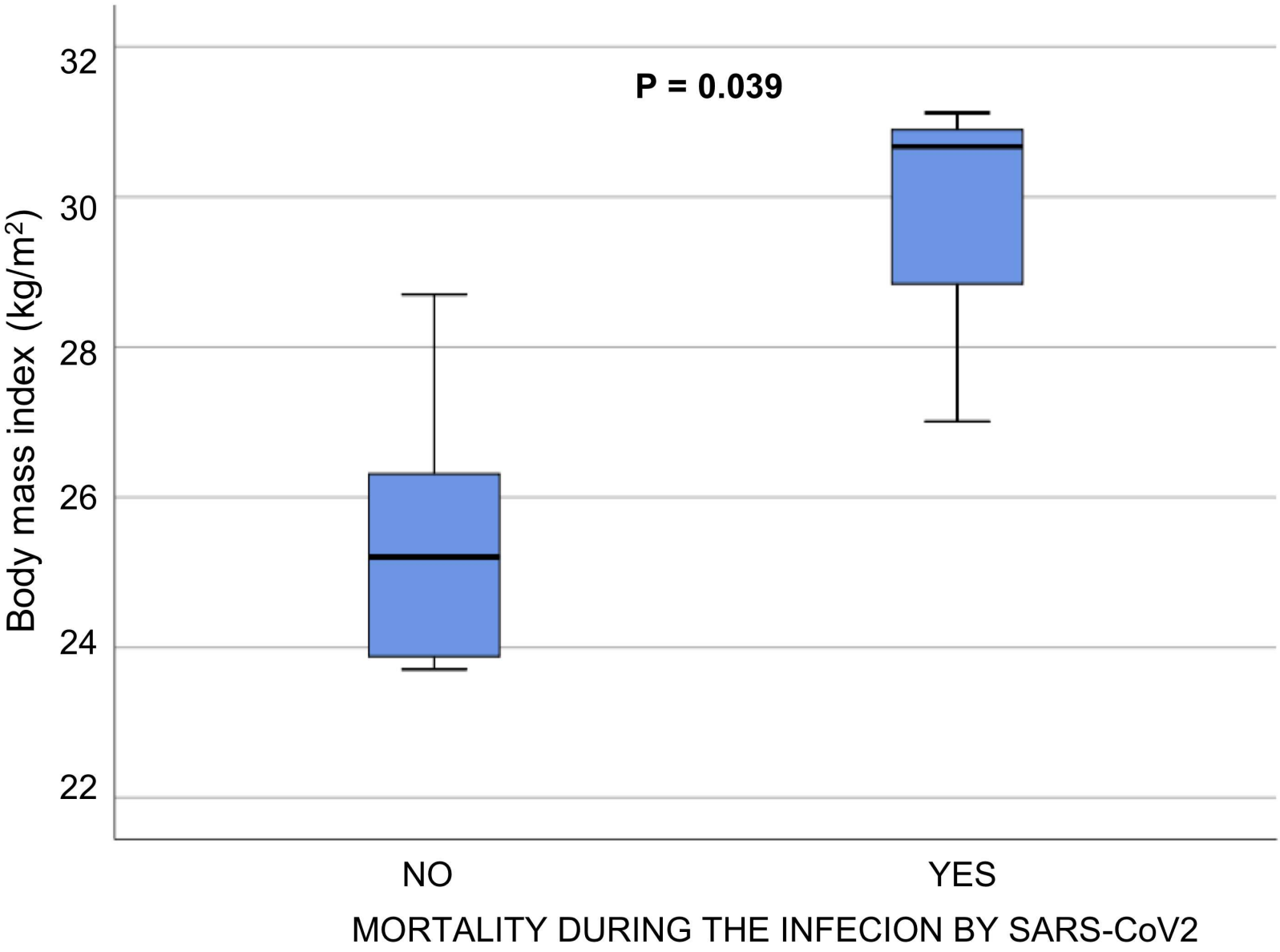
Table 2. Main characteristics of the patients presenting SARS-CoV19 infection that died according to prior randomization to ramipril or standard of care.

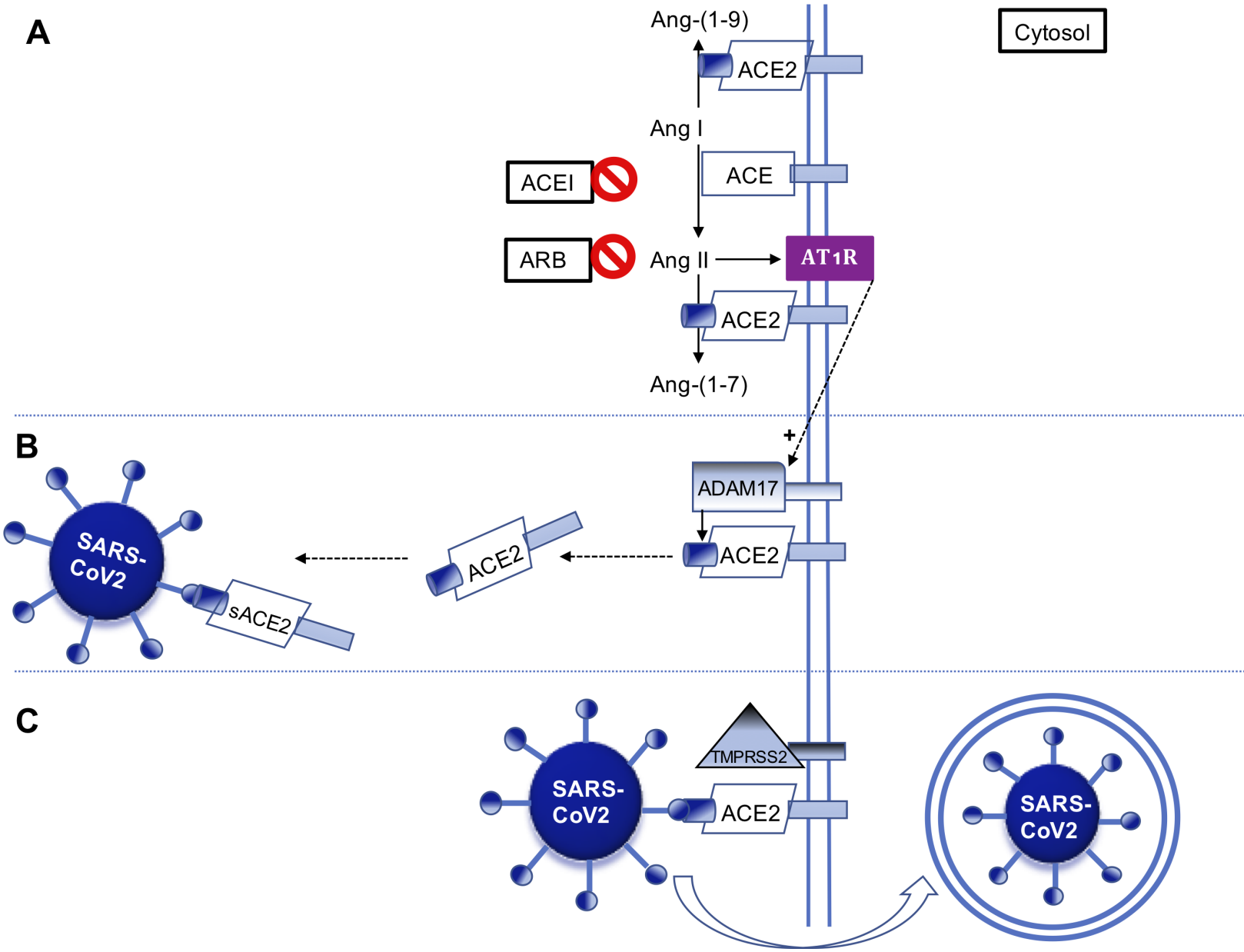
	Patient - 1	Patient - 2	Patient - 3	Patient - 4
Group	**Randomized to Ramipril**		**Randomized to Control**	
Baseline characteristics				
Gender	Male	Female	Female	Male
Age, years	86	83	88	89
Body mass index (kg/m2)	27.01	30.67	29.2	31.12
Hypertension	No	Yes	No	Yes
Diabetes mellitus	No	No	No	No
Dyslipidemia	No	Yes	No	Yes
Smoker	No	No	No	No
Coronary artery disease	Yes	No	No	No
Chronic pulmonary disease	No	No	No	No
Persistent heart failure	**Yes**	**Yes**	**Yes**	**Yes**
NYHA	III	II	II	II
CKD (eGFR <60 ml/min)	Yes	Yes	No	Yes
Moderate or severe COPD	No	No	No	No
Atrial fibrillation	Yes	No	Yes	Yes
Anticoagulation	Dabigatran	No	Apixaban	Edoxaban
Peripheral artery disease	No	No	Yes	Yes
Date of TAVR procedure	04/24/2018	05/17/2019	09/21/2018	09/11/2019
Implanted TAVR device	Evolut	Evolut	Allegra	Evolut
Residual aortic regurgitation	I	0	I	0
EuroSCORE II, %	4.55	3.08	9.32	6.63
STS-PROM, %	3.95	3.84	12.77	6.60
COVID-19 features				
Fever	Yes	Yes	No	Yes
Cough	No	Yes	No	Yes
Dyspnea	Yes	Yes	Yes	Yes
Specific COVID-19 treatment*	L/R+HC+A+C	L/R+HC+A+C	L/R+HC+A+C	L/R+HC+A+C+T
Days from diagnosis to death	15	17	12	21
ICU admission	No	No	No	No
Noninvasive mech. ventilation	No	No	No	Yes
Invasive mech. ventilation	No	No	No	No

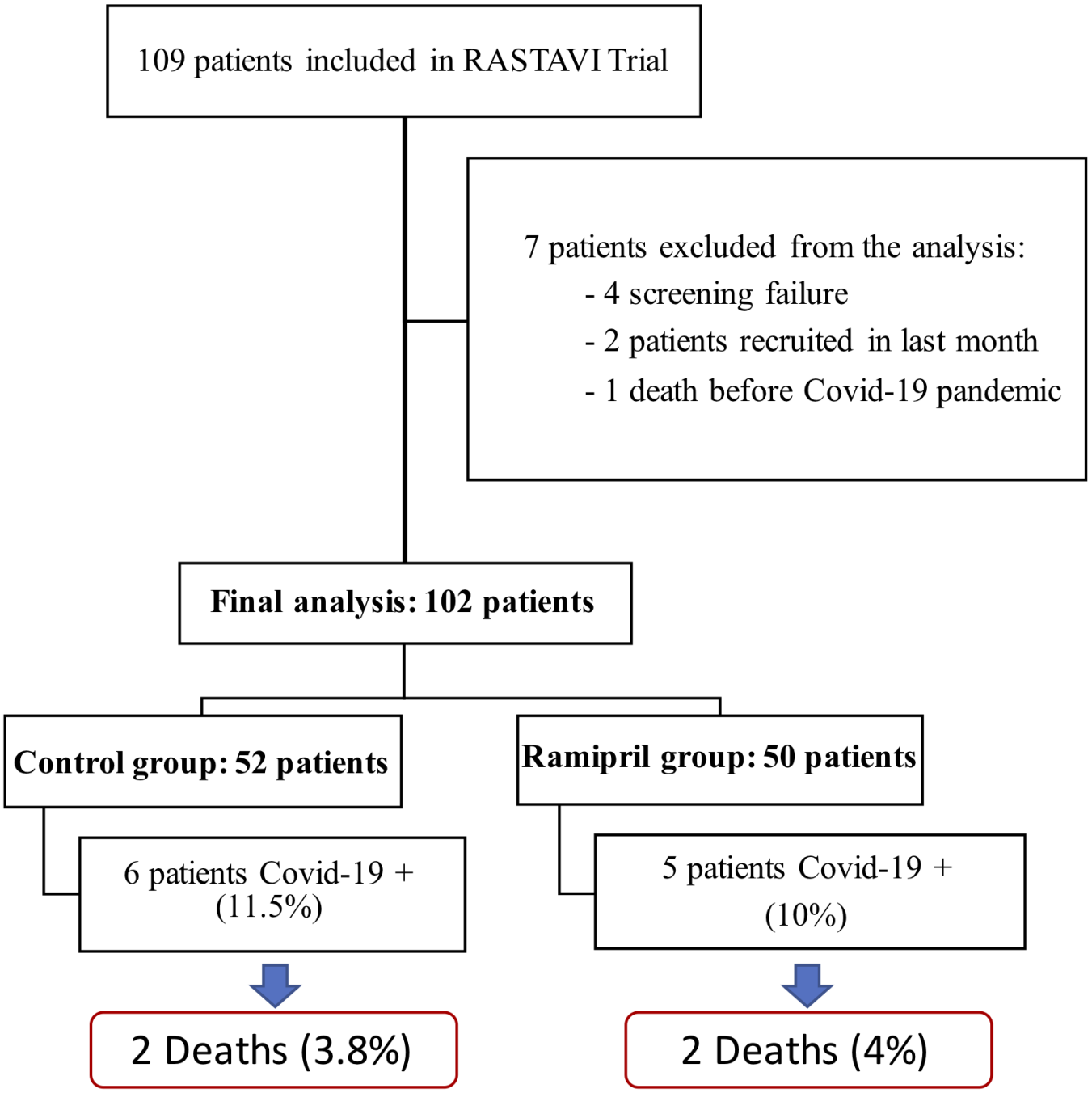
CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; Mech.: Mechanical; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; TAVR: Transcatheter aortic valve implantation.

* L/R+HC+A+C+T: Lopinavir/Ritonavir + Hydroxychloroquine + Azithromycin + Corticoids + Tocilizumab


COVID-19
Cumulative Risk
0.12
0.10
0.08
0.06
0.04
0.02
0.00
0
15
30
45
60
75
90
105
Time (days)
Treatment
No Ramipril
Ramipril
1st January 2020


P = 0.039
32
30
28
26
24
22
Body mass index (kg/m²)
NO
YES
MORTALITY DURING THE INFECION BY SARS-CoV2


A
Ang-(1-9)
Cytosol
ACE2
Ang I
ACE
ACEI
ARB
Ang II
AT1R
ACE2
Ang-(1-7)
+
B
ADAM17
ACE2
ACE2
SARS-CoV2
sACE2
C
TMPRSS2
SARS-CoV2
ACE2
SARS-CoV2


109 patients included in RASTAVI Trial
7 patients excluded from the analysis:
- 4 screening failure
- 2 patients recruited in last month
- 1 death before Covid-19 pandemic
Final analysis: 102 patients
Control group: 52 patients
Ramipril group: 50 patients
6 patients Covid-19 +
(11.5%)
5 patients Covid-19 +
(10%)
2 Deaths (3.8%)
2 Deaths (4%)