Online Supplement 3

This supplement contains the following items:

1. Final Statistical Analysis Plan

2. Summary of changes in the Statistical Analysis Plan

STATISTICAL ANALYSIS PLAN

Suspension of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers and adverse outcomes in hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

The BRACE CORONA Trial

Contents

Introduction

The interaction of pre-existing therapies for chronic diseases, especially in cardiovascular diseases, with therapies used to treat coronavirus disease 2019 (COVID-19) raise doubts about the risks and benefits of maintaining or suspending certain drugs for chronic use. In this study, various indicators will be calculated to assess the risks and benefits of maintaining or suspending the use of angiotensin-converting enzyme (ACEI) inhibitors and angiotensin receptor blockers (ARBs).

Study objectives

The objective of the study is to evaluate the impact of the suspension of the use of ACEI and ARB therapy on the number of days alive and out of the hospital at 30 days in patients hospitalized with COVID-19.

Inclusion Criteria

- Hospitalized patients with confirmed COVID-19 diagnosis, using ACEI or ARBs;
- Age ≥18 years;
- Using no more than 3 antihypertensive drugs;
- Ability of patient (or legal representative) to provide informed consent.

Exclusion Criteria

The exclusion criteria will be the presence of at least one of the following items:

- Patients hospitalized for decompensated congestive heart failure in the last 12 months;
- Use of sacubitril/valsartan;
- Use of mechanical ventilation, and/or hemodynamic instability in the first 24 hours or until confirmation of COVID-19 diagnosis;
- Acute renal failure;
- Shock;
- Pregnancy.

Primary outcome

The primary outcome will be given by the number of days alive and out of the hospital. For each patient included, it will be calculated as the follow-up time (30 days or number of days between the date of randomization and the date of death) minus the days of hospitalization.

Secondary outcomes

Secondary outcomes are as follows:

1. Length of hospital stay, in days;
2. Mortality, in the follow-up period;
3. In-hospital mortality;
4. Cardiovascular mortality;
5. COVID-19 progression (worsening of severity during hospitalization in relation to baseline severity);
6. Acute myocardial infarction;
7. Stroke/transient ischemic attack;
8. New heart failure or worsening of pre-existing heart failure;
9. Myocarditis;
10. Pericarditis;
11. Arrhythmias requiring treatment;
12. Thromboembolic phenomena;
13. Hypertensive crisis;
14. Respiratory failure requiring mechanical ventilation;
15. Hemodynamic decompensation with the need for vasoactive drugs;
16. Renal failure requiring replacement therapy (dialysis);
17. Troponin above upper limit of normal in patients with no change in baseline;
18. B-type natriuretic peptide (BNP) above upper limit of normal in patients with no change in baseline;
19. D-dimer above upper limit of normal in patients with no change in baseline;

All secondary outcomes will be assessed within 30 days.

Calculation of the sample size

To date, there are no studies that allow an adequate sample calculation. Thus, the expected initial sample will be at least 500 patients. This number may increase or decrease depending on the recruitment and event rates, and the Data and Safety Monitoring Committee's (DSMC) interim review.

Using the measures of the ongoing study COALIZAO I [NCT04322123] as a reference (standard deviation of 4 days and average time of 24 days alive and outside the hospital), it will be possible to obtain a power of 90% to detect an average ratio of at least 1.10 in the primary endpoint with a total of 500 patients.

The recruitment of participants occurred faster than expected and in order to be able to carry out the two interim analyzes with a 30-day follow-up of 150 and 250 patients, the recruitment was extended and ended with a number of patients above the initially calculated, which confirmed even greater statistical power for the study.

Interim analysis

In this study, 2 interim analyses were planned when 150 and 250 patients were enrolled. The DSMC used a P value of <0.001 to determine statistically significant differences (in the final analysis of the study a a P value of 0.05 is considered statistically significant).

Basic principles of statistical analysis

In this study, the following population definitions will be used:

1. Intention to treat (ITT): all eligible patients who have been randomized according to the group to which they have been allocated, regardless of the maintenance or suspension of medications.

2. In treatment ("on treatment"): defined by the maintenance or suspension of medication, regardless of the allocated group.

We will carry out analyses of baseline variables and primary and secondary outcomes using the ITT population.

The baseline characteristics of the patients will be presented as described in Table 1. Statistical analyses will be performed using R software (R Core Team, Vienna, Austria, 2020).

Analysis of the primary outcome

The primary outcome of the study will be given as the number of days alive and out of the hospital. The comparison of the two groups (with and without suspension of ACEIs / ARBs) will be made based on the generalized additive model of location, scale, and shape with zero inflated beta binomial distribution. The results will be presented as the ratio of the average times between the groups with the respective 95% confidence interval, as shown in Table 2. The difference in means (95% confidence interval) of the primary outcome, as well as the median difference (25th, 75th) will also be calculated and presented.

Analysis of secondary outcomes

Secondary binary outcomes (such as mortality in the follow-up period, mortality in the hospital period, etc.) will be compared with the use of log-binomial models and relative risks will be reported with the respective 95% confidence intervals.

For continuous secondary outcomes, generalized linear models will be used considering the distribution that best fits the data and the average differences between groups will be reported with the respective 95% confidence intervals.

The outcomes of time until cardiovascular events (alone or in combination) and mortality will be analyzed with Kaplan-Meier curves and proportional hazards model.

The results of these outcomes will be presented as shown in Table 2.

Missing data

For patients with missing data within 30 days, the primary outcome will be analyzed with the outcome imputed based on stratification variables (previous use of ACEI or ARBs), age, time of discharge, and degree of disease severity at hospital admission. This imputation will be done using the Multivariate Imputation by Chained Equations in R package (van Buuren and Groothuis-Oudshoorn, 2011). Secondary outcomes can be imputed using the same method.

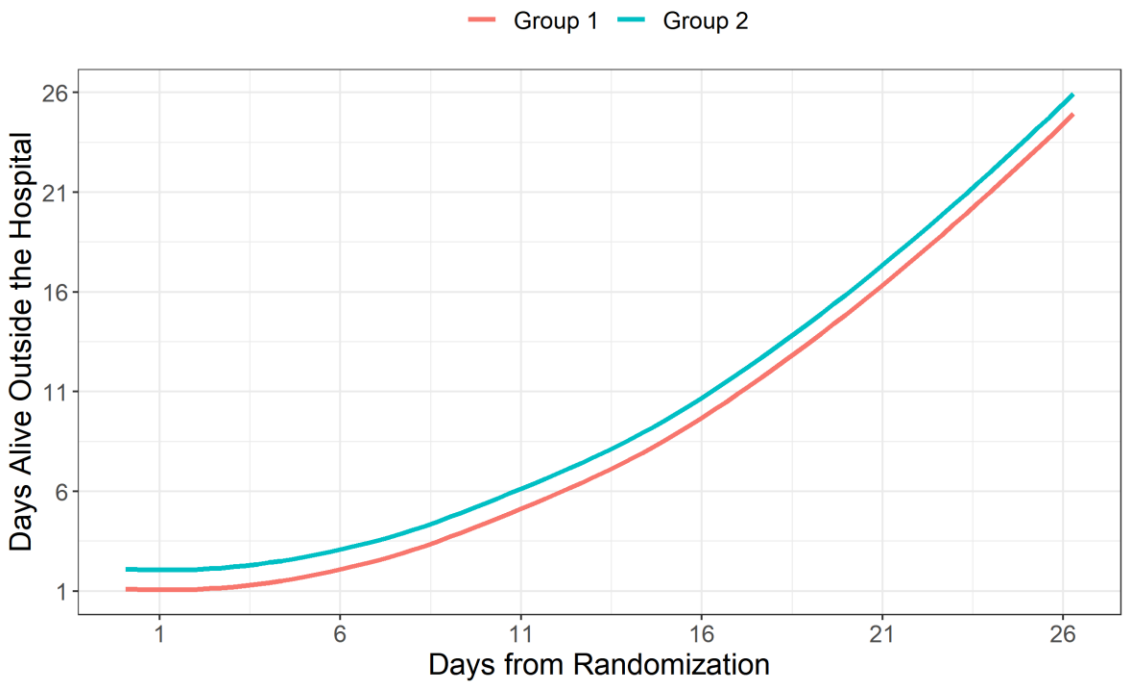
Graphical presentation of results

Some results will be presented graphically. For example, the mean days alive and out of the hospital for each group can be presented according to **Graph 1**. The percentage of each status (living and out of the hospital at 30 days, hospitalized over the 30 days, and died within 30 days) according to the number of days from randomization will be presented according to **Graph 2**.

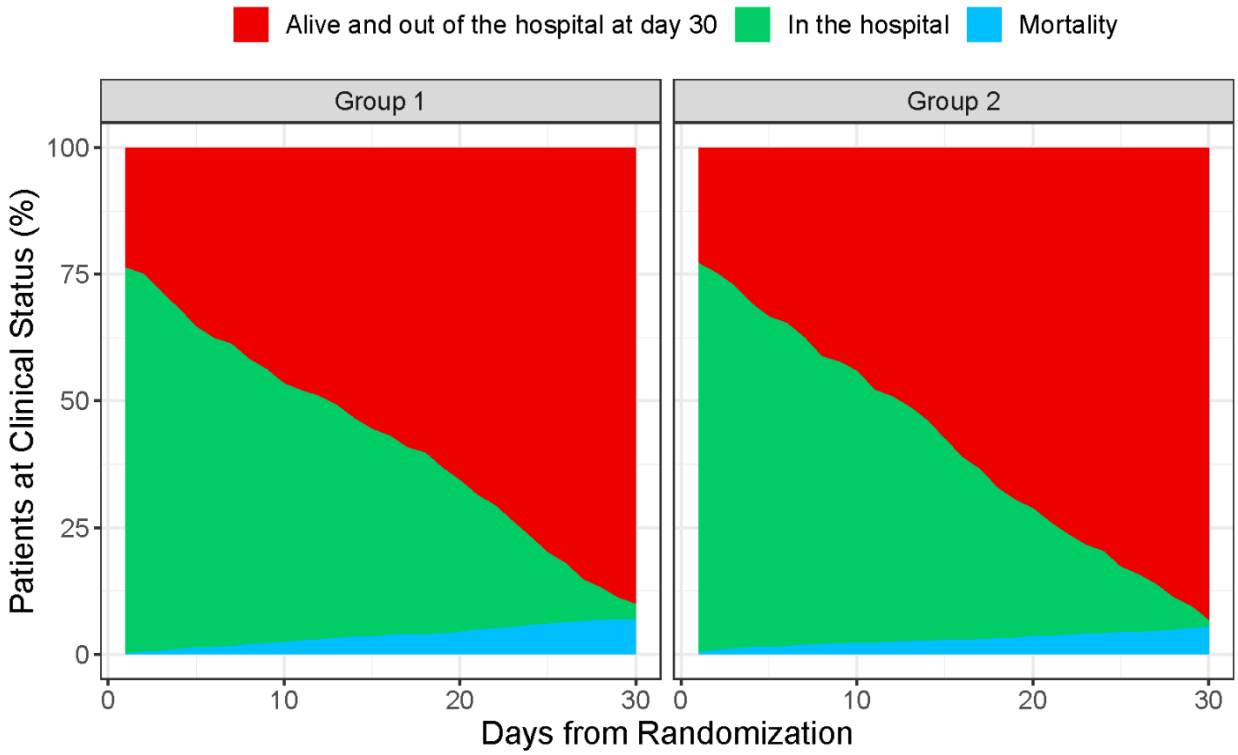
Other ways of presenting the results will be considered. The number of days alive and out of the hospital according to group can be presented with the percentage distribution **(Graph 3)** or as the accumulated percentage **(Graph 4)**. The comparison of groups in relation to the number of days alive and out of the hospital according to some characteristics or outcomes can be presented in the format of **Graph 5.**

These formats can be changed in a more convenient way that will be defined after observing the 30-day follow-up data.

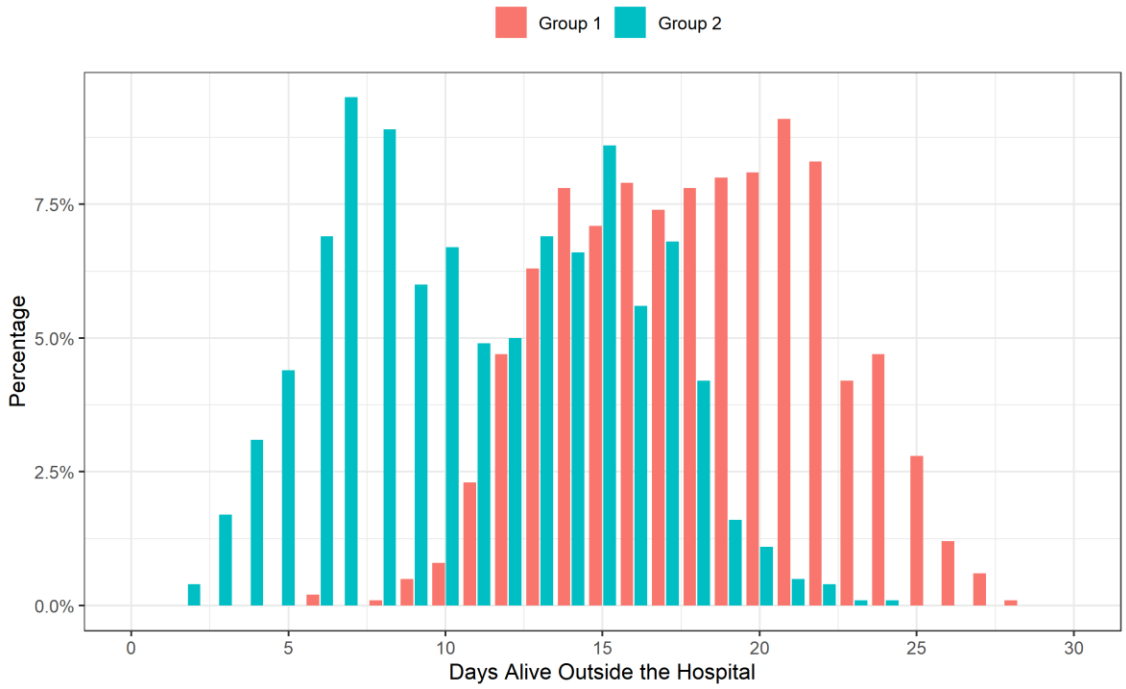
Graph 1. Mean days alive and out of the hospital for total number of days from randomization according to group



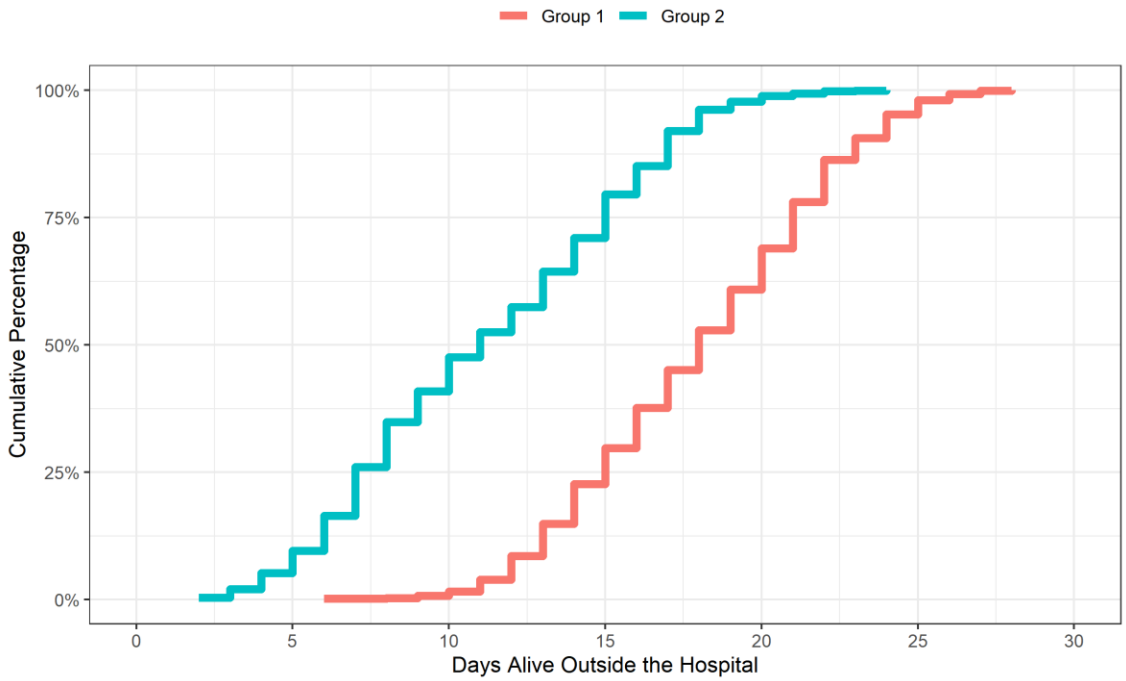
Graph 2. Accumulated percentage of the number of days alive and out of the hospital according to group



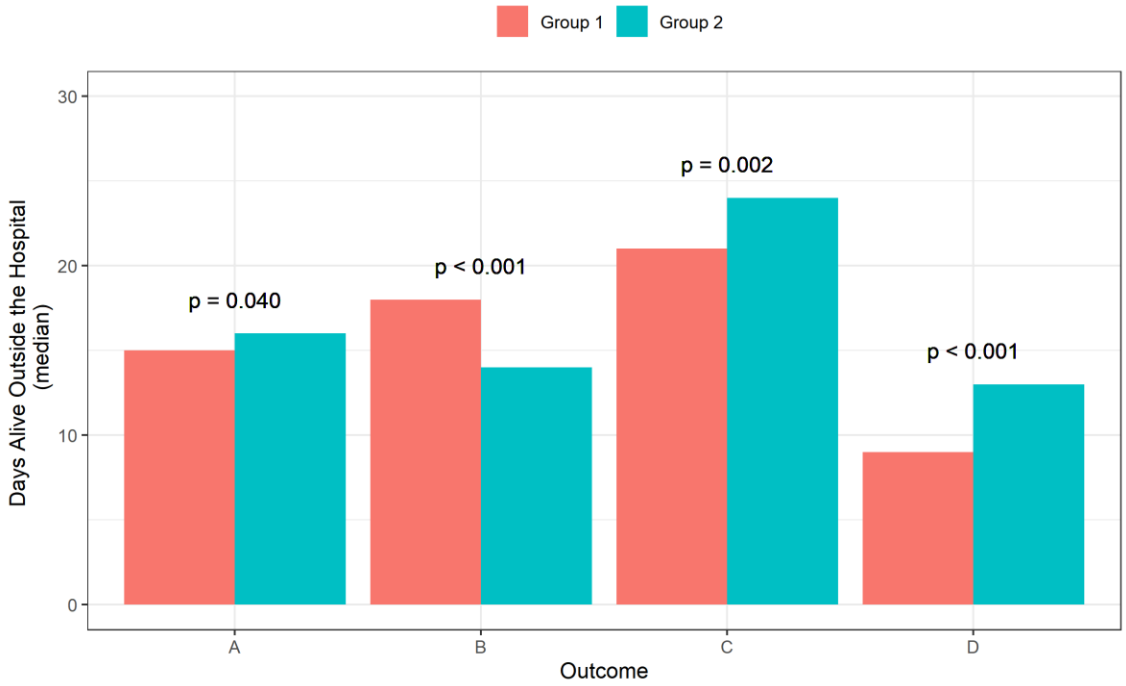
Graph 3. Percentage of number of days alive and out of the hospital according to the group



Graph 4. Accumulated percentage of number of days alive and out of the hospital according to group



Graph 5. Comparison of number of days alive and out of the hospital for some outcomes according to group



Subgroup analyses

The subgroup analyses will be done with the inclusion of parameters of interaction with the groups (with and without suspension of the ACEI / ARB) in the generalized additive model of location, scale, and shape with beta binomial distribution inflated at zero for the main outcome for the variables listed below:

1. Age (<65 years or ≥65 years);
2. Obesity (yes vs no);
3. Previous use of ACEI (yes vs no);
4. Previous use of ARB (yes vs no);
5. O2 saturation (<94% AA vs ≥94% AA);
6. Time from symptom onset to randomization (first tertile, second tertile, and third tertile);
7. Degree of lung involvement assessed by chest computed tomography at hospital admission (≤ 25%, 26-50%; ≥ 51%);
8. Severity of COVID-19 disease (mild, moderate and severe).

The results of the subgroup analyses will be presented in a forest plot graph with data similar to those presented in Table 3**.**

Sensitivity analysis

As the main analysis will done with multiple data imputation, we intend to perform a sensitivity analysis considering only the complete data for the primary outcome.

A sensitivity analysis will be performed in which the value of 0 days will be given as the number of days alive and out of the hospital for the cases in which the patient dies, regardless of the date of death. This will ensure that these cases are not considered positive measures for the study. In addition, the analysis of the primary outcome with a mixed model will be conducted using the centers as a random effect.

Adverse events

Serious adverse events will be defined by at least one of the following criteria, which are not already classified as a secondary outcome of the study:

1. Fatal (AE that causes or leads to death);
2. Risk to life (puts the patient at imminent risk of death);
3. Requires or extends hospitalization;

4. Results in deficiency/incapacity;
5. Significant medical event that may require clinical or surgical intervention to prevent one of the outcomes listed above.

These events will be reported for each group and compared using the Chi-square test.

Table 1. Baseline characteristics of patients

	Discontinuing ACEI/ARB (n =)	Continuing ACEI/ARB (n =)	Total (n =)
	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Age, mean±SD, years	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Women, no. (%)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
BMI, mean ± SD, kg/m^2			
Medical history, no. (%)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Hypertension	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Asthma	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Kidney disease	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
History of cancer	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Obesity	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Diabetes			
Smoking	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Active smoker	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Former smoker	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Never smoked	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Heart failure	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Coronary heart disease	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Arrhythmias			
Medication on admission, no. (%)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
ARB	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
ACEI	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Beta-blockers	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Calcium-channel blockers	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Diuretics	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Oral anticoagulants (yes)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

	Discontinuing ACEI/ARB (n =)	Continuing ACEI/ARB (n =)	Total (n =)
Antiplatelet drug (yes)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Insulin (yes)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Statin (yes)	xx.x [xx.x; xx.x]	xx.x [xx.x; xx.x]	xx.x [xx.x; xx.x]
Duration of ACEI/ ARB use prior to randomization, median (25th, 75th), yrs			
Laboratory on admission	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Troponin above normal, no. (%)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
D-dimer above normal, no. (%)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Lymphocytes, mean±SD, cell/mm^3	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Leukocytes, mean±SD, cells/mm^3	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Serum creatinine, mean±SD, mgl/dl	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
C-reactive protein, mean±SD, mgl/dl	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Potassium, mean±SD	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Sodium, mean±SD			
Clinical severity on first 24 hours, no. (%)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Mild	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Moderate	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Severe			
Degree of lung involvement on chest CT on hospital admission, no. (%)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
≤25%,	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
25 to 50%	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
>50%	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Clinical characteristics on admission	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Systolic blood pressure, mm Hg, mean±SD			
Diastolic blood pressure, mm Hg, mean±SD	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x

	Discontinuing ACEI/ARB (n =)	Continuing ACEI/ARB (n =)	Total (n =)
Heart rate, bpm, mean±SD	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Respiratory frequency, bpm, mean±SD	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
SaO_2, %, mean±SD	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
SaO_2 <94 % RA, no. (%)	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Cough, no. (%)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Dyspnea, no. (%)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Fever, no. (%)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Temperature (ºC), mean±SD	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Time from the beginning of the first symptom to hospitalization, median (25th, 75th), days	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
Time from the start of the first symptom to randomization, median (25th, 75th), days			
Time between hospitalization and randomization, median (25th, 75th), days	xx.x [xx.x; xx.x]	xx.x [xx.x; xx.x]	xx.x [xx.x; xx.x]
Treatment during hospitalization, no. (%)	xx.x [xx.x; xx.x]	xx.x [xx.x; xx.x]	xx.x [xx.x; xx.x]
Chloroquine/hydroxycloroquine	xx.x [xx.x; xx.x]	xx.x [xx.x; xx.x]	xx.x [xx.x; xx.x]
Azithromycin			
Any antibiotics	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Corticosteroids	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Antiviral drugs	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Tocilizumab	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Therapeutic anticoagulation	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

ACEI denotes angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CT, computed tomography; SD, standard deviation; SaO_2, oxygen saturation.

278 **Table 2. Primary and secondary endpoints**

	Discontinuing ACEI/ARB (n =)	Continuing ACEI/ARB (n =)	Effect Type	Effect size (95% CI)	P value
Primary Outcome					
Days alive and out of hospital, mean±SD	x.xx [x.xx - x.xx]	x.xx [x.xx - x.xx]	Mean Ratio	xx.x (xx.x – xx.x)	x.xx
Secondary outcomes					
Length of hospitalization, median (25th, 75th), days	xx.x ± xx.x	xx.x ± xx.x	Mean Ratio	xx.x (xx.x – xx.x)	x.xx
Length of hospitalization, mean ± SD, days	xx.x (xx.x)	xx.x (xx.x)	Mean Ratio	xx.x (xx.x – xx.x)	x.xx
Mortality at 30 days, no. (%)	xx.x (xx.x)	xx.x (xx.x)	Hazard Ratio	xx.x (xx.x – xx.x)	x.xx
In-hospital mortality, no. (%)	xx.x (xx.x)	xx.x (xx.x)	Hazard Ratio	xx.x (xx.x – xx.x)	x.xx
Cardiovascular mortality, no. (%)	xx.x (xx.x)	xx.x (xx.x)	Hazard Ratio	xx.x (xx.x – xx.x)	x.xx
Progression of COVID-19 disease, no. (%)	xx.x (xx.x)	xx.x (xx.x)	Relative Risk	xx.x (xx.x – xx.x)	x.xx
Acute MI, no. (%)	xx.x (xx.x)	xx.x (xx.x)	Relative Risk	xx.x (xx.x – xx.x)	x.xx
Type II acute MI/Myocardial injury, no. (%)	xx.x (xx.x)	xx.x (xx.x)	Relative Risk	xx.x (xx.x – xx.x)	x.xx
Stroke/TIA, no. (%)	xx.x (xx.x)	xx.x (xx.x)	Relative Risk	xx.x (xx.x – xx.x)	x.xx
New or worsening heart failure, no. (%)	xx.x (xx.x)	xx.x (xx.x)	Relative Risk	xx.x (xx.x – xx.x)	x.xx
Myocarditis, no. (%)	xx.x (xx.x)	xx.x (xx.x)	Relative Risk	xx.x (xx.x – xx.x)	x.xx

	Discontinuing ACEI/ARB (n =)	Continuing ACEI/ARB (n =)	Effect Type	Effect size (95% CI)	P value
Pericarditis, no. (%)	xx.x (xx.x)	xx.x (xx.x)	Relative risk	xx.x (xx.x – xx.x)	x.xx
Arrhythmias requiring treatment, no. (%)	xx.x (xx.x)	xx.x (xx.x)	Relative risk	xx.x (xx.x – xx.x)	x.xx
Thromboembolic events, no. (%)	xx.x (xx.x)	xx.x (xx.x)	Relative risk	xx.x (xx.x – xx.x)	x.xx
Hypertensive crisis, no. (%)	xx.x (xx.x)	xx.x (xx.x)	Relative risk	xx.x (xx.x – xx.x)	x.xx
Respiratory failure requiring invasive mechanical ventilation, no. (%)	xx.x (xx.x)	xx.x (xx.x)	Relative risk	xx.x (xx.x – xx.x)	x.xx
Hemodynamic decompensation requiring vasoactive drugs, no. (%)	xx.x (xx.x)	xx.x (xx.x)	Relative risk	xx.x (xx.x – xx.x)	x.xx
Acute renal failure requiring renal replacement therapy, no. (%)	xx.x (xx.x)	xx.x (xx.x)	Relative risk	xx.x (xx.x – xx.x)	x.xx
Troponin above the ULN, no. (%)	xx.x (xx.x)	xx.x (xx.x)	Relative risk	xx.x (xx.x – xx.x)	x.xx

ACEI denotes angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; COVID-19, coronavirus disease 2019; MI, myocardial infarction; SD, standard deviation; TIA, transient ischemic attack; ULN, upper limit of normal.

281 **Table 3. Subgroup analysis**

	Discontinuing ACEI/ARB (n =)	Continuing ACEI/ARB (n =)	Effect Size (95% CI)	P value	P value (interection)
Age, mean±SD					
<65 years	xx.x ± xx.x	xx.x ± xx.x	xx.x (xx.x – xx.x)	x.xx	x.xx
≥65 years	xx.x ± xx.x	xx.x ± xx.x	xx.x (xx.x – xx.x)	x.xx	
Obesity, mean±SD					
Yes	xx.x ± xx.x	xx.x ± xx.x	xx.x (xx.x – xx.x)	x.xx	x.xx
No	xx.x ± xx.x	xx.x ± xx.x	xx.x (xx.x – xx.x)	x.xx	
Previous use of ACEI, mean±SD					
Yes	xx.x ± xx.x	xx.x ± xx.x	xx.x (xx.x – xx.x)	x.xx	x.xx
No	xx.x ± xx.x	xx.x ± xx.x	xx.x (xx.x – xx.x)	x.xx	
Previous use of ARBs, mean±SD					
Yes	xx.x ± xx.x	xx.x ± xx.x	xx.x (xx.x – xx.x)	x.xx	x.xx
No	xx.x ± xx.x	xx.x ± xx.x	xx.x (xx.x – xx.x)	x.xx	
Saturation O_2, mean±SD					
<94 %RA	xx.x ± xx.x	xx.x ± xx.x	xx.x (xx.x – xx.x)	x.xx	x.xx
≥94 %RA	xx.x ± xx.x	xx.x ± xx.x	xx.x (xx.x – xx.x)	x.xx	
Time from the start of the first symptom to randomization, mean±SD					
First tertile (up to 5 days)	xx.x ± xx.x	xx.x ± xx.x	xx.x (xx.x – xx.x)	x.xx	x.xx
Second tertile (5 to 8 days)	xx.x ± xx.x	xx.x ± xx.x	xx.x (xx.x – xx.x)	x.xx	
Third tertile (more than 8 days)	xx.x ± xx.x	xx.x ± xx.x	xx.x (xx.x – xx.x)	x.xx	

Chest CT staging on admission, mean±SD					
≤25%	xx.x ± xx.x	xx.x ± xx.x	xx.x (xx.x – xx.x)	x.xx	x.xx
26–50%	xx.x ± xx.x	xx.x ± xx.x	xx.x (xx.x – xx.x)	x.xx	
>51%	xx.x ± xx.x	xx.x ± xx.x			
Clinical severity on admission, mean±SD					
Mild	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x – xx.x)	x.xx	x.xx
Moderate	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x – xx.x)	x.xx	
Severe	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x – xx.x)	x.xx	

ACEI denotes angiotensin-converting enzyme inhibitors; ARB, angiotenin receptor blocker; CT, computed tomography; SD, standard deviation.

References

R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

van Buuren S, Groothuis-Oudshoorn K (2011). “mice: Multivariate Imputation by Chained Equations in R.” Journal of Statistical Software, 45(3), 1-67. https://www.jstatsoft.org/v45/i03/.

STATISTICAL ANALYSIS PLAN (SAP)

CHANGES IN 1.0 VERSION (05/30/2020) of the SAP TO 2.0 VERSION (07/31/2020) of the SAP

1. Creation of a section about sensitivity analyses in which the analysis mentioned in version 1.0: “Will be performed as well a sensitivity analysis in which the value of 0 days will be given as the number of days alive and out of the hospital for the cases in which the patient dies, regardless of the date of death. This will ensure that these cases are not considered positive measures for the study.”* was included with other sensitivity analyses**.

* This was removed from the primary outcomes section in version 1.0 and placed in the sensitivity analyses section of version 2.0.

**The following sensitivity analyses were included: analysis considering only the complete data for the primary outcome; analysis of the primary outcome with a mixed model considering the sites as a random effect.

2. Expanded descriptions of some secondary outcomes:

- The description of “Respiratory insufficiency” (version 1.0) became “Respiratory insufficiency with need for mechanical ventilation” in version 2.0.
- The description of “Hemodynamic decompensation and sepsis” (version 1.0) became “Hemodynamic decompensation with need for vasoactive drug” in version 2.0.
- The description of “Renal failure” (version 1.0) became “Renal failure with need for replacement therapy (dialysis)” in version 2.0.
- The description of “Troponin” (version 1.0) became “Troponin above the upper limit of normal in patients with normal values at baseline” in version 2.0.
- The description of “B-type natriuretic peptide (BNP)” (version 1.0) became “B-type natriuretic peptide (BNP) above the upper limit of normal in patients with normal levels at baseline” in version 2.0.
- The description of “D-dimer” (version 1.0) became “D-dimer above the upper limit of normal in patients with normal value at baseline” in version 2.0.

1. Explanation about the increase in sample size:

A paragraph explaining the rationale for the increase in sample size was added (The recruitment of participants occurred faster than expected and in order to be able to carry out the two interim analyzes with a 30-day follow-up of 150 and 250 patients, the recruitment was extended and the sample size increased to approximately 700 patients.).

2. Addition to the section of the analysis of secondary outcomes:

The following information was included: The time, cardiovascular events (isolated or combined) and mortality outcomes can be analyzed with Kaplan-Meier curves and a proportional hazards model.

3. Addition of section about missing data and graphic presentation of the results:

Two new sections which were not in the initial version were included.

4. Changes in section about subgroup analysis:

As the number of cases of patients with previous CVA was small (<1%), it would not make sense to perform a subgroup analysis so this item was not included in version 2.0.

The same rationale was applied to the patients with previous acute myocardial infarction; the rate was also low so this was not included in version 2.0. Other subgroups that were common and/or important to the prognostic information of COVID-19 were included (such as obesity, baseline O_2 saturation, time from symptom onset to randomization, degree of lung involvement assessed by chest computed tomography at hospital admission, and severity of COVID-19 disease) for subgroup analysis in version 2.0:

1. Age (< 65 years or ≥65 years);
2. Obesity (yes vs no);
3. Previous use of ACEI (yes vs no);
4. Previous use of ARB (yes vs no);
5. O_2 saturation (< 94% AA vs ≥94% AA);
6. Time from symptom onset to randomization (divided in tertiles);
7. Degree of lung involvement assessed by chest computed tomography at hospital admission (≤25%, 26-50%; ≥51%);
8. Severity of COVID-19 disease (mild or moderate).

5. Changes in Table 1 and 2:

Changes were made to some labels and variables in Tables 1 and 2.