# Supplemental Online Content

Lopes RD, Macedo AVS, de Barros E Silva PGM, et al. Effect of discontinuing vs continuing angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on days alive and out of the hospital in patients admitted with COVID-19: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2020.25864



This supplemental material has been provided by the authors to give readers additional information about their work.

# eMethods

## Inclusion and exclusion criteria

Inclusion criteria
1. Patients aged ≥18 years hospitalized with a confirmed diagnosis of COVID-19 under use of angiotensin receptor blockers or angiotensin converting enzyme inhibitors;
2. The patient (or legal representative) must be able to give informed consent in accordance with ICH GCP guidelines and local legislation and/or regulations.

Exclusion criteria
1. Hospitalization due to decompensated heart failure in the last 12 months
2. Use of more than 3 anti-hypertensive drugs
3. Use of Sacubitril/Valsartan
4. Patients under mechanical ventilation
5. Hemodynamic instability in the first 24 hours until the moment of confirmed diagnosis of COVID-19; acute renal failure; shock
6. Pregnancy

## Secondary endpoint definitions

Death
Deaths will be classified as cardiovascular, non-cardiovascular, and unknown. The cause of the death is determined by the main condition that caused the death, not the immediate modality of the death. All death causes will be considered of cardiovascular nature, unless there is one non-cardiovascular cause clearly defined, except for the death without any additional information that will be classified as Unknown cause. Cardiovascular death includes, but is not limited to, atherosclerotic coronary heart disease (acute myocardial infarction, sudden cardiac death, non-sudden death associated with cardiac symptoms with gradual worsening, unwitnessed death without defined alternative cause, death related to the cardiac surgical procedure or to coronary angiography), vascular atherosclerotic disease (cerebrovascular disease including ischemic and hemorrhagic cerebrovascular stroke, aortic, mesenteric, renal vascular, or peripheral arterial disease, death related to the non-coronary vascular procedure), and other cardiovascular (pulmonary embolism, endocarditis, congestive heart failure, cardiac valvular disease, arrhythmias). Example of non-cardiovascular death includes the primary cause of death as being infectious, related to malignancy, pulmonary, gastrointestinal, accidental trauma, suicide, renal.
Cardiovascular death will be then classified as sudden, non-sudden and unwitnessed.

Acute Myocardial Infarction
Acute myocardial infarction is defined by elevation and/or decrease of cardiac biomarkers (CKMB or troponin) with at least one value above the reference and at least one of the following criteria:

- Clinical presentation consistent with ischemia
- Electrocardiographic evidence of acute myocardial ischemia
- Development of new pathological Q wave
- Evidence on imaging test of new change in segmental contractility of myocardial wall or loss of viable myocardium
- Identification of a coronary thrombus by angiography including intracoronary imaging.

* The autopsy exam with AMI evidence may be used as isolated criterion for the infarction if there is a Post-mortem demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large circumscribed area of necrosis with or without intramyocardial haemorrhage, meets the type 1 MI criteria regardless of cTn values.
** Troponin elevation in the setting of an infection without clear type I MI (chest pain, ECG changes, coronary disease on the angiogram, percutaneous coronary intervention) will be considered a type II MI/myocardial injury.

Stroke/Transient Ischemia Attack
Stroke is defined as an acute focal neurological deficit of sudden onset:
a) that is not reversible in 24 hours or that results in death (in less than 24 hours) and is not due to an identifiable cause (e.g. tumor or trauma) OR
b) that resolves in <24 hours and is accompanied by a clear evidence of stroke in brain imaging test.
Stroke will be subclassified in subtypes:

- Ischemic Stroke: it is the stroke without intracerebral blood focal collections due to primary hemorrhage in brain imaging test.
- Primary hemorrhage
    - Intracerebral hemorrhage: stroke with focal collections of intracerebral blood seen in brain imaging tests (computed tomography (CT) or MRI) or in postmortem exam, not representing hemorrhagic conversion. Primary hemorrhages cause hematomas that are usually easily distinguished by their subcortical location and round or elliptical shape. Micro hemorrhages incidentally found in brain imaging tests in the absence of symptomatology will not be considered a primary intracranial hemorrhagic outcome.
    - Subarachnoid hemorrhage: collection of high density fluid in the subarachnoid space in brain imaging tests or presence of blood in the subarachnoid space at autopsy.
- Uncertain: any stroke without brain imaging test (CT or MRI) or documentation by autopsy or if tests are inconclusive.

Subdural or Epidural hematoma will not be classified as stroke.
Transient ischemic attack is defined as:

a. a focal neurological deficit lasting <24 hours and no identifiable non-vascular cause (e.g. cerebral tumor,

trauma), AND

b. absence of new infarction in brain imaging test (if available).

New or worsening heart failure

New or worsening heart failure heart failure is defined as an event that meets ALL of the following criteria (1-4):

1. The patient is admitted to the hospital with a primary diagnosis of heart failure (HF) or the participant's length of stay in the hospital extends for at least additional 24 hours* due to worsening of symptoms of heart failure (items 2 to 4).

* or a change in calendar date if the hospital admission and discharge times are unavailable

2. The patient exhibits documented new or worsening symptoms of HF, including at least ONE of the following:
    a. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea, nocturnal cough in supine position, tachypnea)
    b. Decreased exercise tolerance
    c. Fatigue
    d. Worsened end-organ perfusion (worsening cerebral, renal, liver, abdominal or gastrointestinal, peripheral circulatory function as manifested by symptoms such as dizziness, lightheadedness, syncope, confusion, altered mental status, restlessness, decline in cognitive state, nausea, vomiting, abdominal pain, abdominal fullness, abdominal discomfort or abdominal tenderness, cold clammy extremities, discoloration of extremities or lips, jaundice, pain in extremities, reduced urine output, darkening of urine color, chest pain, palpitations)
    e. Volume overload (swelling of lower extremities, swelling or indentation of pressure marks in areas of fluid accumulation such as legs, ankles, lower back; increase in abdominal girth, right-sided abdominal fullness, discomfort or tenderness, increase in body weight, oozing and development of skin breakdown in lower extremities)
3. The patient exhibits objective evidence of new or worsening HF, consisting of at least TWO physician examination findings OR ONE physical examination finding and at least ONE laboratory criterion.
    <u>3.1 Physical examination findings considered to be due to HF, include new or worsened:</u>
    a. Peripheral edema (swelling or pitting indentation when pressed in feet, ankles, legs, thighs, upper extremities, scrotal, presacral area, or abdominal wall)
    b. Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
    c. Pulmonary rales/crackles/crepitations
    d. Increased jugular venous pressure and/or hepatojugular reflux
    e. S3 gallop
    f. Clinically significant or rapid weight gain thought to be related to fluid retention (usually more than 3-4 lbs in 3-4 days)
    <u>3.2 Laboratory Evidence of HF: Laboratory evidence of new or worsening HF including:</u>
    a. Increased B-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP) concentrations.
    b. Radiological evidence of pulmonary congestion.
    c. Non-invasive diagnostic evidence of HF (echocardiography, cardiac MRI, Cardiac PET scan, nuclear imaging).
    d. Invasive diagnostic evidence of HF.
4. Initiation or intensification of HF treatment, including at least ONE of the following:
    a. Augmentation in oral diuretic therapy
    b. Intravenous diuretic, or intravenous vasoactive/inotropic therapy
    c. Mechanical or surgical intervention (including mechanical circulatory support or fluid removal).

Hypertensive crisis

Hypertensive crisis is defined as systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥120 mmHg plus the presence of acute symptoms related to high blood pressure (e.g. chest pain, dyspnea, shortness of breath) and/or need for IV vasodilator.

Acute pericarditis

For diagnosis, patient must present two of the following items:

• Chest pain typical of pericarditis;
• typical ECG for pericarditis;

• Pericardial friction rub;
• Compatible image examination (magnetic resonance imaging is the gold standard).

Acute myocarditis
For diagnosis, patient must meet the 3 criteria below or magnetic resonance imaging characteristic of myocarditis:
• Compatible clinical presentation (chest pain, acute symptoms of heart failure, unexplained arrhythmias);
• Cardiac damage (troponin elevation or new echocardiogram change);
• Absence of known coronary disease or other diagnosis that justifies clinical and laboratory findings.

Deep vein thrombosis (DVT)
DVT is generally documented by one of the following methods:
• Positive non-invasive imaging (e.g. ultrasound);
• Defect of intraluminal filling in venography;
• At autopsy.

Pulmonary embolism (PE)
PE is generally documented in one of the following ways:
• A defect in intraluminal filling in segmental or more proximal branches of spiral computed tomography;
• An intraluminal filling defect or an extension of an existing defect or sudden cut-off point of vessels over 2.5 mm in diameter on pulmonary angiography;
• Perfusion defect with normal local ventilation considered high probability in pulmonary ventilation-perfusion scintigraphy;
• Inconclusive spiral CT, pulmonary angiography or pulmonary scintigraphy with demonstration of DVT in the lower limbs by compression ultrasound or venography;
• At autopsy.

## Progression of COVID-19

Progression of COVID-19 was defined as change on clinical severity status during hospitalization.

COVID-19 clinical severity classification[1]:

- Mild: blood oxygen saturation ≥94% and lung infiltrates ≤50%
- Moderate: blood oxygen saturation <94%, or lung infiltrates >50%, or ratio of partial pressure of arterial oxygen to fraction of inspired oxygen <300
- Severe: invasive mechanical ventilation or hemodynamic instability or multiple organ dysfunction or failure.

## Additional analysis of the primary outcome

The primary outcome analysis was performed using generalized additive models for location, scale and shape (GAMLSS) with zero inflated beta-binomial distribution. GAMLSS is an extension of generalized linear models. This model allows different probabilities of observing zero days alive and out of the hospital according to the group and beta-binomial is a discrete distribution ranging from 0 to 30 days (maximum days alive and out of hospital observed). Details of the primary outcome model are shown below.

**eTable 1.** Characteristics of the 29 enrolling hospitals

| **Enrolling Hospital Characteristics** | |
|---|---|
| Number of beds avaliable at peak[a], median (IQR) | 166 (139, 202) |
| Number of beds occupied at peak[b], median (IQR) | 126 (101, 164) |
| Percentage of beds with COVID-19 patients at peak, median (IQR) | 32.8 (18.7, 41.5) |
| Number of patients enrolled, median (IQR) | 11 (4, 24) |
| Academic hospitals, no. (%) | 8 (27.6) |

COVID-19 denotes coronavirus disease 2019; IQR, interquartile range.
[a]Median of number of beds available in general (including for COVID-19 patients) at the peak of pandemic during the period of the study enrollment.
[b]Median of number of beds occupied in general (including for COVID-19 patients) at the peak of pandemic during the period of the study enrollment.

**eTable 2.** Patient characteristics

| | **Discontinuing ACEI/ARB (n=334)[a]** | **Continuing ACEI/ARB (n=325)[a]** |
|---|---|---|
| Clinical characteristics on admission | | |
| Diastolic blood pressure, median (IQR), mm Hg | 81.0 (75.0, 90.0) | 80.0 (70.0, 90.0) |
| $SaO_2$ % RA, median (IQR) | 95 (93, 97) | 95 (93, 97) |
| Temperature, median(IQR), (ºC) | 36.7 (36.2, 37.2) (n=324) | 36.7 (36.2, 37.2) (n=319) |
| Medical history, no. (%) | | |
| Arrhythmias no. (%) | 5 (1.5) | 12 (3.7) |
| Laboratory values at hospital admission | | |
| Troponin above ULN[b] , no. (%) | 20 (6.0) | 19 (5.8) |
| D-dimer above ULN[c], no. (%) | 155 (46.4) | 147 (45.2) |
| Leukocytes, median (IQR) x $10^9$ / L | 5.750 (4.480, 7.540) (n=325) | 5.440 (4.410; 6.970) (n=313) |
| Sodium, median (IQR), mmol/L | 137.0 (135.0,139.0) (n=279) | 137.5 (135.0, 139.0) (n=260) |
| Time from symptom start to randomization, median (IQR), d | 9.0 (6.0, 11.0) | 9.0 (6.0, 12.0) |
| Concomitant therapy, no. (%) | | |
| Any antibiotics | 325 (97.3) | 317 (97.5) |

ACEI denotes angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; IQR, interquartile range; RA, room air; $SaO_2$, oxygen saturation; SD, standard deviation. ULN, upper limit of normal

[a]Number of patients in each group, unless otherwise indicated.

[b]Upper limit of normal for Troponin: Troponin I: 0.16 ng/mL; Troponin T: 14 ng/L

[c]Upper limit of normal for D-Dimer: 500 µg/L. D-Dimer was not age adjusted.

**eTable 3.** Secondary outcomes

| | Discontinuing ACEI/ARB (n=334)[a] | Continuing ACEI/ARBs (n=325)[a] | Effect Size (95% CI)[b] | Absolute Difference (95% CI)[b] |
|---|---|---|---|---|
| Secondary outcomes, no. (%) | | | | |
| BNP above the ULN[c] | 28 (8.4) | 39 (12.0) | RR: 0.70(0.44–1.10) | -3.62 (-8.23–1.00) |
| D-dimer, above the ULN[d] | 107 (59.8) (n=179) | 97(54.5) (n=178) | RR: 1.1 (0.92–1.32) | 5.28 (-4.97–15.53) |
| Treated arrhythmias, no. (%) | 8 (2.4) | 8 (2.5) | RR: 0.97 (0.36–2.62) | -0.07 (-2.42–2.28) |
| Myocarditis | 0 (0%) | 0(0%) | ----- | ----- |
| Pericarditis | 1 (0.3%) | 0(0.0%) | ----- | ----- |
| Hypertensive crisis | 1 (0.3) | 3 (0.9) | RR:0.32 (0.02–2.52) | -0.62 (-1.82–0.57) |

ACEI denotes angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; CI, confidence interval; RR, Relative Risk; ULN, upper limit of normal,

[a]Number of patients in each group, unless otherwise indicated

[b]Data based on model results.

[c]Upper limit of normal for BNP: 100 pg/mL.

[d]Upper limit of normal for D-Dimer: 500 µg/L. D-Dimer was not age adjusted.

**eTable 4.** On-treatment analysis of primary and secondary outcomes

| | Discontinuing ACEI/ARB (n=237)[a] | Continuing ACEI/ARB (n=302)[a] | Effect Size (95% CI)[b] | Absolute Difference (95% CI)[b] |
|---|---|---|---|---|
| **Primary outcome** | | | | |
| Days alive and out of hospital, mean (SD) | 21.4 (8.7) | 23.3 (6.4) | MR: 0.91 (0.84–0.96) | -2.14 (-3.46–0.77) |
| Days alive and out of hospital, median (IQR) | 25.0 (19.0, 27.0) | 25.0 (22.0, 27.0) | | |
| **Secondary outcomes** | | | | |
| Length of hospitalization, mean (SD), d | 8.2 (8.1) | 6.3 (5.6) | MR: 1.40 (1.18–1.68) | 2.56 (1.25–4.08) |
| Length of hospitalization, median (IQR), d | 5.0 (3.0, 10.0) | 5.0 (3.0, 8.0) | | |
| Mortality at 30 days, no. (%) | 8 (3.4) | 7 (2.3) | OR: 1.47 (0.52–4.26) | 1.06 (-1.80–3.92) |
| In-hospital mortality, no. (%) | 8 (3.4) | 5 (1.7) | OR: 2.08 (0.68–6.95) | 1.72 (-0.99–4.43) |
| Cardiovascular mortality, no. (%) | 2 (0.8) | 1 (0.3) | OR: 2.56 (0.24–55.32) | 0.51 (-0.82–1.85) |
| Respiratory failure, treated with invasive mechanical ventilation[c], no. (%) | 26 (11.0) | 17 (5.6) | RR: 1.95 (1.09–3.58) | 5.34 (0.59–10.09) |
| Progression of COVID-19 disease[d], no. (%) | 92 (38.8) | 92 (30.5) | OR: 1.45 (1.01–2.07) | 8.35 (0.27–16.44) |
| Cardiovascular outcomes | | | | |
| Acute myocardial infarction, no. (%) | 18 (7.6) | 11 (3.6) | RR: 2.09 (1.02–4.48) | 3.95 (-0.03–7.93) |
| Stroke/TIA, no. (%) | 3 (1.3) | 3 (1.0) | RR: 1.27 (0.24–6.83) | 0.27 (-1.54–2.08) |
| New or worsening heart failure, no. (%) | 9 (3.8) | 13 (4.3) | RR: 0.88 (0.37–2.01) | -0.51 (-3.85–2.83) |
| Arrhythmias requiring treatment, no. (%) | 6 (2.5) | 7 (2.3) | RR: 1.09 (0.36–3.25) | 0.21 (-2.41–2.84) |
| Thromboembolic events, no. (%) | 4 (1.7) | 3 (1.0) | RR: 1.70 (0.38–8.56) | 0.69 (-1.29–2.68) |
| Shock, treated with vasopressors, no. (%) | 24 (10.1) | 16 (5.3) | RR: 1.91 (1.05–3.59) | 4.83 (0.23–9.43) |
| Acute kidney failure, treated with hemodialysis, no. (%) | 11 (4.6) | 7 (2.3) | RR: 2.00 (0.80–5.37) | 2.32 (-0.85–5.49) |
| Myocarditis no. (%) | 0 (0) | 0 (0) | --- | --- |
| Pericarditis no. (%) | 0 (0) | 0 (0) | --- | --- |
| Hypertensive crisis no. (%) | 1 (0.4) | 2 (0.7) | RR: 0.64 (0.03–6.61) | -0.24 (-1.47–0.99) |
| D-dimer above the ULN[e] no. (%) | 78 (59.5) (n=131) | 90 (53.3) | RR: 1.12 (0.91–1.37) | 6.29 (-4.99–17.57) |

| | Discontinuing ACEI/ARB (n=237)[a] | Continuing ACEI/ARB (n=302)[a] | Effect Size (95% CI)[b] | Absolute Difference (95% CI)[b] |
|---|---|---|---|---|
| | | (n=169) | | |
| Troponin above the ULN[f] no. (%) | 18 (8.0) (n=225) | 11 (3.9) (n=284) | RR: 2.07 (1.01–4.43) | 4.13 (-0.07–8.32) |
| BNP above the ULN[g] no. (%) | 18 (7.6) | 36 (11.9) | RR: 0.64 (0.36–1.08) | -4.43 (-9.30–0.65) |

Legend: ACEI denotes angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; CI, confidence interval; COVID-19, coronavirus 2019; IQR, interquartile range; MR, mean ratio; OR, odds ratio; RR, relative risk; SD, standard deviation; TIA, transient ischemic attack; ULN, upper limit of normal.

[a]Number of patients in each group, unless otherwise indicated.

[b]Data based on model results.

[c]In patients with respiratory failure, the decision for intubation was according clinical judgment.

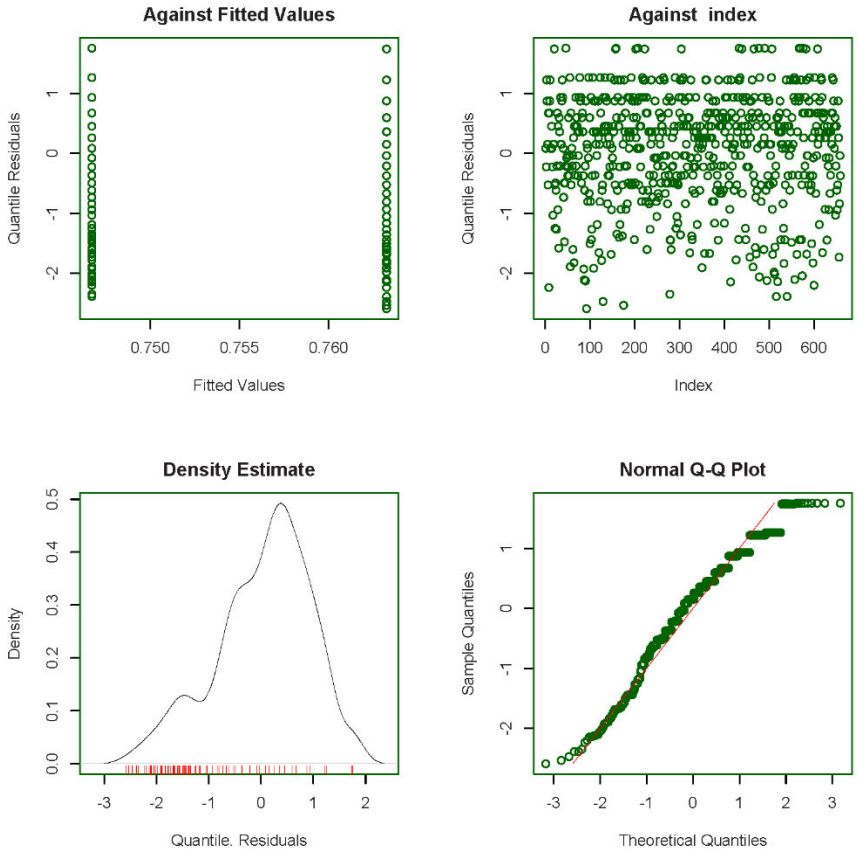
[d]Progression of COVID-19 was defined as change in clinical severity status during hospitalization. COVID-19 clinical severity classification: Mild: blood oxygen saturation ≥94% and lung infiltrates ≤50%; Moderate: blood oxygen saturation <94%, or lung infiltrates >50%, or ratio of partial pressure of arterial oxygen to fraction of inspired oxygen <300; Severe: invasive mechanical ventilation or hemodynamic instability or multiple organ dysfunction or failure.

[e]Upper limit of normal for D-Dimer: 500 µg/L. D-Dimer was not age adjusted.

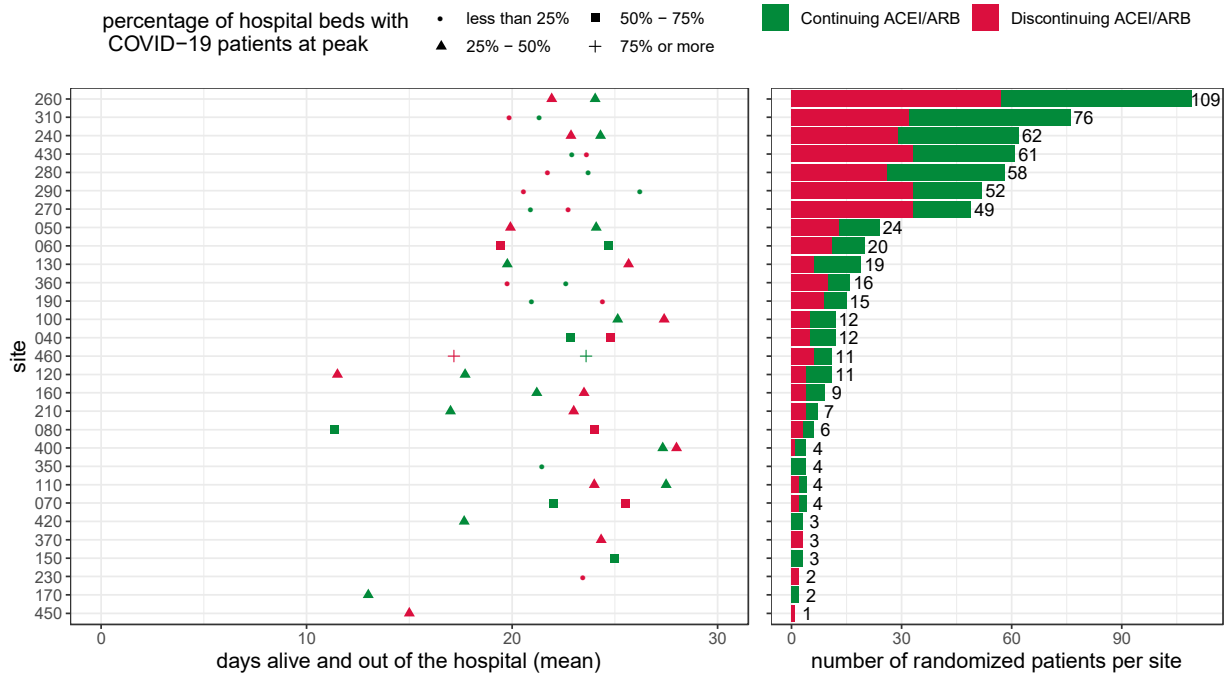
[f]Upper limit of normal for Troponin: Troponin I: 0.16 ng/mL; Troponin T: 14 ng/L.

[g]Upper limit of normal for BNP: 100 pg/mL.

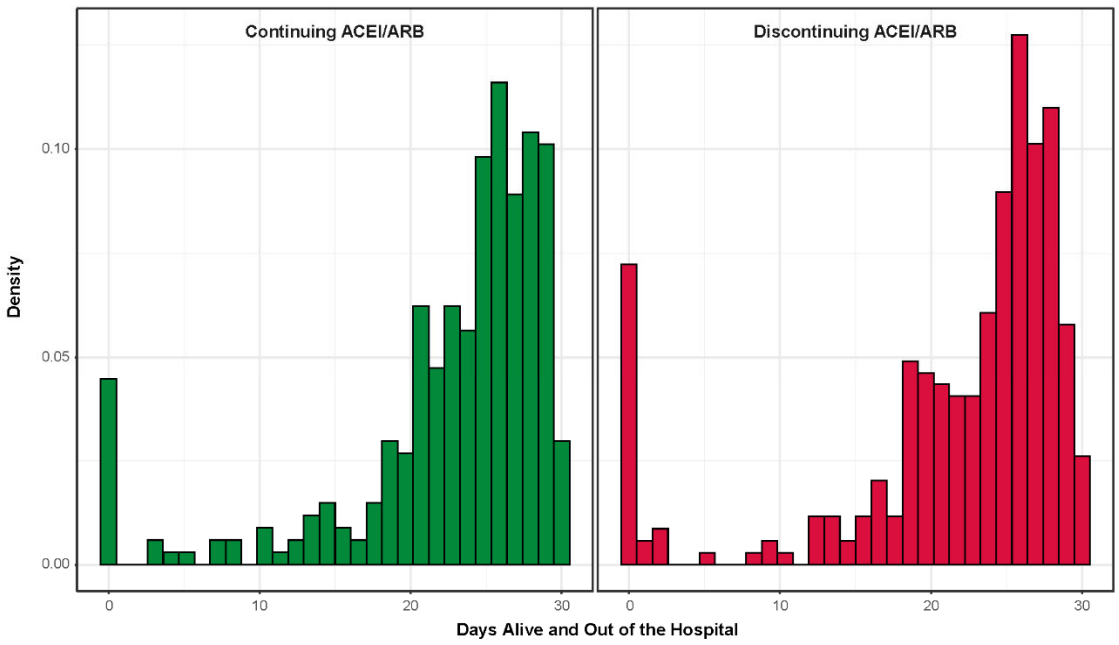
**eFigure 1.** Details of the primary outcome model diagnosis



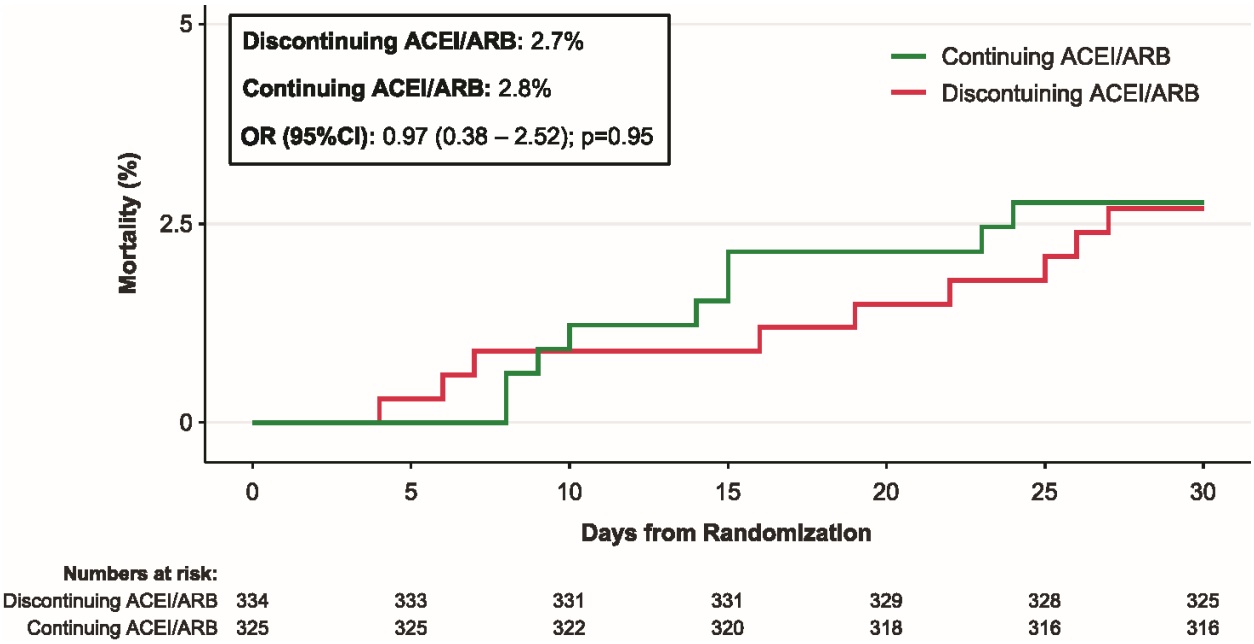
**eFigure 2.** Number of randomized patients and percentage of occupancy with COVID-19 at peak per individual site



**eFigure 3.** Primary outcome analysis using GAMLSS



**eFigure 4.** All-cause mortality at 30 days




| Numbers at risk: | | | | | | | |
|---|---|---|---|---|---|---|---|
| Discontinuing ACEI/ARB | 334 | 333 | 331 | 331 | 329 | 328 | 325 |
| Continuing ACEI/ARB | 325 | 325 | 322 | 320 | 318 | 316 | 316 |

## eLists

### Executive Committee
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### CEC Reviewers
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## Data Collected (Registry-Based)

**Baseline**
Signs and symptoms of hospital admission, date of onset of symptoms, date and time of hospitalization, demographic data, laboratory results on admission, chest tomography, comorbidities, medical history, medication on admission, clinical characteristics on admission, pathogen test in Infectious Respiratory Diseases.

**In-hospital evaluation**
Evaluation Form: ICU/ Critical care unit admission if applicable, mechanical ventilation, non-invasive mechanical ventilation data, oxygen support, medications and procedures during hospitalization, clinical outcomes, laboratory and image results, adherence to the study treatment assignment.

**30-day follow up**
Re-hospitalization, clinical outcomes evaluation, adherence to the study treatment assignment

## Enrolling Centers and Site Principal Investigators

São Paulo–SP, Brazil: Hospital Assunção: Jeffer Luiz de Morais; Hospital Bartira: Thiago Líbano Csernik Monteiro; Hospital São Luiz São Caetano: Guilherme D`Andréa Saba Arruda; Hospital e Maternidade São Luiz Itaim; Rafael Franco; Hospital Villa Lobos: Karla Gouvea Dias; Hospital São Luiz Morumbi: Fábio Augusto de Luca; Hospital São Luiz Anália Franco: André Feldman; Hospital São Luiz Jabaquara: Ariane Vieira Scarlatelli Macedo; Hospital Sino Brasileiro: Rodrigo Mendonça Dionísio.

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Pernambuco–PE, Brazil: Hospital Memorial: Audes Diógenes Feitosa; Hospital São Marcos: Alexandre Lucena.
Maranhão–MA, Brazil: Hospital UDI: Marco Túlio Hercos Juliano.
Salvador–BA, Brazil: Hospital São Rafael: Márcia M Noya-Rabelo.

**eReference**

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