Generating High Quality Evidence During a Pandemic: The Brazilian Coalition Experience

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Disclosures

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- Funding for consulting or other services from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb
- Details at: https://dcri.org/about-us/conflict-of-interest/
COVID-19 Pandemic

- COVID-19 was considered a pandemic by WHO on March 11, 2020.
- Variable clinical presentation, from asymptomatic/oligosymptomatic cases to critical conditions.
- 10% of cases may present with pneumonia and progress to acute respiratory distress syndrome (ARDS), multiple organ failure and death.
- The infection causes a direct impact on the cardiovascular system.
- SARS-CoV2 infection is associated with cardiovascular complications such as myocardial ischemia, myocarditis, arrhythmias, and thromboembolic events.
- These manifestations result mainly from the intense systemic inflammatory response and disorders of the coagulation system.

Zhou F et al. Lancet. 2020
Zheng et al. Nature Reviews Cardiology. 2020
How to treat these patients based on reliably evidence?
Medical Decision Making

Reality

For most medical decisions we simply do not know whether the recommendations we make regarding therapies lead to better patient outcomes.
Clinicians make most decisions on the basis of flawed evidence and, without structural changes to the clinical trial ecosystem, they will continue to do so.
Across 26 current ACC/AHA guidelines… 8.5% [of recommendations] were classified as LOE A.

Across 25 ESC guidelines… 14.2% [of recommendations] were classified as LOE A.

This pattern does not appear to have meaningfully improved from 2008 to 2018.
Randomized Trials Versus Common Sense and Clinical Observation

*JACC Review Topic of the Week*

Alexander C. Fanaroff, MD, MHS, a Robert M. Califf, MD, b Robert A. Harrington, MD, c Christopher B. Granger, MD, d John J.V. McMurray, MD, e Manesh R. Patel, MD, d Deepak L. Bhatt, MD, MPH, f Stephan Windecker, MD, g Adrian F. Hernandez, MD, d C. Michael Gibson, MD, h John H. Alexander, MD, d Renato D. Lopes, MD, PhD d
We need less common sense
### Common Sense vs Clinical Trial Evidence

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Common Sense</th>
<th>Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen for 2&lt;sup&gt;o&lt;/sup&gt; prev</td>
<td>reduces MI</td>
<td>↑ MI first yr</td>
</tr>
<tr>
<td>Vitamin E for 2&lt;sup&gt;o&lt;/sup&gt; prev</td>
<td>reduces MI</td>
<td>15%↑ CHF</td>
</tr>
<tr>
<td>Folate/B6 for 2&lt;sup&gt;o&lt;/sup&gt; prev</td>
<td>reduces MI</td>
<td>0-20%↑ death/MI</td>
</tr>
<tr>
<td>Increase Hgb in ESRD</td>
<td>reduces death</td>
<td>34%↑ D/MI/HF/stroke</td>
</tr>
<tr>
<td>Torcetrapib</td>
<td>reduces MACE</td>
<td>↑ MACE 25%</td>
</tr>
<tr>
<td>Glucose control</td>
<td>reduces CVD</td>
<td>↑ death 22%</td>
</tr>
<tr>
<td>BP control in DM</td>
<td>reduces CVD</td>
<td>no effect</td>
</tr>
<tr>
<td>Fibrates in DM</td>
<td>reduces CVD</td>
<td>no effect</td>
</tr>
</tbody>
</table>

Fanaroff A, ……, Lopes RD. JACC, 2020
Why doesn’t common sense work?

- Incomplete understanding of pathophysiology
- Incomplete understanding of how drugs work
- Incomplete understanding of how to balance risk and benefit
- Incomplete understanding of dose response relationships

Fanaroff A, ……, Lopes RD. JACC, 2020
“The problem with common sense is that it isn’t so common.”

Voltaire
To move toward a world in which most clinical decisions are supported by high-quality evidence will require structural changes in the clinical trials ecosystem.
Classic Theme in Academic Medicine

★ “Publish or Perish”

Logan Wilson, 1942
Classic Theme in Academic Medicine

“Publish or Perish”
Logan Wilson, 1942

Modern Theme in Academic Medicine

“Collaborate or Perish”
COALITION COVID-19 BRAZIL
Executive committee

Otávio Berwanger - Hospital Israelita Albert Einstein
Alexandre Biasi Cavalcanti - HCOR
Luciano Azevedo - Hospital Sírio Libanes
Régis Rosa - Hospital Moinhos de Vento
Viviane Cordeiro Veiga - Beneficência Portuguesa
Álvaro Avezum - Hospital Alemão Oswaldo Cruz
Flávia Machado - BRICNet
Renato Delascio Lopes - Brazilian Clinical Research Institute (BCRI)
Steering committee

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Henrique Fonseca
Remo Holanda Furtado
Ary Serpa-Neto
Thiago Correa
Cláudio Galvão
Leonardo Rolim Ferraz
Guilherme Schettino
Luiz Vicente Rizzo

**HCor:**
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Fernando Godinho Zampieri
Thiago Lisboa
Israel Silva Maia
Letícia Kawano Dourado

**Hospital Alemão Oswaldo Cruz:**
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Bruno Martins Tomazini

**Hospital Moinhos de Vento:**
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João Prats
Philip Scheinberg

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Eduardo Ramacciotti
Ariane Vieira Scarlatelli Macedo

**BRICNet:**
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Antonio Paulo Nassar Cintia Grion
Carlos Eduardo Brandão
Felipe Dal Pizzol
Fernando Augusto Bozza
Flávia Machado
Flavio Geraldo Rezende de Freitas
Glauco Westphal
Eliana Casr
Hugo Urbano
Marcelo Romano
Rodrigo Biondi
Rodrigo Cruvinel Figueiredo
Viviane Cordeiro Veiga
Wilson Lovato
- 18 Years and older
- Suspected or confirmed diagnosis of COVID-19
- Onset of symptoms < 14 days; and

- Oxygen with flow greater than 4 L per min; or
- High flow nasal catheter; or
- Non-invasive ventilation; or
- Invasive ventilation.

No

COALIZÃO I
Moderate infection

Randomization
n=630

- HCQ + Azithro 400mg 12/12h 7 days
- 500 mg 1x day 7 days
- HCQ 400mg 12/12h 7 days
- Control No HCQ or Azithro

Yes

COALIZÃO II
Severe infection

Randomization
n=436

- HCQ + Azithro 400mg 12/12h 10 days
- 500 mg 1x day 10 days
- HCQ 400mg 12/12h 10 days

Yes

COALIZÃO III
Severe infection ARDS

Randomization
n=290

- Dexamethasone 20 mg 1x day 5 days
- 10 mg 1x day 5 days
- Control No Dexamethasone

PRIMARY OUTCOME
Clinical improvement according to ordinal scale on day 15

Yes

PRIMARY OUTCOME
Ventilator-free days alive up to day 28
**COALIZÃO IV**
Covid-19 positive + Elevated D-Dimer

Randomization
$n = 600$

- Full anticoagulation with rivaroxaban +/- heparin when needed
- Prophylaxis anticoagulation

**COALIZÃO V**
Mild Infection (not hospitalized)

Randomization
$n = 1300$

- HCQ
- PLACEBO

**COALIZÃO VI**
Severe infection

Randomization
$n = 150$

- IL 6 antagonist
- Control
COALIZÃO VII
n = 1800

Long-term clinical outcomes + Quality of Life
Effects of chloroquine on viral infections: an old drug against today’s diseases?

“This old drug may experience a revival in the clinical management of viral diseases such as AIDS and severe acute respiratory syndrome, which afflict mankind in the era of globalisation.”
667 Underwent randomization

217 Assigned to Hydroxychloroquine plus Azithromycin
- 13 did not receive hydroxychloroquine and received azithromycin
- 3 did not receive azithromycin and hydroxychloroquine

217 complete 15-days follow-up
217 included in the ITT analysis
- 45 unconfirmed COVID-19

172 included in the mITT analysis
- 140 were not hospitalized at day 15
- 29 were hospitalized at day 15
- 3 were dead at day 15

221 Were assigned to Hydroxychloroquine
- 8 did not receive hydroxychloroquine and received azithromycin
- 21 received azithromycin and hydroxychloroquine

221 completed 15-days follow-up
221 included in the ITT analysis
- 62 unconfirmed COVID-19

159 included in the mITT analysis
- 129 were not hospitalized at day 15
- 25 were hospitalized at day 15
- 5 were dead at day 15

229 Assigned to Control
- 29 received only azithromycin
- 7 received only hydroxychloroquine
- 17 received azithromycin and hydroxychloroquine

227 completed 15-days follow-up
227 included in the ITT analysis
- 54 unconfirmed COVID-19

173 included in the mITT analysis
- 146 were not hospitalized at day 15
- 22 were hospitalized at day 15
- 5 were dead at day 15

1 withdrew consent after randomization
1 duplicated randomization
Figure 1. Status of Patients on Day 15.
Distribution of the Ordinal-Scale Results over Time.
Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19

Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19

The RECOVERY Collaborative Group*

Hospitalised adults with severe pneumonia * caused by SARS-CoV2

Standard-of-care + Azithromycin 500 mg QD for 10 days

Randomised (Concealed) Open-label

Standard-of-care (control group)

In all patients, standard-of-care included support measures and hydroxychloroquine 400 mg BID for 10 days

Primary Endpoint: Clinical status (adjudicated) - 6-point ordinal scale at 15 days

Key Secondary Endpoint: Total mortality at 29 days

*At least ONE from the following severity criteria:
- Need for supplemental oxygen > 4 L/min OR
- Use of high-flow nasal canula OR
- Use of non-invasive positive pressure ventilation OR
- Use of invasive mechanical ventilation (MV)
Primary Endpoint - Clinical Status at 15 days

Control group
N = 183

(26.8%)  (28.4%)  (30.1%)

Odds ratio* = 1.36 (0.94 – 1.97); p = 0.11

*To be in a worse category with azithromycin compared to standard of care

Azithromycin
N = 214

(21.5%)  (32.2%)  (30.8%)

Percent
0%  10%  20%  30%  40%  50%  60%  70%  80%  90%  100%
Key Secondary Endpoint (Total Mortality at 29 days)

HR = 1.08 (95% CI 0.79-1.47); p = 0.63
Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial

Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

RECOVERY Collaborative Group

- Azithromycin group
- Usual care group

Rate ratio 0.97 (0.87–1.07); log-rank p = 0.50

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Time since randomisation (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin group</td>
<td>2582 2337 2155 2056 2014</td>
</tr>
<tr>
<td>Usual care group</td>
<td>5181 4658 4298 4108 4010</td>
</tr>
</tbody>
</table>

www.thelancet.com Published online February 2, 2021 https://doi.org/10.1016/S0140-6736(21)00149-5
Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group

**A All Participants (N=6425)**

- Usual care: 4321, 3754, 3427, 3271, 3205
- Dexamethasone: 2104, 1903, 1725, 1659, 1621

**B Invasive Mechanical Ventilation (N=1007)**

- Usual care: 683, 573, 481, 424, 400
- Dexamethasone: 324, 290, 248, 232, 228

**C Oxygen Only (N=3883)**

- Dexamethasone: 1279, 1135, 1036, 1006, 981

**D No Oxygen Received (N=1535)**

- Usual care: 1034, 987, 928, 897, 889
- Dexamethasone: 501, 478, 441, 421, 412

Figure 2. Ventilator-Free Days at 28 Days

## Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

<table>
<thead>
<tr>
<th>Drug and trial</th>
<th>Clinical Trials.gov identifier</th>
<th>Initial dose and administration</th>
<th>No of deaths/total No of patients</th>
<th>Odds ratio (95% CI)</th>
<th>Favors steroids</th>
<th>Favors no steroids</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEXA-COVID 19</td>
<td>NCT04325061</td>
<td>High: 20 mg/d intravenously</td>
<td>2/7 2/12</td>
<td>2.00 (0.21-18.69)</td>
<td></td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td>CoDEX</td>
<td>NCT04327401</td>
<td>High: 20 mg/d intravenously</td>
<td>69/126 76/128</td>
<td>0.80 (0.49-1.31)</td>
<td></td>
<td></td>
<td>18.69</td>
</tr>
<tr>
<td>RECOVERY</td>
<td>NCT04381936</td>
<td>Low: 6 mg/d orally or intravenously</td>
<td>95/324 283/683</td>
<td>0.59 (0.44-0.78)</td>
<td></td>
<td></td>
<td>57.00</td>
</tr>
<tr>
<td></td>
<td>Subgroup fixed effect</td>
<td></td>
<td>166/459 361/823</td>
<td>0.64 (0.50-0.82)</td>
<td></td>
<td></td>
<td>76.60</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPE COVID</td>
<td>NCT02517489</td>
<td>Low: 200 mg/d intravenously</td>
<td>11/75 20/73</td>
<td>0.46 (0.20-1.04)</td>
<td></td>
<td></td>
<td>6.80</td>
</tr>
<tr>
<td>COVID STERIOD</td>
<td>NCT04348305</td>
<td>Low: 200 mg/d intravenously</td>
<td>6/15 2/14</td>
<td>4.00 (0.65-24.66)</td>
<td></td>
<td></td>
<td>1.39</td>
</tr>
<tr>
<td>REMAP-CAP</td>
<td>NCT02735707</td>
<td>Low: 50 mg every 6 h intravenously</td>
<td>26/105 29/92</td>
<td>0.71 (0.38-1.33)</td>
<td></td>
<td></td>
<td>11.75</td>
</tr>
<tr>
<td></td>
<td>Subgroup fixed effect</td>
<td></td>
<td>43/195 51/179</td>
<td>0.69 (0.43-1.12)</td>
<td></td>
<td></td>
<td>19.94</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids-SARI</td>
<td>NCT04244591</td>
<td>High: 40 mg every 12 h intravenously</td>
<td>13/24 13/23</td>
<td>0.91 (0.29-2.87)</td>
<td></td>
<td></td>
<td>3.46</td>
</tr>
<tr>
<td>Overall (fixed effect)</td>
<td></td>
<td></td>
<td>222/678 425/1025</td>
<td>0.66 (0.53-0.82)</td>
<td></td>
<td></td>
<td>100.0</td>
</tr>
<tr>
<td>Overall (random effects)</td>
<td></td>
<td></td>
<td>222/678 425/1025</td>
<td>0.70 (0.48-1.01)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Effect of Tocilizumab on clinical status at 15 days in patients with severe covid-19: randomised controlled trial

COALITION VI
Objective

To determine whether tocilizumab improve outcomes for patients with severe covid-19.
<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>Tocilizumab (n = 65)</th>
<th>Control (n = 64)</th>
<th>Effect estimate</th>
<th>Effect size (CI 95%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead or on mechanical ventilation at day 15 – no. (%)*</td>
<td>18 (27.7)</td>
<td>13 (20.3)</td>
<td>Odds ratio 1-5 vs 6-7</td>
<td>1.54 (0.66 to 3.66)</td>
<td>0.32</td>
</tr>
<tr>
<td>Clinical status (7-level ordinal scale) at day 15 – no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Not hospitalised with no limitation on activities</td>
<td>32 (49.2)</td>
<td>26 (40.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Not hospitalised but with limitation on activities</td>
<td>3 (4.6)</td>
<td>5 (7.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Hospitalised, not receiving supplemental oxygen</td>
<td>6 (9.2)</td>
<td>6 (9.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Hospitalised, receiving supplemental oxygen</td>
<td>6 (9.2)</td>
<td>10 (15.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Hospitalised, receiving non-invasive ventilation or high-flow nasal cannula</td>
<td>0 (0.0)</td>
<td>4 (6.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Patient on mechanical ventilation</td>
<td>7 (10.8)</td>
<td>11 (17.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Death</td>
<td>11 (16.9)</td>
<td>2 (3.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Adjudicated causes of in-hospital deaths

<table>
<thead>
<tr>
<th>Causes of in-hospital death</th>
<th>Tocilizumab (n = 14)</th>
<th>Control (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covid-19 related acute respiratory failure or multiple organ dysfunction</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Covid-19 and cerebral haemorrhage</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
In this trial including hospitalised patients with severe covid-19, the use of tocilizumab plus standard care was not superior to standard care alone in improving patients’ clinical status at 15 days and might have increased mortality.
Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial

The COVID-19 Coagulopathy

- Pulmonary -

Direct Viral Alveolar Epithelial Injury

Tissue Factor
Collagen
Platelet Act/Agg.
Thrombosis (Local)
Progressive hypoxia

Inflammation

Local / Systemic
Activates coagulation
Thrombosis (Systemic)
DVT/PE, Stroke, Art. & Cor. Thrombosis, DIC

“Cytokine Storm”
Autopsy Findings and Venous Thromboembolism in Patients With COVID-19

*Pulmonary Embolism (Unsuspected)*

*Deep Vein Thrombosis (Unsuspected)*

Wichmann D., et al
Ann Int. Med. 2020, May 6: epub
Autopsy Findings and Venous Thromboembolism in Patients With COVID-19

*Thrombosis of Prostatic Veins*
*(Found in 67% of men)*
Observational data

**CENTRAL ILLUSTRATION** In-Hospital Anticoagulation and Outcomes in Coronavirus Disease-2019

**Thrombosis in COVID-19**

![Image of thrombosis in COVID-19 with statistical data on anticoagulation outcomes]

*Anticoagulation Associated With Better Outcomes*

↓ Clinical Trial ↓

Therapeutic vs. Prophylactic LMWH vs. DOAC?

Observational data – CAUTION!!

Anticoagulation in COVID-19
It Is Time for High-Quality Evidence

Renato D. Lopes, MD, PhD, Alexander C. Fanaroff, MD, MHS

“Although this observational analysis was carefully done, lack of randomization precludes the conclusion that anticoagulation, either prophylactic or therapeutic, caused the observed reduction in mortality and intubation.”¹

“Over the past 40 years, dozens of cardiovascular therapies and treatment strategies that were mechanistically promising and supported by observational comparative effectiveness studies showed no benefit or harm in rigorous randomized controlled trials.”²

“Prospective cohorts and or randomized controlled trials are desperately needed in exploring the definitive effects of therapeutic-dose anticoagulants in hospitalized patients with COVID-19.”³

Study Design

Randomization will be stratified by the patient's clinical condition at the time of randomization: unstable (on mechanical ventilation and/or use of vasopressors) or stable.

Randomization will be stratified by the patient's clinical condition at the time of randomization: unstable (on mechanical ventilation and/or use of vasopressors) or stable.

- **Group 1**: full anticoagulation (rivaroxaban 20mg/d) for 30 days
- **Group 2**: usual standard management and currently have no indication of full anticoagulation

N=600

**End of Treatment (EOT)**: 30 days

**End of Study (EOS)**: 30 days

EOT: End of Treatment

EOS: End of Study

COALIZAO-ACTION
CARE Study (Coalition VIII)

COALIZÃO COVID-19 BRASIL

Randomized, pragmatic, open-controlled, multicenter study, evaluating the use of rivaroxaban in mild or moderate COVID-19 patients

To assess the efficacy and safety of rivaroxaban use and the clinical impact on reducing hospitalization of patients with confirmed or probable diagnosis of COVID-19 who have no clear indication for hospitalization upon first medical care.
Apixaban for Prophylaxis of thromboembolic Outcomes in COVID-19 – the Apollo Trial – COALITION XI

Randomized, double-blinded, placebo-controlled trial comparing oral anticoagulation with placebo for community-dwelling patients with symptomatic COVID-19 infection and risk factors for thrombosis.
HYPOTHESIS 1: RAAS inhibition is harmful.

ACEI and ARB could increase ACE2 receptor expression and thus enhance viral binding and viral entry leading to worse outcomes in patients with COVID-19.

HYPOTHESIS 2: RAAS inhibition is protective.

Diminishing production of angiotensin II with an ACEI or ARB enhances the generation of angiotensin (1–7), which attenuates inflammation and fibrosis and therefore could attenuate lung injury.

Lopes RD et al. Am Heart J 2020;226:1-10
Every time a patient encounters the health-care system an opportunity is created to enroll that patient in an RCT... but only if the necessary structures are in place...
Trial Design

Multicenter, phase IV, randomized clinical trial

**INCLUSION**
- Patients aged ≥ 18 years
- Hospitalized with a confirmed diagnosis of COVID-19
- Chronic use of ACEI or ARB

**RANDOMIZE**
N: 659 patients

**EXCLUSION**
- Hospitalization due to decompensated heart failure in the last 12 months
- Use of more than 3 anti-hypertensive drugs
- Use of sacubitril/valsartan
- Hemodynamic instability in the first 24 hours until the moment of confirmed diagnosis of COVID-19

**PRIMARY OUTCOME**
Days alive and out of hospital at 30 days

Lopes RD et al. Am Heart J 2020;226:1-10
BRACE CORONA Trial Timelines

Protocol development
March 21

First patient randomized
April 09

Last patient randomized
June 26

Last patient last visit
July 26

Database lock
August 17

ESC presentation
September 1

Lopes RD et al. Am Heart J 2020;226:1-10
Primary Outcome: Days Alive and Out of Hospital at 30 Days

- **Suspending ACEI/ARB**
  - Mean days ± SD: 21.9 ± 8.0

- **Continuing ACEI/ARB**
  - Mean days ± SD: 22.9 ± 7.1

**Mean ratio** (95%CI): 0.95 (0.90–1.01); p=0.09

**Mean difference** (95%CI): -1.1 days (-2.33–0.17)
All-Cause Mortality at 30 Days

- Suspending ACEI/ARB: 2.7%
- Continuing ACEI/ARB: 2.8%
- HR (95%CI): 0.97 (0.38 – 2.52); p=0.95

Numbers at risk:
- Suspending ACEI/ARB: 334
  - Days 0-5: 333, 331, 331
  - Days 10-15: 329, 328, 325
- Continuing ACEI/ARB: 325
  - Days 0-5: 325, 322, 320
  - Days 10-15: 318, 316, 316
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

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Conclusions

• Brazil is playing an important role in the scientific world by generating high quality evidence to guide the treatment of patients with COVID-19

• Testing important clinical questions

• Contributing to the knowledge in a field where RCTs are desperately needed

• Unique research collaborative national program (COALITION) among several major hospitals and research institutes

• Collaboration is key to survive in modern academic medicine

• Legacy for future Clinical Research in Brazil and in the world!!!
“Without data you’re just another person with an opinion.”
– W. Edwards Deming
Thank you!

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