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

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Disclosures

- Research grants or contracts from Amgen, Bristol-Myers Squibb, GlaxoSmithKline, Medtronic, Pfizer, Sanofi-Aventis
- Funding for educational activities or lectures from Pfizer
- 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?

Reality

For most medical decisions we simply do not know whether the recommendations we make regarding therapies lead to better patient outcomes

High-quality evidence to inform clinical practice

One of the basic tenets o
based medicine is that ran
is crucial to understanding
effects. Observational studi
ject to confounding and sel
Researchers can adjust for
differences between treatm
but unmeasured or unmea
ferences might exist betw
that obscure true treatm
and cannot be accounted
statistical method.[1] The
medical literature is filled wit
of associations between tre
outcome identified in ob
studies that were subseq
proven by well conducted r
controlled trials (RCTs).[2-4]

Framed this way, findin
analysis of cardiovascular
which showed that less th
American College of Card
American Heart Association and less
than 85% of European Society of
Cardiology guideline recommendations
were based on evidence from RCTs,

patients, obtain informed consent, collect baseline information, track patients through the trial, and obtain follow-up information. Owing to this expense, the focus on basic research by

with international data standards, would facilitate these trials on a global basis.

Creation of such an infrastructure will require cooperation among academia,

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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

but only if the necessary structures are in place to efficiently identify patients appropriate for enrolment in an RCT, consent patients for enrolment, and

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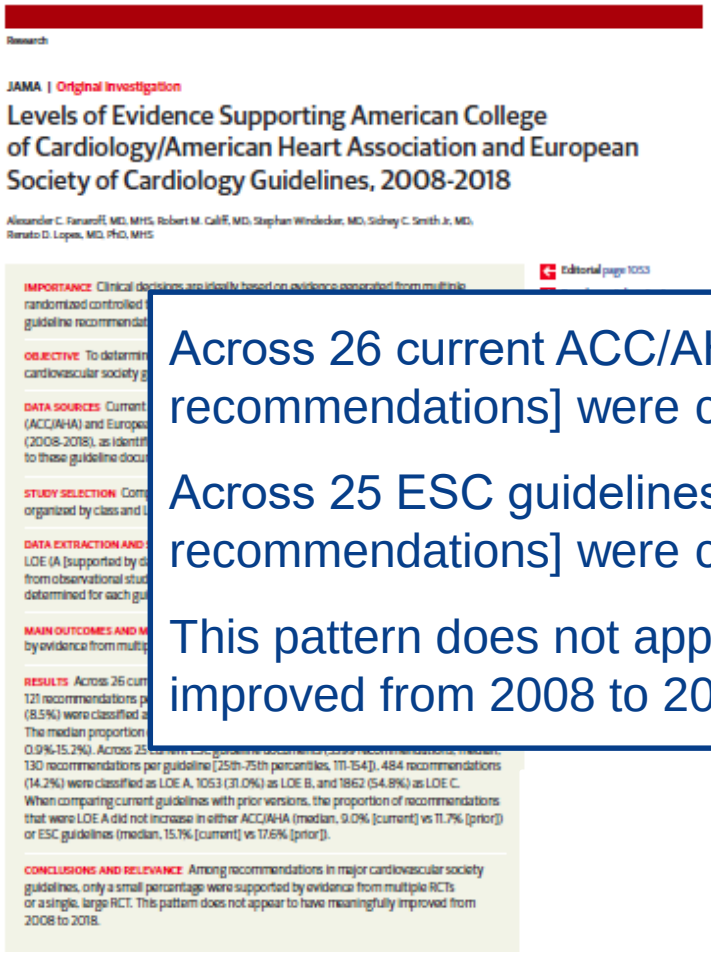
Fanaroff AC, Califf RM, Lopes RD. Lancet 2019;394:633



JAMA | Original Investigation

Levels of Evidence Supporting American College of Cardiology/American Heart Association and European Society of Cardiology Guidelines, 2008-2018

Alexander C. Fanaroff, MD, MHS; Robert M. Califf, MD; Stephan Windecker, MD; Sidney C. Smith Jr, MD; Renato D. Lopes, MD, PhD, MHS

Editorial page 1053

IMPORTANCE Clinical decisions are ideally based on evidence generated from multiple randomized controlled guideline recommendat

OBJECTIVE To determin cardiovascular society g

DATA SOURCES Current (ACC/AHA) and Europe (2008-2018), as identif to these guideline docu

STUDY SELECTION Com organized by class and l

DATA EXTRACTION AND LOE (A [supported by c from observational stud determined for each gu

MAIN OUTCOMES AND M by evidence from multi

RESULTS Across 26 cur 121 recommendations p (8.5%) were classified a The median proportion 0.9%-15.2%). Across 25 130 recommendations per guideline [25th-75th percentiles, 111-154]), 484 recommendations (14.2%) were classified as LOE A, 1053 (31.0%) as LOE B, and 1862 (54.8%) as LOE C. When comparing current guidelines with prior versions, the proportion of recommendations that were LOE A did not increase in either ACC/AHA (median, 9.0% [current] vs 11.7% [prior]) or ESC guidelines (median, 15.1% [current] vs 17.6% [prior]).

CONCLUSIONS AND RELEVANCE Among recommendations in major cardiovascular society guidelines, only a small percentage were supported by evidence from multiple RCTs or a single, large RCT. This pattern does not appear to have meaningfully improved from 2008 to 2018.

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

Fanaroff, Lopes et al. J Am Med Assoc 2019;321:1069-1080

JACC REVIEW TOPIC OF THE WEEK

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

	Common Sense	Clinical Trials
Estrogen for 2^{o} prev	reduces MI	↑ MI first yr
Vitamin E for 2^{o} prev	reduces MI	15 %↑ CHF
Folate/B6 for 2^{o} prev	reduces MI	0-20%↑ death/MI
Increase Hgb in ESRD	reduces death	34%↑ D/MI/HF/stroke
Torcetrapib	reduces MACE	↑ MACE 25%
Glucose control	reduces CVD	↑ death 22%
BP control in DM	reduces CVD	no effect
Fibrates in DM	reduces CVD	no effect

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

CARDIOVASCULAR MEDICINE AND SOCIETY

New Approaches to Conducting Randomized Controlled Trials

Alexander C. Fanaroff, MD, MHS,[a] Robert M. Califf, MD,[b] Renato D. Lopes, MD, PhD[c]

The role of randomization in understanding treatment effects is one of the foundational principles of evidence-based medicine. Non-randomized, observational studies are useful for descriptive purposes, but are subject to confounding when used to compare treatments. There are multiple sophisticated methods to adjust for measured differences between treatment groups in observational analyses, but none of these methods can account for unmeasured differences.

However, in major cardiovascular society guideline documents, 90% of recommendations are not supported by evidence from definitive, high-quality randomized controlled trials (RCTs); other subspecialty guidelines are similarly based on limited evidence (1). The lack of high-quality evidence from RCTs is a consequence of the ecosystem of clinical trials, which has changed minimally since the 1980s, when a confluence of factors led to the development of the modern RCT as an instrument intended to win regulatory approval for a new drug or device. Each RCT is a largely self-contained enterprise, purposely built for the study, and then deconstructed. Patients are identified by trial investigators by happenstance, are consented and enrolled into the trial during a lengthy in-person conversation with research staff and return frequently to the research site for study follow-up.

Due to their cost and complexity, most RCTs that address clinical outcomes have historically been funded by pharmaceutical and medical device companies that profit from the regulatory approval of a new product. Such a structure creates an enormous financial barrier to the conduct of trials that are not designed to yield a positive net present value calculation for a company, including trials that compare treatment strategies, health services interventions, or the rela
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statistical techniques, and new approaches to composite endpoints, can reduce costs by reducing sample size. Others, like combined Phase II/III designs, can reduce costs associated with trial startup. Registry-based RCTs can re-purpose data collected for quality improvement and/or administrative purposes into data for an RCT, reducing both cost and complexity. Virtual trials, in which patients are recruited and followed electronically and never visit a study site, can also reduce cost and complexity. All of these innovations have provided examples of less

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

Fanaroff AC, Califf RM, Lopes RD. J Am Coll Cardiol 2020;75:556

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

Hospital Israelita Albert Einstein:
Otávio Berwanger
Henrique Fonseca
Remo Holanda Furtado
Ary Serpa-Neto
Thiago Correa
Cláudio Galvão
Leonardo Rolim Ferraz
Guilherme Schettino
Luiz Vicente Rizzo

Hospital Sírio Libanes:
Luciano Azevedo
Eduardo Leite Vieira Bruno
Bruno Martins Tomazini

HCor:
Alexandre Biasi Cavalcanti
Fernando Godinho Zampieri
Thiago Lisboa
Israel Silva Maia
Letícia Kawano Dourado

Hospital Alemão Oswaldo Cruz
Álvaro Avezum

Hospital Moinhos de Vento
Régis Rosa
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Beneficência Portuguesa
Viviane Cordeiro Veiga
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Glauco Westphal
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Hugo Urbano
Marcelo Romano
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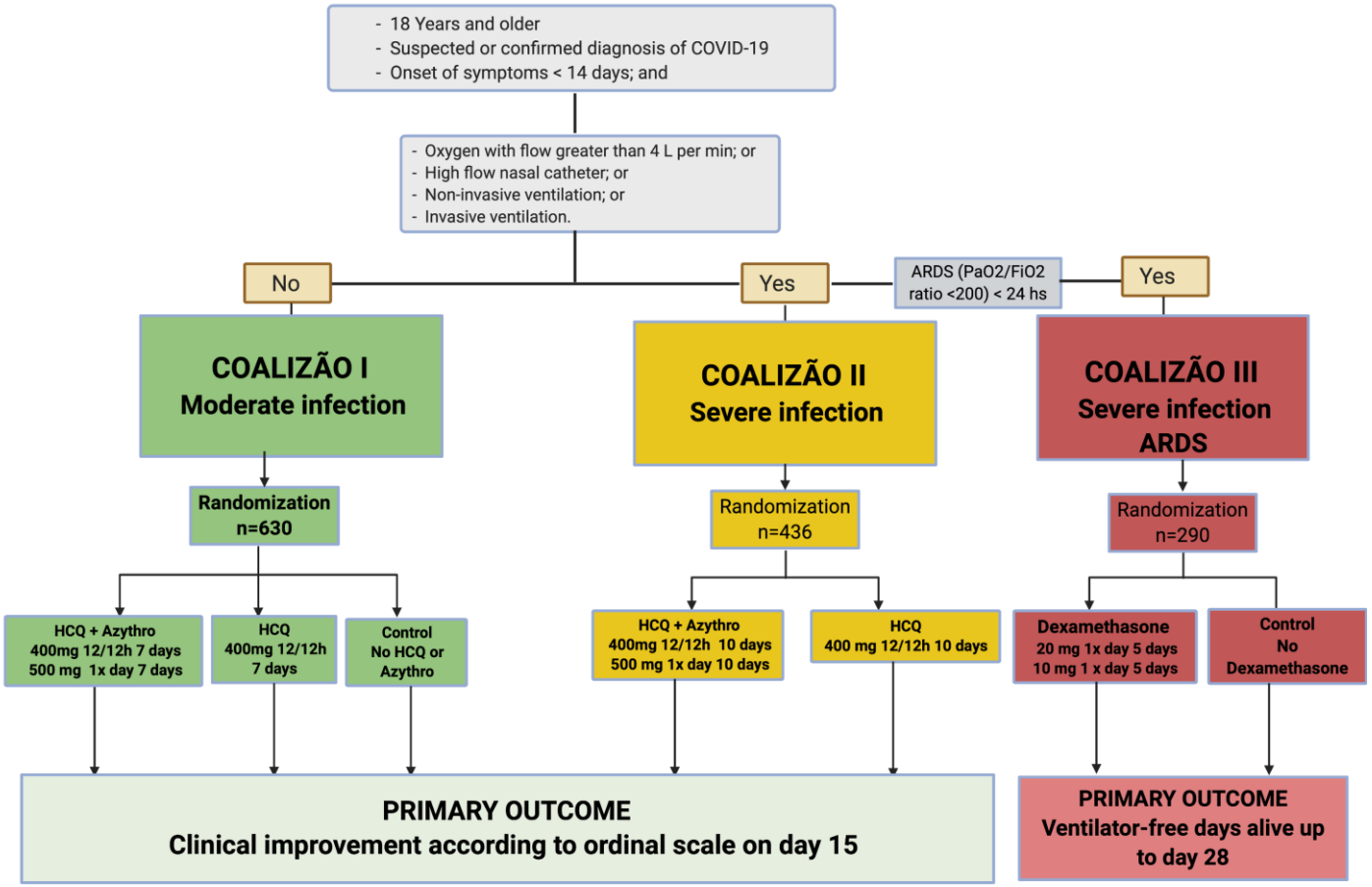
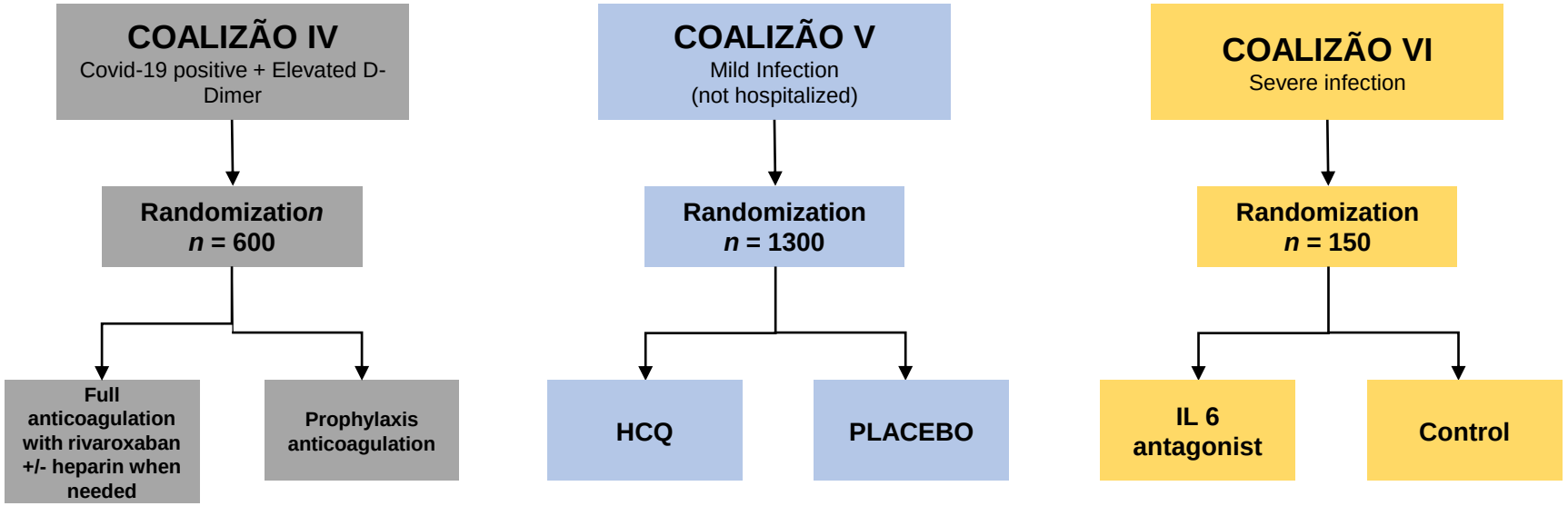
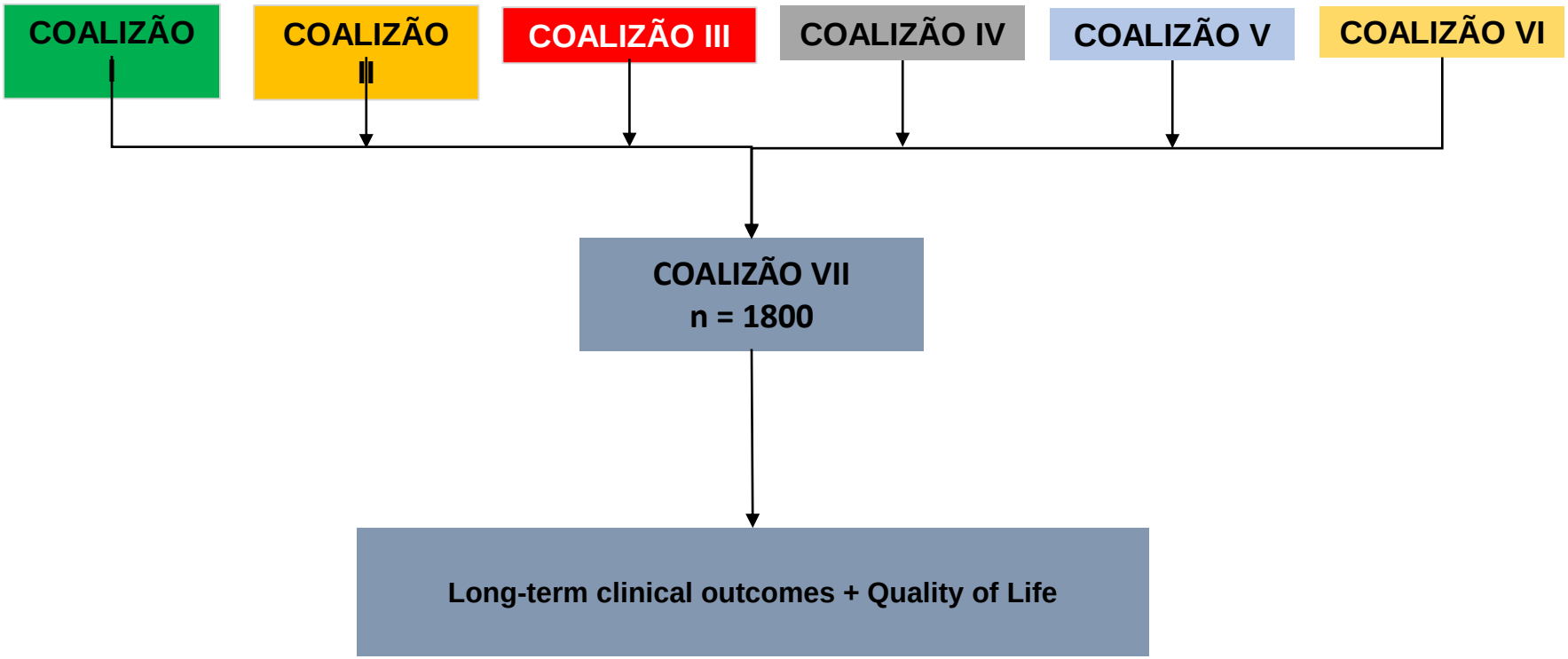
Rodrigo Cruvinel Figueiredo
Viviane Cordeiro Veiga
Wilson Lovato


- 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
Yes
ARDS (PaO2/FiO2 ratio <200) < 24 hs
Yes
COALIZÃO I
Moderate infection
COALIZÃO II
Severe infection
COALIZÃO III
Severe infection
ARDS
Randomization n=630
Randomization n=436
Randomization n=290
HCQ + Azythro 400mg 12/12h 7 days 500 mg 1x day 7 days
HCQ 400mg 12/12h 7 days
Control No HCQ or Azythro
HCQ + Azythro 400mg 12/12h 10 days 500 mg 1x day 10 days
HCQ 400 mg 12/12h 10 days
Dexamethasone 20 mg 1x day 5 days 10 mg 1 x day 5 days
Control No Dexamethasone
PRIMARY OUTCOME
Clinical improvement according to ordinal scale on day 15
PRIMARY OUTCOME
Ventilator-free days alive up to day 28

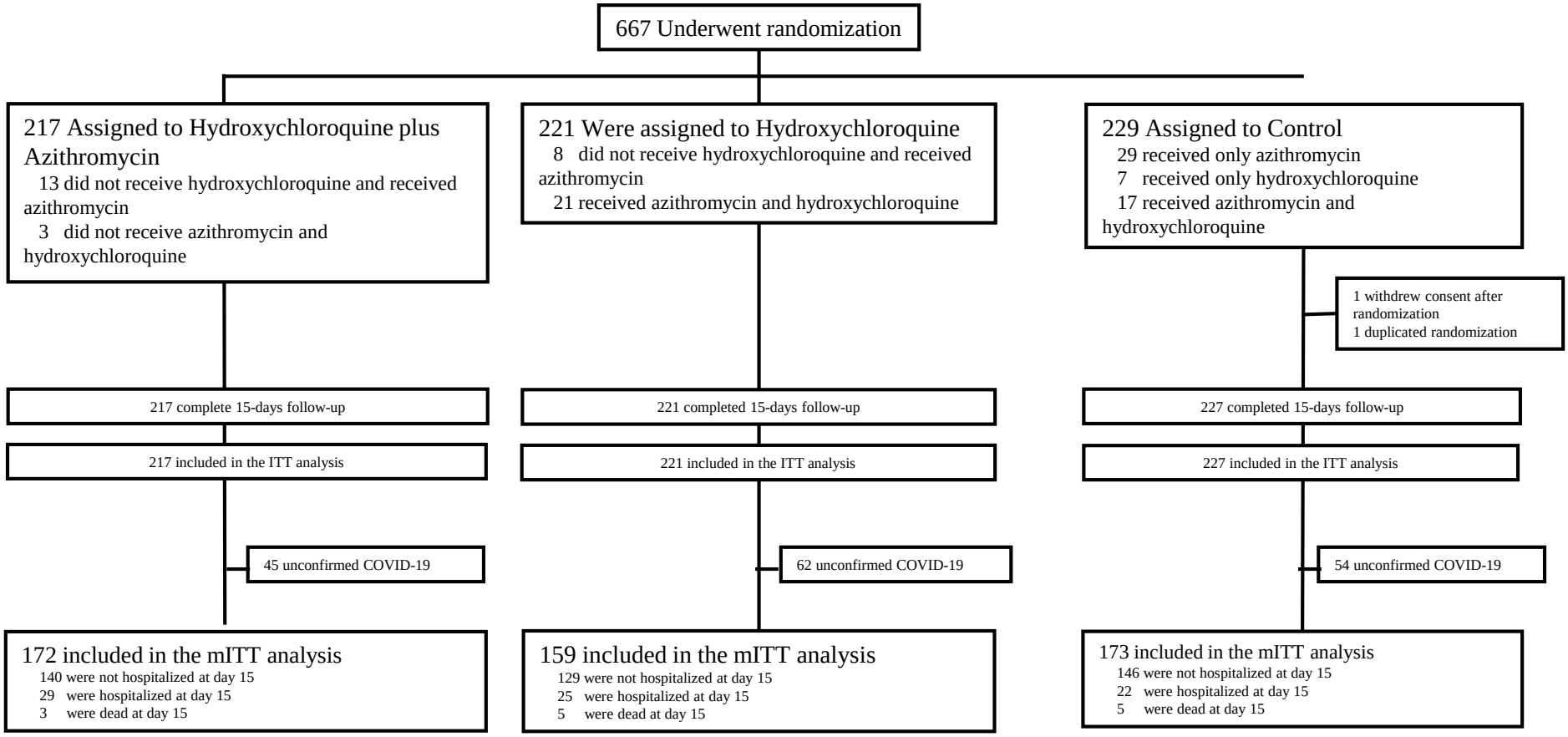

COALIZÃO IV
Covid-19 positive + Elevated D-Dimer
Randomization
n = 600
Full anticoagulation with rivaroxaban +/- heparin when needed
Prophylaxis anticoagulation
COALIZÃO V
Mild Infection
(not hospitalized)
Randomization
n = 1300
HCQ
PLACEBO
COALIZÃO VI
Severe infection
Randomization
n = 150
IL 6 antagonist
Control


COALIZÃO I
COALIZÃO II
COALIZÃO III
COALIZÃO IV
COALIZÃO V
COALIZÃO VI
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."

Lancet Infect Dis 2003; **3:** 722–27


667 Underwent randomization
217 Assigned to Hydroxychloroquine plus Azithromycin
13 did not receive hydroxychloroquine and received azithromycin
3 did not receive azithromycin and hydroxychloroquine
221 Were assigned to Hydroxychloroquine
8 did not receive hydroxychloroquine and received azithromycin
21 received azithromycin and hydroxychloroquine
229 Assigned to Control
29 received only azithromycin
7 received only hydroxychloroquine
17 received azithromycin and hydroxychloroquine
1 withdrew consent after randomization
1 duplicated randomization
217 complete 15-days follow-up
221 completed 15-days follow-up
227 completed 15-days follow-up
217 included in the ITT analysis
221 included in the ITT analysis
227 included in the ITT analysis
45 unconfirmed COVID-19
62 unconfirmed COVID-19
54 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
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
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

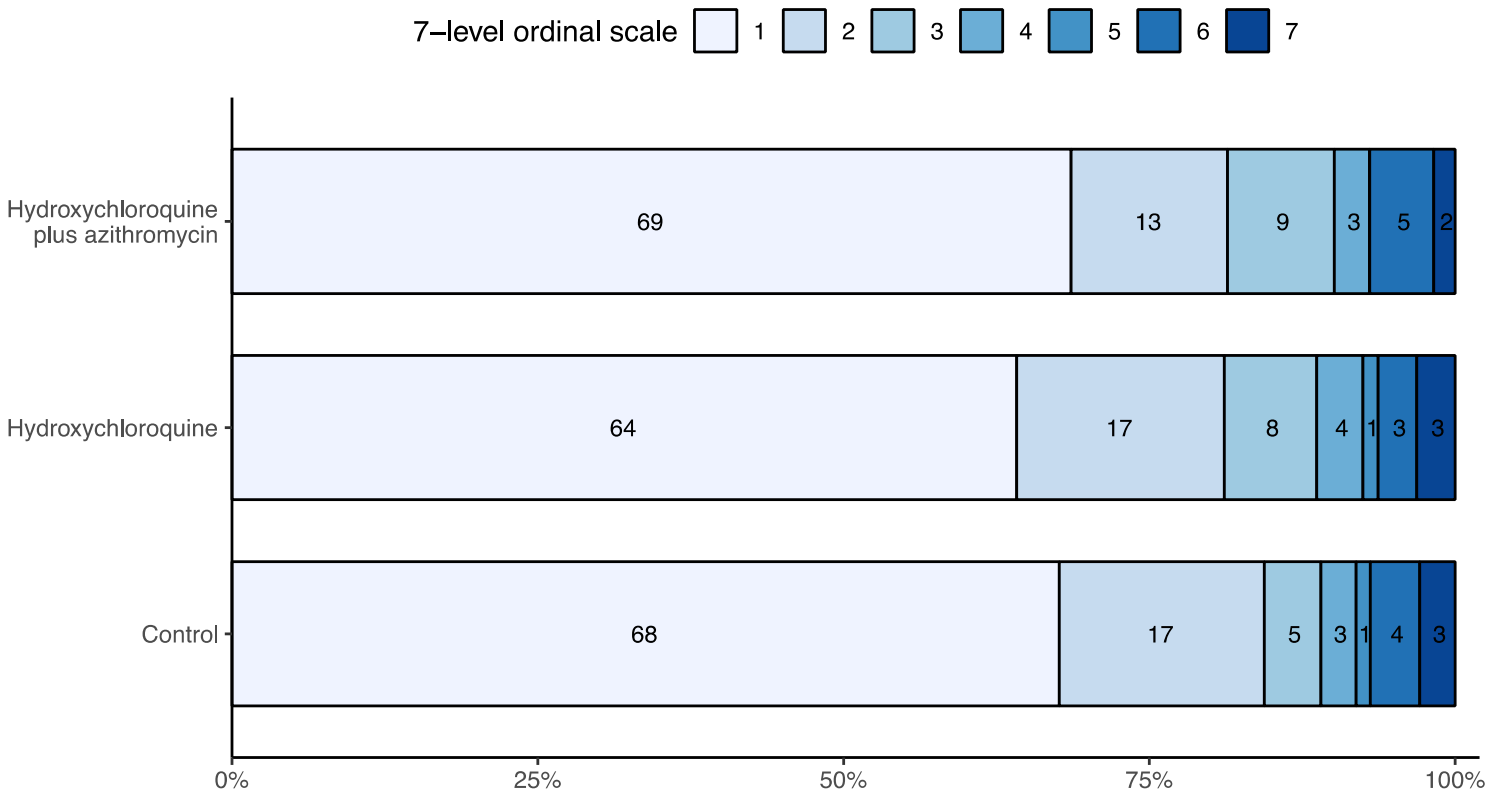
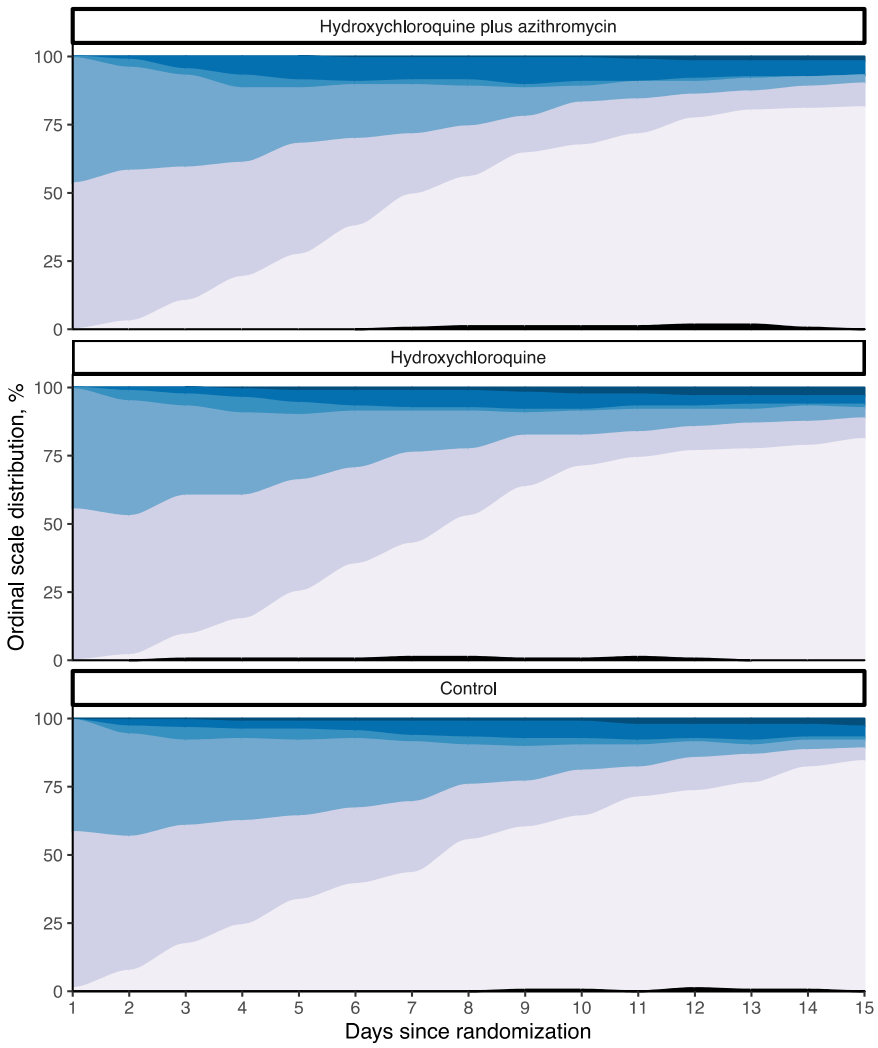


Figure 1. Status of Patients on Day 15.

Distribution of the Ordinal-Scale Results over Time.



Seven-Level Ordinal Scale: Missing | 1 and 2 | 3 | 4 | 5 | 6 | 7

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19

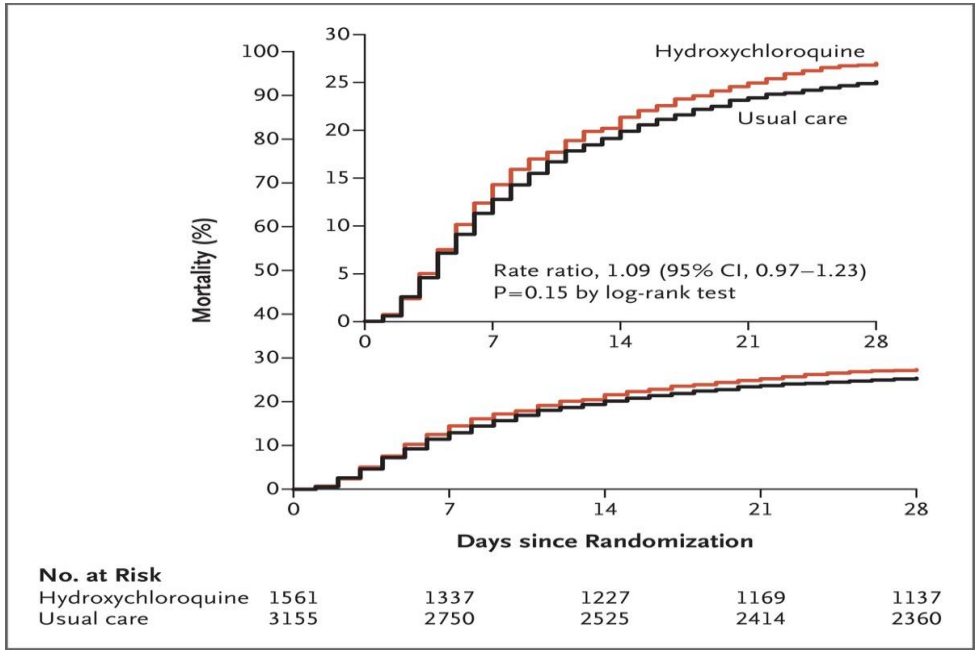
A.B. Cavalcanti, F.G. Zampieri, R.G. Rosa, L.C.P. Azevedo, V.C. Veiga, A. Avezum, L.P. Damiani, A. Marcadenti, L. Kawano-Dourado, T. Lisboa, D.L.M. Junqueira, P.G.M. de Barros e Silva, L. Tramujas, E.O. Abreu-Silva, L.N. Laranjeira, A.T. Soares, L.S. Echenique, A.J. Pereira, F.G.R. Freitas, O.C.E. Gebara, V.C.S. Dantas, R.H.M. Furtado, E.P. Milan, N.A. Golin, F.F. Cardoso, I.S. Maia, C.R. Hoffmann Filho, A.P.M. Kormann, R.B. Amazonas, M.F. Bocchi de Oliveira, A. Serpa-Neto, M. Falavigna, R.D. Lopes, F.R. Machado, and O. Berwanger, for the Coalition Covid-19 Brazil I Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19

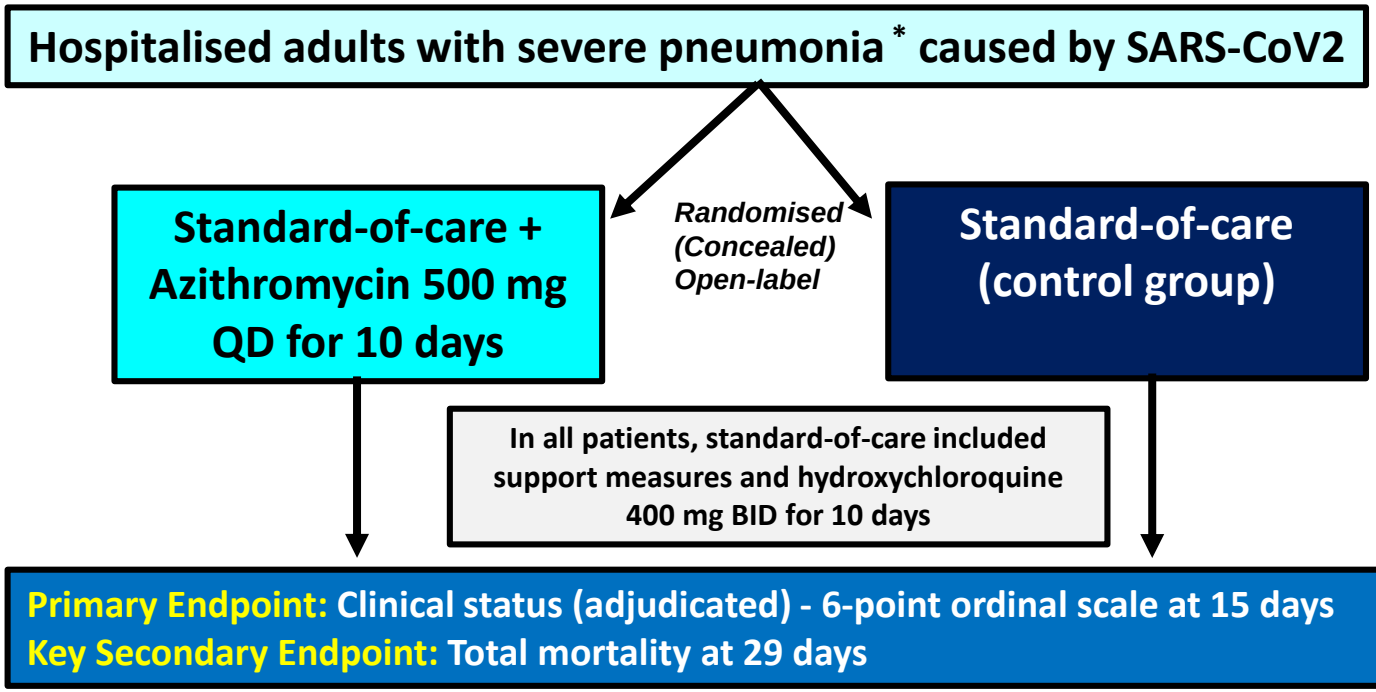
The RECOVERY Collaborative Group*



N Engl J Med 2020;383:2030-2040.

BCRI Brazilian Clinical Research Institute

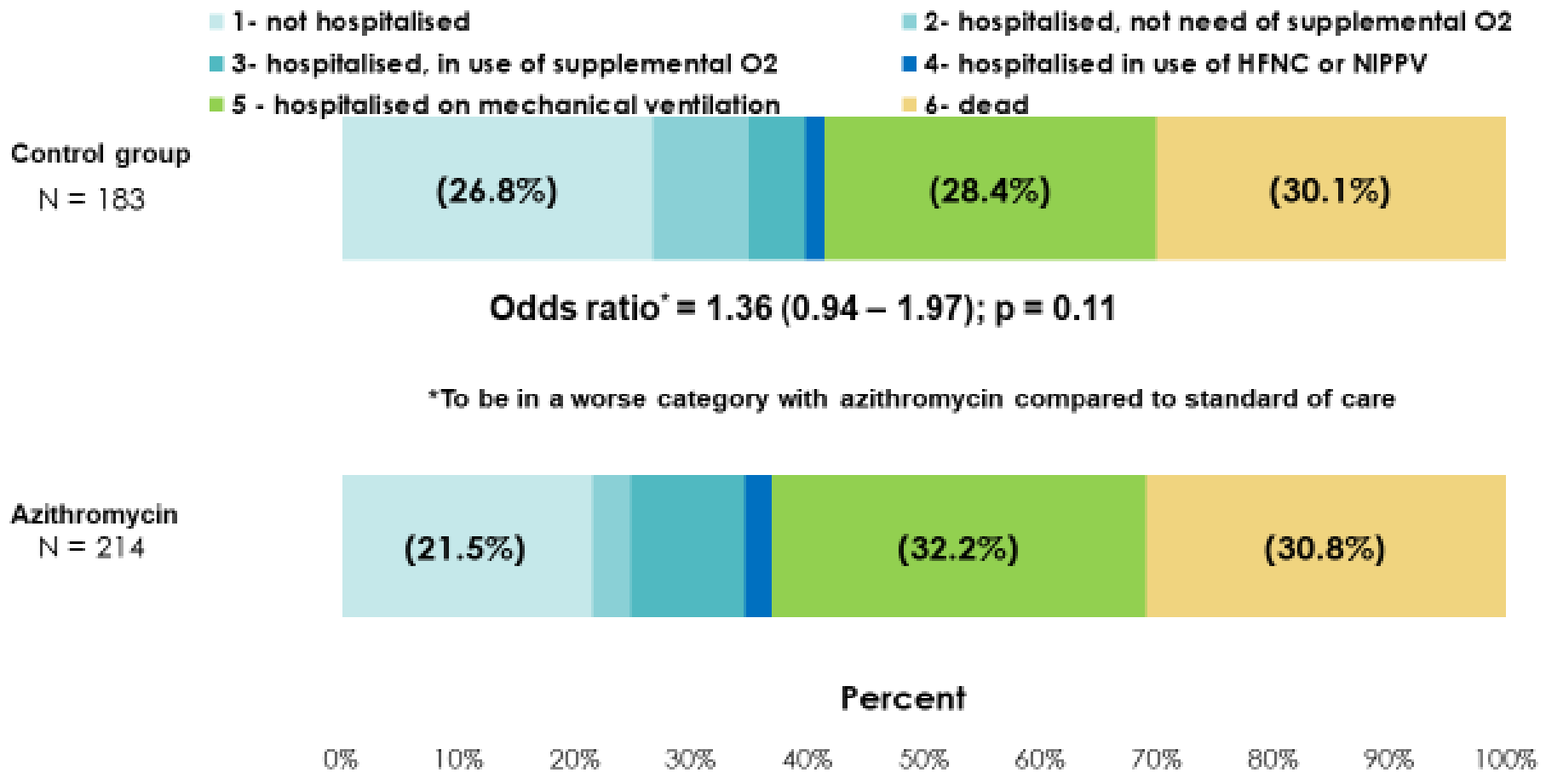
Trial Design



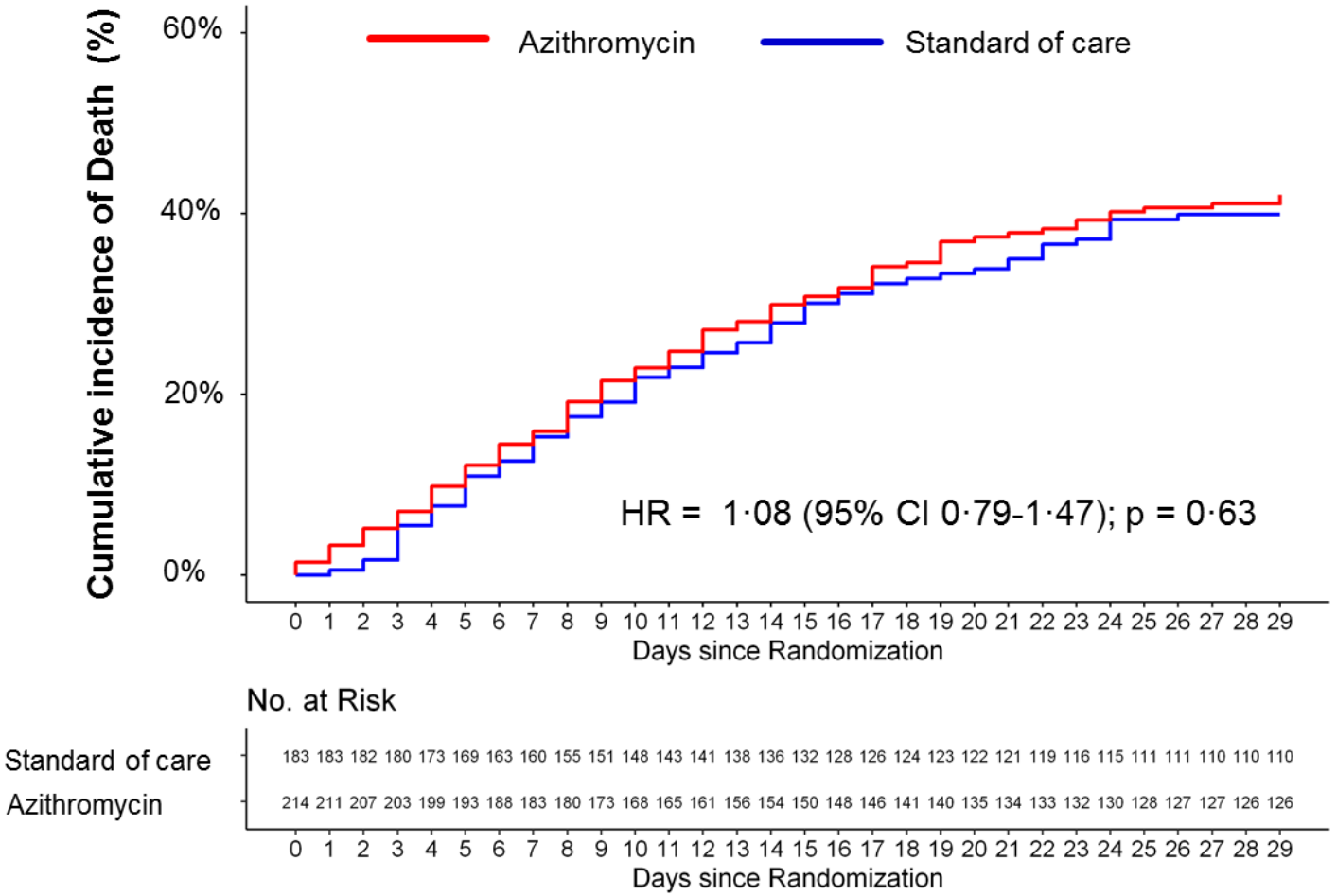
**At least ONE from the following severity criteria:*

- *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



Key Secondary Endpoint (Total Mortality at 29 days)

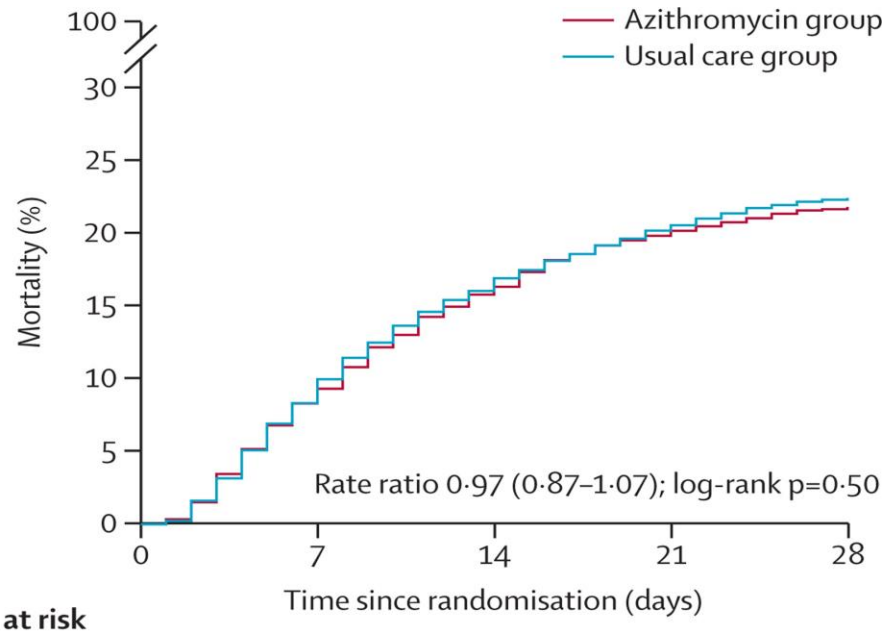


Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial

Remo H M Furtado, Otavio Berwanger*, Henrique A Fonseca, Thiago D Corrêa, Leonardo R Ferraz, Maura G Lapa, Fernando G Zampieri, Viviane C Veiga, Luciano C P Azevedo, Regis G Rosa, Renato D Lopes, Alvaro Avezum, Airton L O Manoel, Felipe M T Piza, Priscilla A Martins, Thiago C Lisboa, Adriano J Pereira, Guilherme B Olivato, Vicente C S Dantas, Eveline P Milan, Otavio C E Gebara, Roberto B Amazonas, Monalisa B Oliveira, Ronaldo V P Soares, Diogo D F Moia, Luciana P A Piano, Kleber Castilho, Roberta G R A P Momesso, Guilherme P P Schettino, Luiz Vicente Rizzo, Ary Serpa Neto, Flávia R Machado, Alexandre B Cavalcanti, for the COALITION COVID-19 Brazil II Investigators†*

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

RECOVERY Collaborative Group*



Number at risk

Azithromycin group	2582	2337	2155	2056	2014
Usual care group	5181	4658	4298	4108	4010

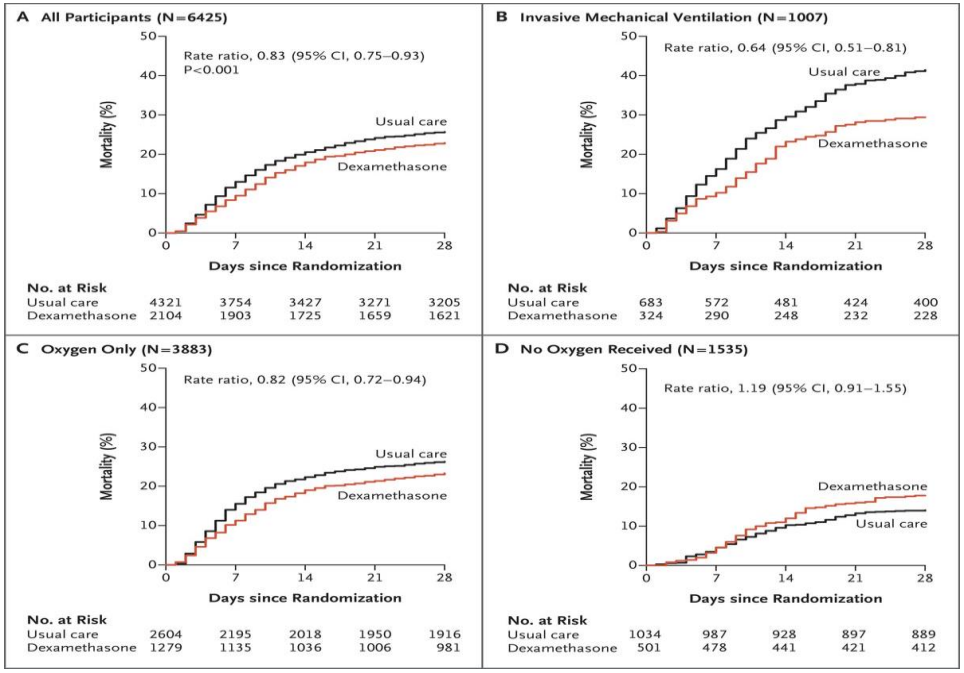
www.thelancet.com Published online February 2, 2021 https://doi.org/10.1016/S0140-6736(21)00149-5

The NEW ENGLAND JOURNAL of MEDICINE

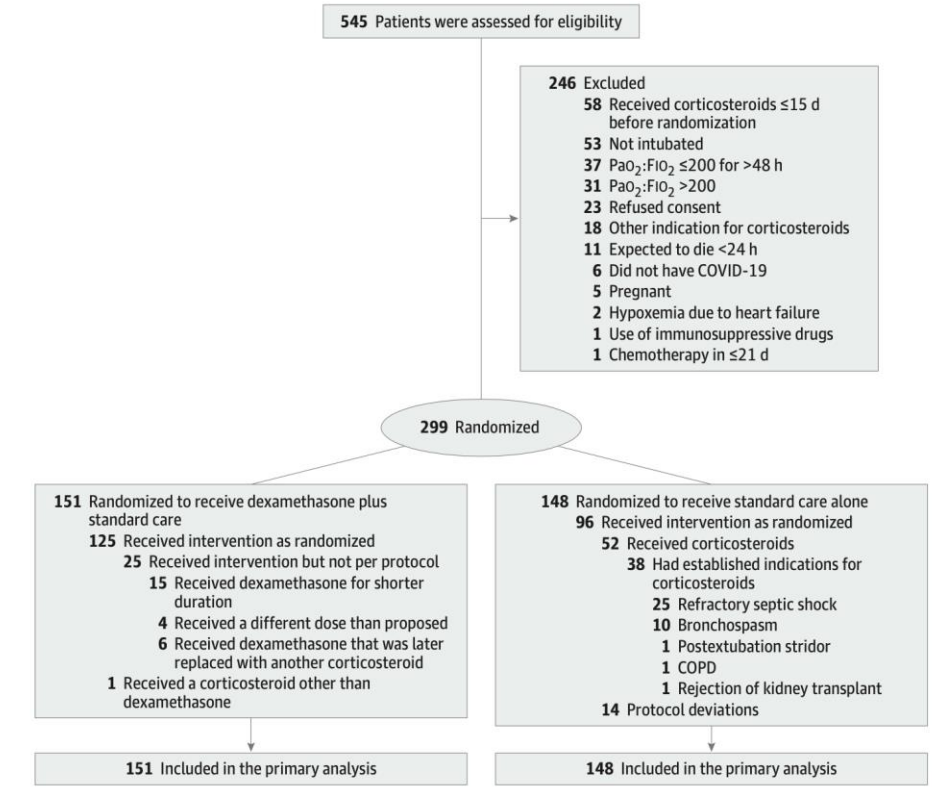
ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

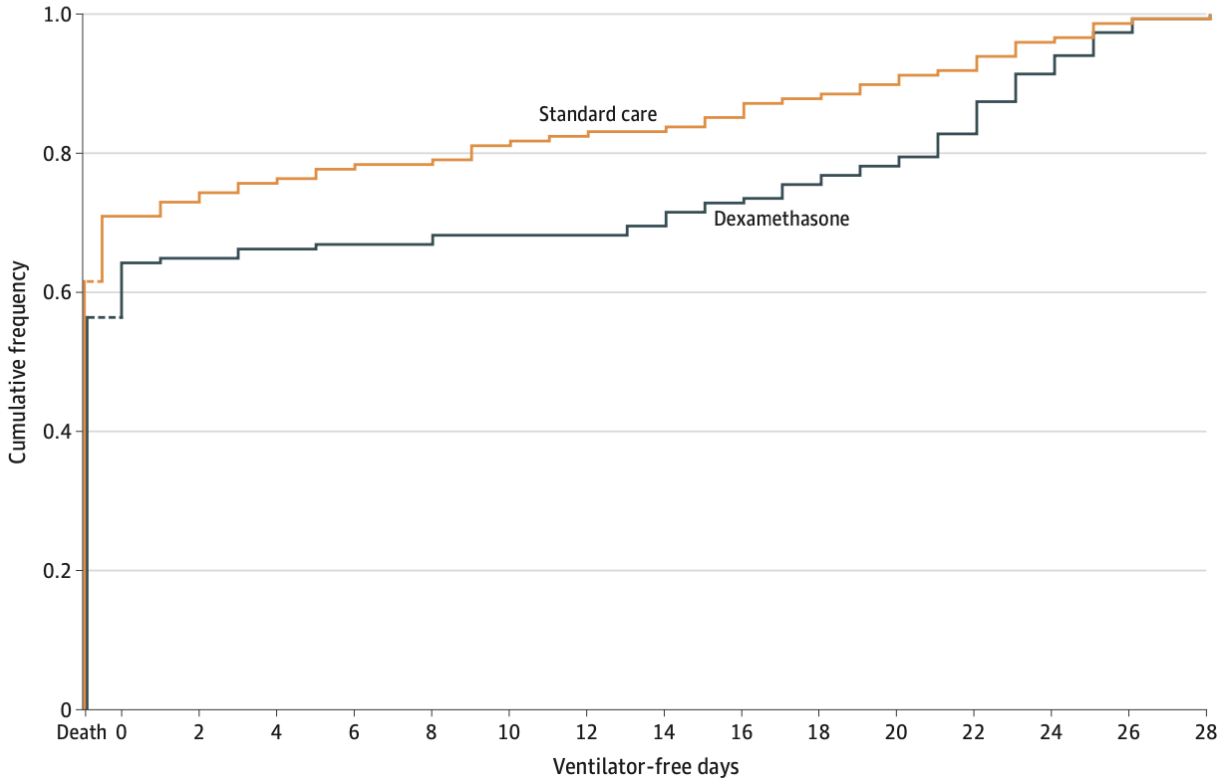


The RECOVERY Collaborative Group. N Engl J Med 2020. DOI: 10.1056/NEJMoa2021436



Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19 JAMA. 2020;

Figure 2. Ventilator-Free Days at 28 Days



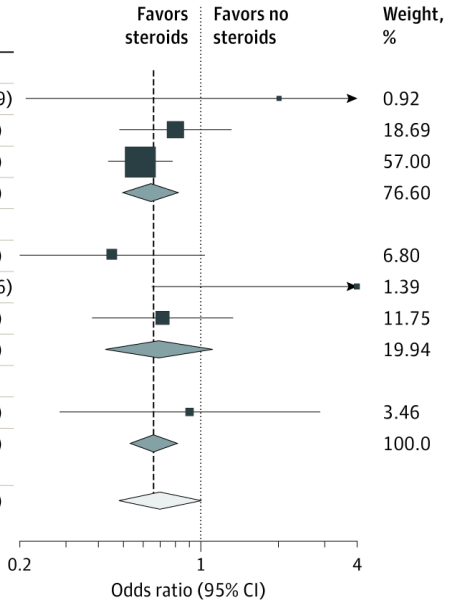
Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19 JAMA. 2020;

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)	Weight, %
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60
Hydrocortisone						
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)	6.80
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)	1.39
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)	11.75
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)	19.94
Methylprednisolone						
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)	3.46
Overall (fixed effect) $P = .31$ for heterogeneity; $I^2 = 15.6\%$			222/678	425/1025	0.66 (0.53-0.82)	100.0
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)	



JAMA. 2020;324(13):1330-1341. doi:10.1001/jama.2020.17023

BCRI Brazilian Clinical Research Institute

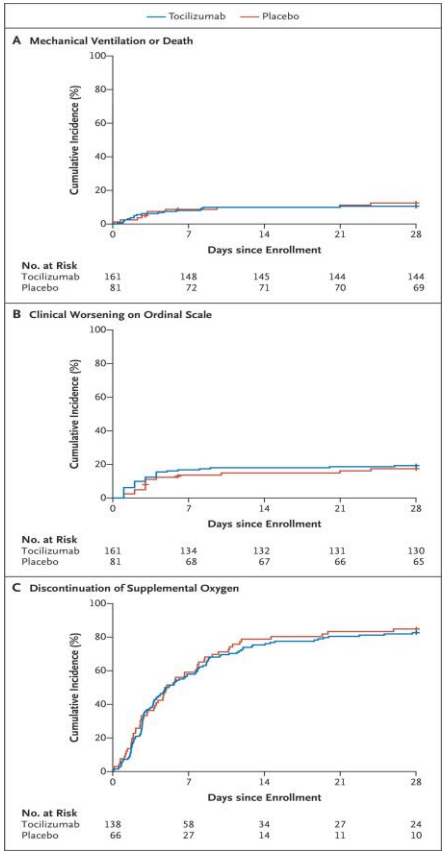
Effect of Tocilizumab on clinical status at 15 days in patients with severe covid-19: randomised controlled trial

COALITION VI

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of Tocilizumab in Patients Hospitalized with Covid-19



N Engl J Med 2020;383:2333-2344.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia

Table 2. Primary and Key Secondary Efficacy Outcomes by Day 28 in the Modified Intention-to-Treat Population.*

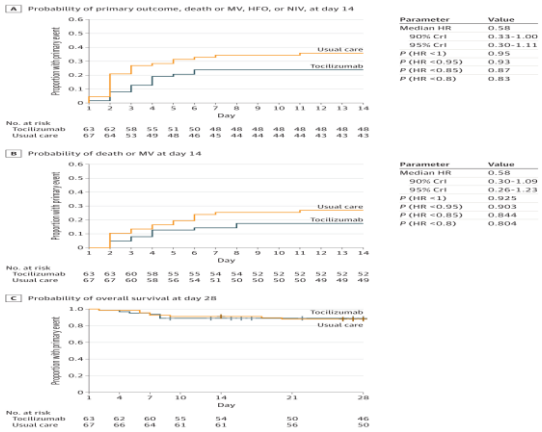
Outcome	Tocilizumab (N=249)	Placebo (N=128)	Hazard Ratio (95% CI)	Weighted Difference (95% CI)	P Value†
Primary outcome: mechanical ventilation or death — % (95% CI)‡	12.0 (8.5 to 16.9)	19.3 (13.3 to 27.4)	0.56 (0.33 to 0.97)	NA	0.04
Secondary outcomes					
Median time to hospital discharge or readiness for discharge (95% CI) — days§	6.0 (6.0 to 7.0)	7.5 (7.0 to 9.0)	1.16 (0.91 to 1.48)	NA	
Median time to improvement in clinical status (95% CI) — days§¶	6.0 (6.0 to 7.0)	7.0 (6.0 to 9.0)	1.15 (0.90 to 1.48)	NA	
Median time to clinical failure (95% CI) — days§	NE	NE	0.55 (0.33 to 0.93)	NA	
Death — no. (% [95% CI])‖	26 (10.4 [7.2 to 14.9])	11 (8.6 [4.9 to 14.7])	NA	2.0 (−5.2 to 7.8)**	

N Engl J Med 2021;384:20-30.

JAMA Internal Medicine | Original Investigation

Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia

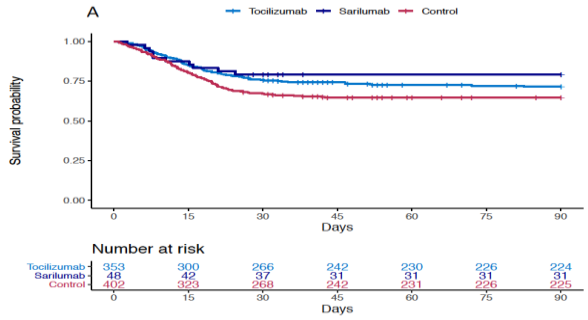
A Randomized Clinical Trial



JAMA Intern Med. 2021;181(1):32-40.

Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary report

The REMAP-CAP Investigators

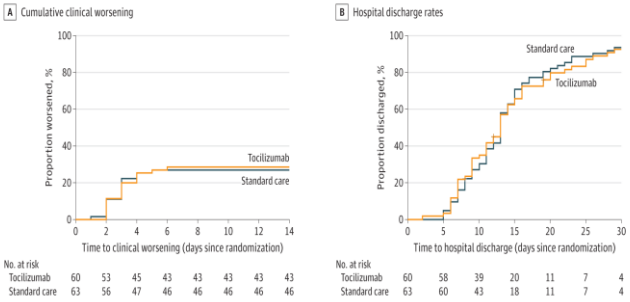


https://doi.org/10.1101/2021.01.07.21249390

JAMA Internal Medicine | Original Investigation

Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia

A Randomized Clinical Trial



JAMA Intern Med. 2021;181(1):24-31.

BCRI
Brazilian Clinical Research Institute

Objective

To determine whether tocilizumab improve outcomes for patients with severe covid-19.

Primary Outcome

	Tocilizumab	Control	Effect estimate	Effect size	
	(n = 65)	(n = 64)		(CI 95%)	p-value
Primary Endpoint					
Dead or on mechanical ventilation at day 15 – no. (%)*	18 (27.7)	13 (20.3)	Odds ratio 1-5 vs 6-7	1.54 (0.66 to 3.66)	0.32
Clinical status (7-level ordinal scale) at day 15 – no. (%)					
1. Not hospitalised with no limitation on activities	32 (49.2)	26 (40.6)			
2. Not hospitalised but with limitation on activities	3 (4.6)	5 (7.8)			
3. Hospitalised, not receiving supplemental oxygen	6 (9.2)	6 (9.4)			
4. Hospitalised, receiving supplemental oxygen	6 (9.2)	10 (15.6)			
5. Hospitalised, receiving non-invasive ventilation or high-flow nasal cannula	0 (0.0)	4 (6.2)			
6. Patient on mechanical ventilation	7 (10.8)	11 (17.2)			
7. Death	11 (16.9)	2 (3.1)			

Adjudicated causes of in-hospital deaths

Causes of in-hospital death	Tocilizumab (n = 14)	Control (n=6)
Covid-19 related acute respiratory failure or multiple organ dysfunction	14	5
Covid-19 and cerebral haemorrhage	0	1

CONCLUSIONS

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.

Check for updates

FAST TRACK

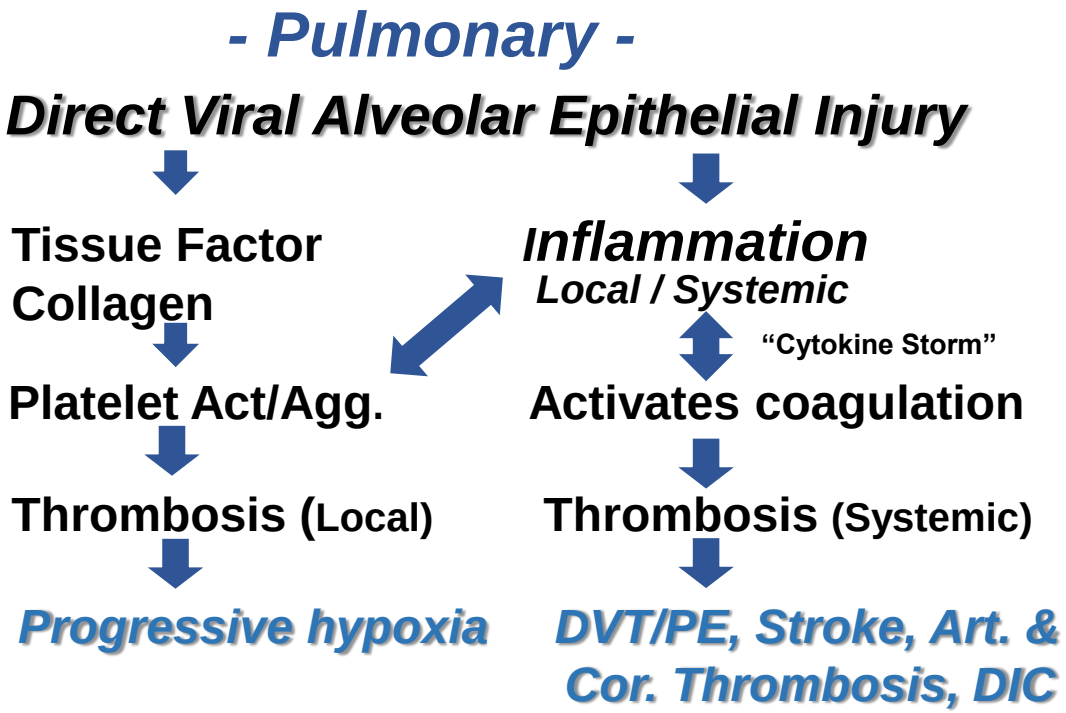
Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial

Viviane C Veiga,[1,2] João A G G Prats,[1] Danielle L C Farias,[1] Regis G Rosa,[2,3] Leticia K Dourado,[4] Fernando G Zampieri,[2,4] Flávia R Machado,[2,5] Renato D Lopes,[6,7] Otavio Berwanger,[8] Luciano C P Azevedo,[2,9] Álvaro Avezum,[10] Thiago C Lisboa,[2,4] Salomón S O Rojas,[1] Juliana C Coelho,[1] Rodrigo T Leite,[1] Júlio C Carvalho,[1] Luis E C Andrade,[11] Alex F Sandes,[11] Maria C T Pintão,[11] Claudio G Castro Jr,[8,12] Sueli V Santos,[4] Thiago M L de Almeida,[5] André N Costa,[9] Otávio C E Gebara,[13] Flávio G Rezende de Freitas,[2,14] Eduardo S Pacheco,[14] David J B Machado,[15] Josiane Martin,[15] Fábio G Conceição,[15] Suellen R R Siqueira,[15] Lucas P Damiani,[4,16] Luciana M Ishihara,[16] Daniel Schneider,[3] Denise de Souza,[3] Alexandre B Cavalcanti,[2,4] Phillip Scheinberg[1]; on behalf of the Coalition covid-19 Brazil VI Investigators

BMJ 2021;372:n84

BCRI

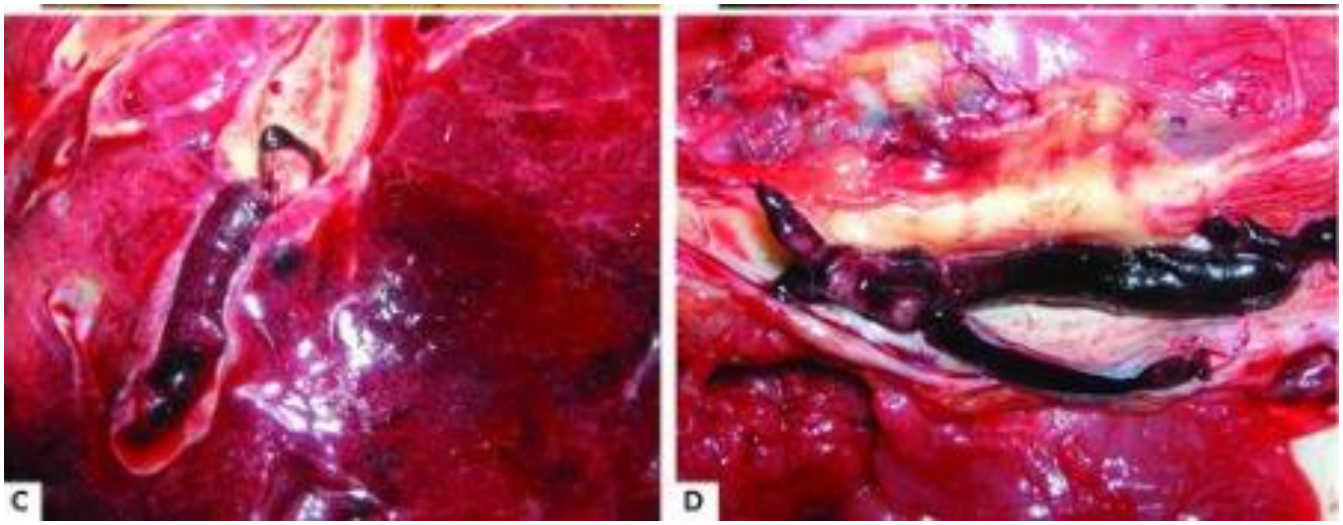
The COVID-19 Coagulopathy



Autopsy Findings and Venous Thromboembolism in Patients With COVID-19 FREE

Pulmonary Embolism
(Unsuspected)

Deep Vein Thrombosis
(Unsuspected)

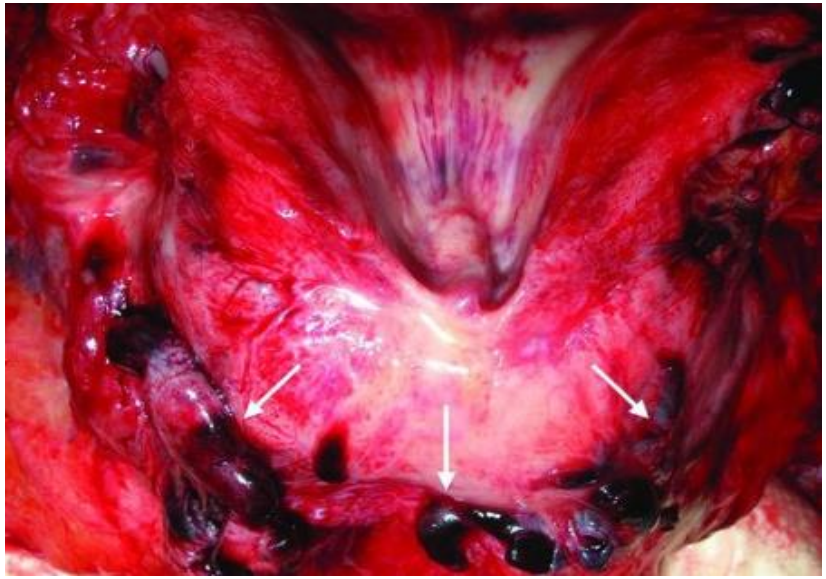


Wichmann D., et al Ann Int. Med. 2020, May 6: epub

Autopsy Findings and Venous Thromboembolism in Patients With COVID-19 FREE

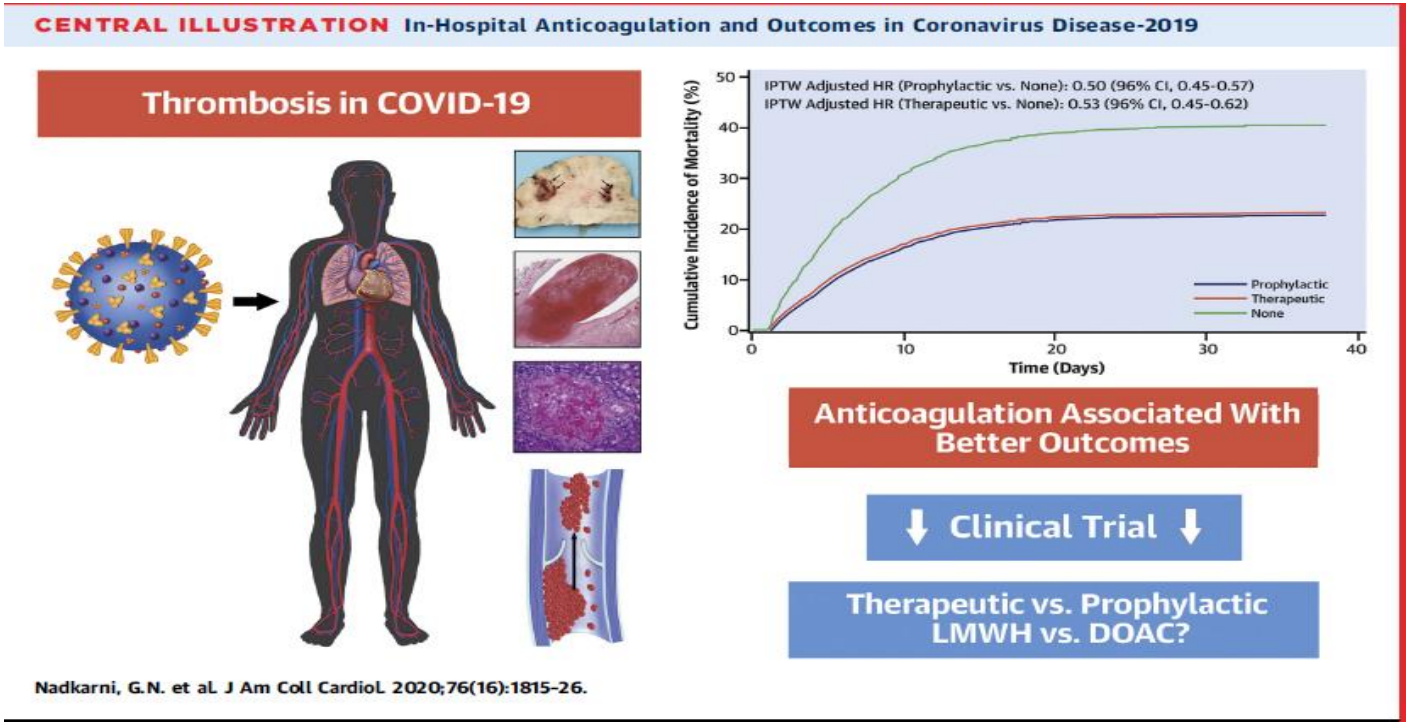
Thrombosis of Prostatic Veins

(Found in 67% of men)



Wichmann D., et al
Ann Int. Med. 2020, May 6: epub

Observational data



J Am Coll Cardiol. 2020 Oct 20;76(16):1815-1826.

Observational data – CAUTION!!

Anticoagulation in COVID-19

It Is Time for High-Quality Evidence*

Renato D. Lopes, MD, PhD,[a] Alexander C. Fanaroff, MD, MHS[b]

"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]

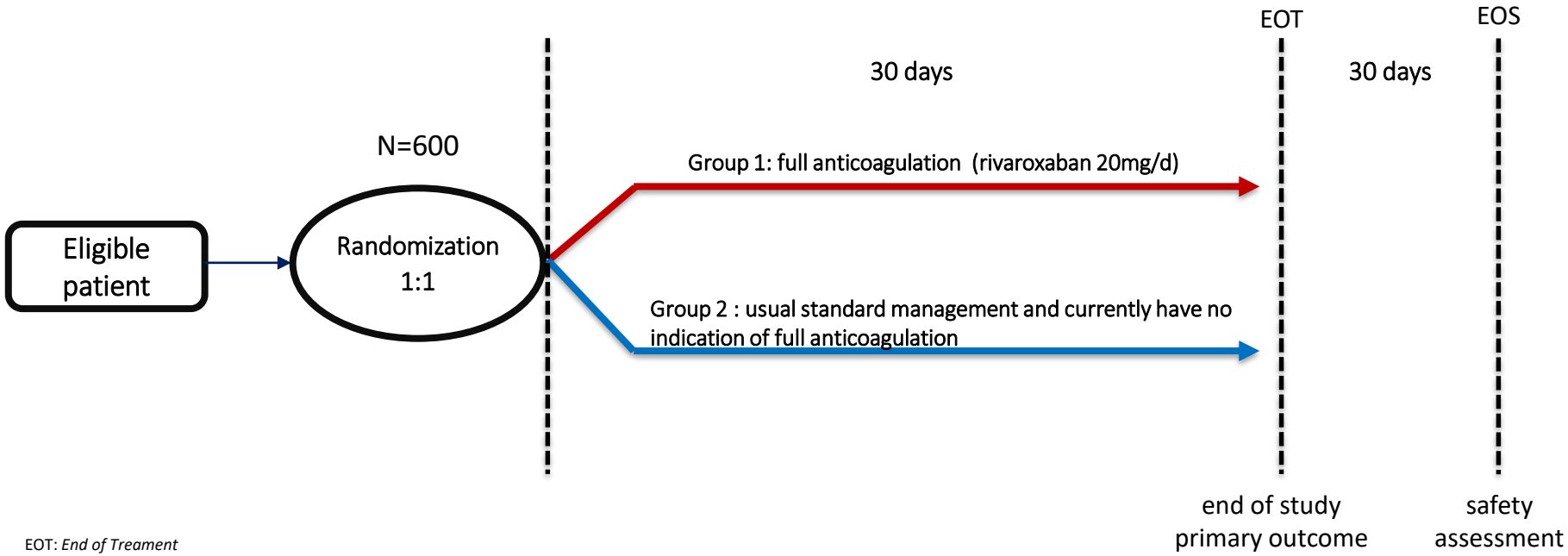
"Over the past 40 years, dozens of cardiovascular therapies and treatment strategies that were mechanistically promising and supported by observational comparative effectiveness studies showed no benefit or harm in rigorous randomized controlled trials."[2]

"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]

1. Lopes RD, Fanaroff AC. Anticoagulation in COVID-19: It Is Time for High-Quality Evidence. J Am Coll Cardiol. 2020 Oct 20;76(16):1827-1829.
2. Fanaroff AC, Califf RM, Harrington RA, et al. Randomized trials versus common sense and clinical observation. J Am Coll Cardiol 2020;76:580–9.
3. Wijaya I, et al. The Use of Therapeutic-Dose Anticoagulation and Its Effect on Mortality in Patients With COVID-19: A Systematic Review. Clin Appl Thromb Hemost. 2020.

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.



EOT: *End of Treament*
EOS: *End of Study*

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.

Equipoise on the Effects of RAAS Inhibition in COVID-19

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
Jarcho JA et al. N Engl J Med 2020;382:2462-2464

High-quality evidence to inform clinical practice

One of the basic tenets of
based medicine is that ran
is crucial to understanding
effects. Observational studi
ject to confounding and sel
Researchers can adjust for
differences between treatm
but unmeasured or unmeas
ferences might exist betwe
that obscure true treatm
and cannot be accounted
statistical method.[1] The
medical literature is filled wit
of associations between trea
outcome identified in obs
studies that were subsequ
proven by well conducted r
controlled trials (RCTs).[2-4]

Framed this way, findin
analysis of cardiovascular
which showed that less th
American College of Cardiology and American Heart Association and less than 85% of European Society of Cardiology guideline recommendations were based on evidence from RCTs,

patients, obtain informed consent, collect baseline information, track patients through the trial, and obtain follow-up information. Owing to this

with international data standards, would facilitate these trials on a global basis.

Creation of such an infrastructure will

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Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Medtronic, Pfizer, and Sanofi.

*Alexander C Fanaroff, Robert M Califf, *Renato D Lopes*
renato.lopes@duke.edu
Department of Medicine and Duke Clinical Research

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

how to take care of patients like them, but only if the necessary structures are in place to efficiently identify patients appropriate for enrolment in an RCT, consent patients for enrolment, and

Gala Image/Science Photo Library

Fanaroff AC, Califf RM, Lopes RD. Lancet 2019;394:633

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

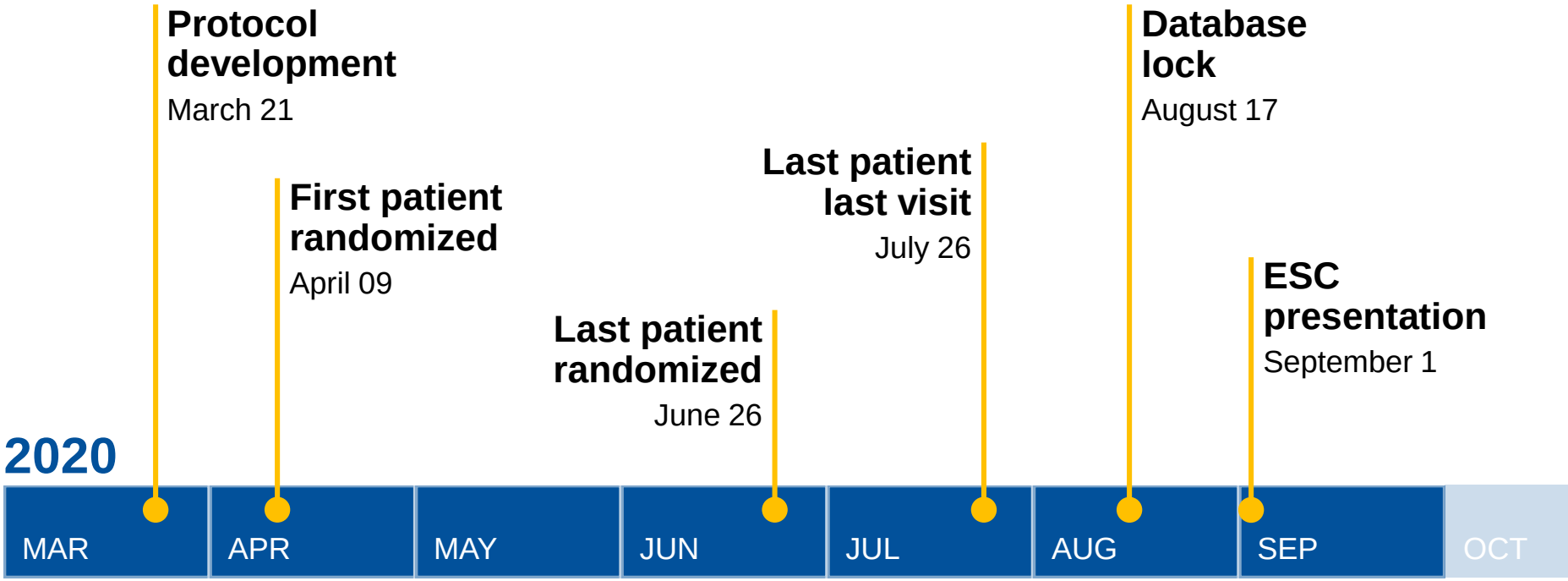
Temporarily suspend ACEI/ARB treatment for 30 days

Continue to use ACEI/ARB treatment

PRIMARY OUTCOME
Days alive and out of hospital at 30 days

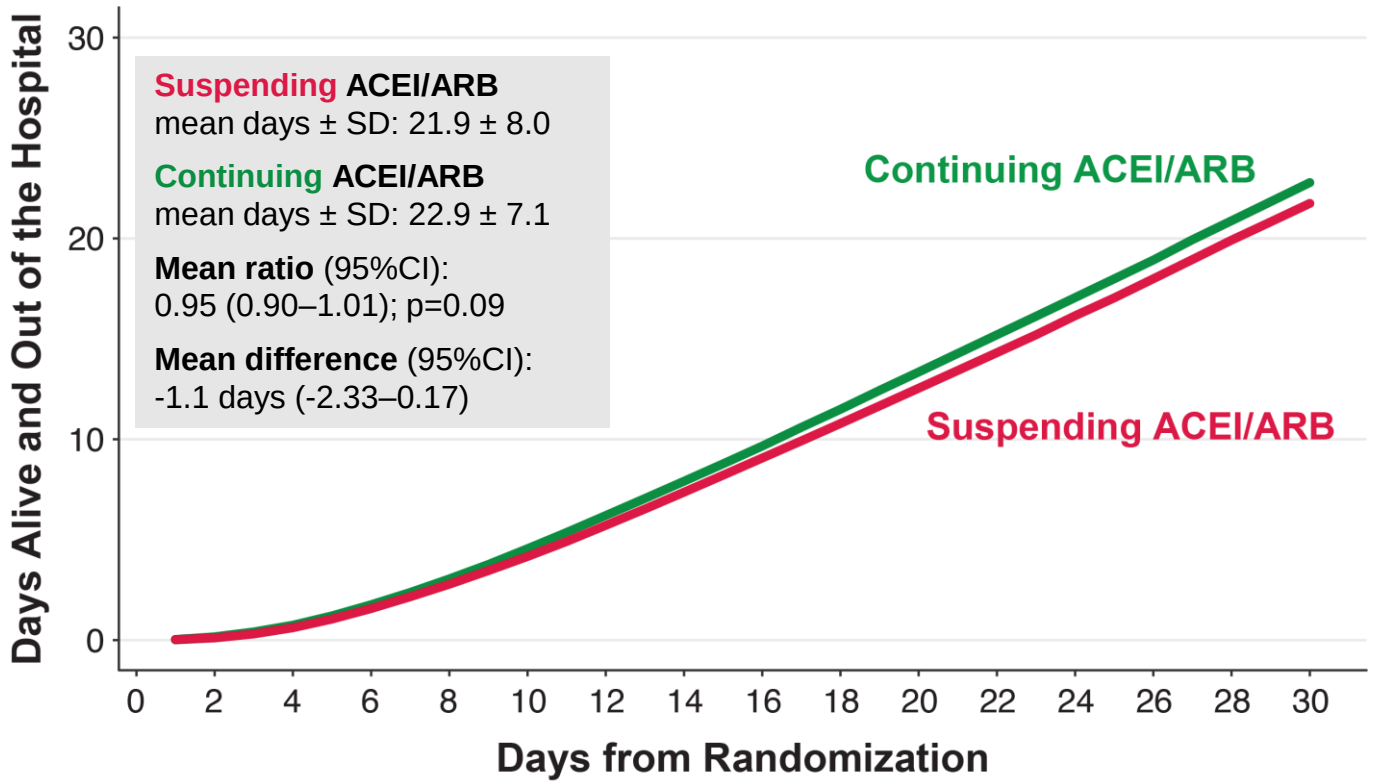
Lopes RD et al. Am Heart J 2020;226:1-10

BRACE CORONA Trial Timelines

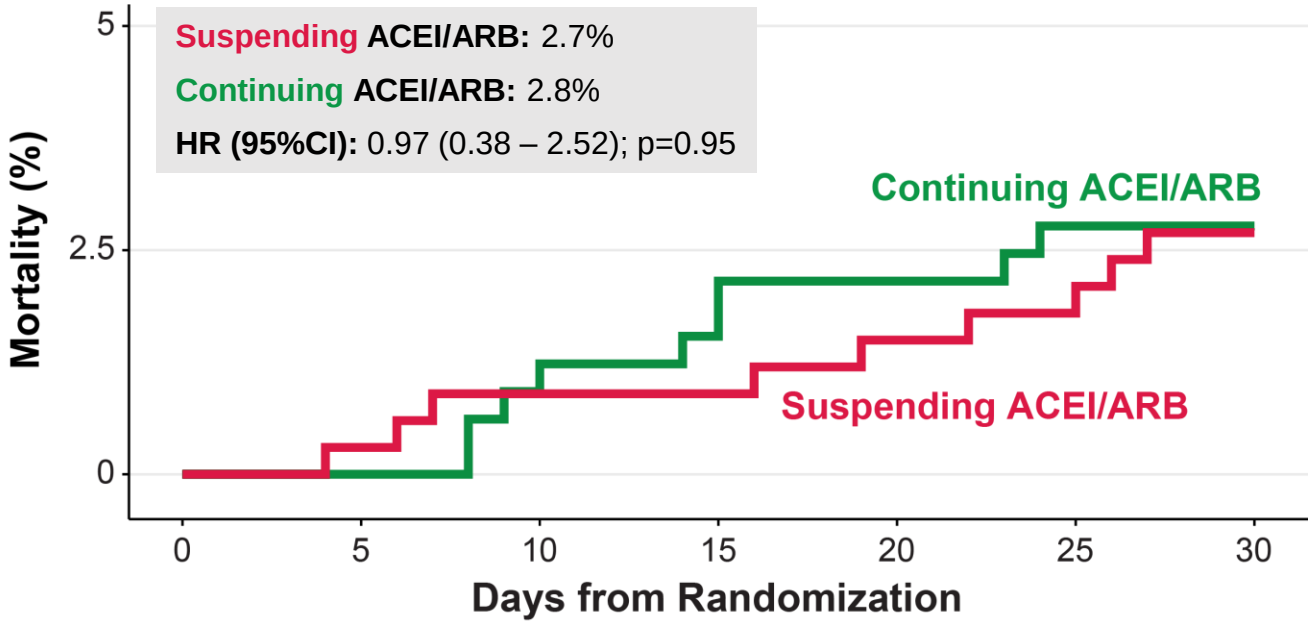


Lopes RD et al. Am Heart J 2020;226:1-10

Primary Outcome: Days Alive and Out of Hospital at 30 Days



All-Cause Mortality at 30 Days



Numbers at risk:

Suspending ACEI/ARB	334	333	331	331	329	328	325
Continuing ACEI/ARB	325	325	322	320	318	316	316

Research

JAMA | Original Investigation

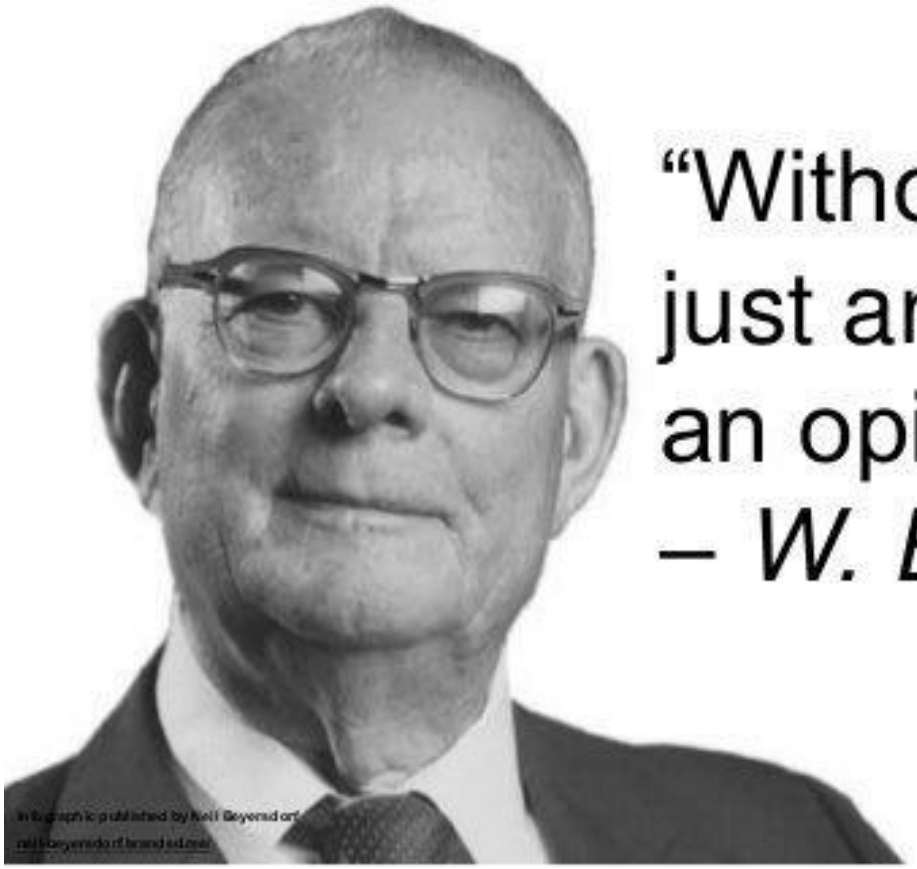
Effect of Discontinuing vs Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on Days Alive and Out of the Hospital in Patients Admitted With COVID-19

A Randomized Clinical Trial

Renato D. Lopes, MD, PhD; Ariane V. S. Macedo, MD, MSc; Pedro G. M. de Barros E Silva, MD, PhD; Renata J. Moll-Bernardes, MD, PhD; Tiago M. dos Santos, MSc; Lilian Mazza, RT; André Feldman, MD, PhD; Guilherme D'Andréa Saba Arruda, MD; Denílson C. de Albuquerque, MD, PhD; Angelina S. Camiletti, RN, MSc; Andréa S. de Sousa, MD, PhD; Thiago C. de Paula, MD; Karla G. D. Giusti, MD; Rafael A. M. Domiciano, MD; Márcia M. Noya-Rabelo, MD, MHS, PhD; Alan M. Hamilton, MD; Vitor A. Loures, MD; Rodrigo M. Dionísio, MD; Thyago A. B. Furquim, MD; Fábio A. De Luca, MD, MBA, PhD; Ítalo B. dos Santos Sousa, MD; Bruno S. Bandeira, MD; Cleverson N. Zukowski, MD, PhD; Ricardo G. G. de Oliveira, MD; Noara B. Ribeiro, MD; Jeffer L. de Moraes, MD; João L. F. Petriz, MD, MHS, PhD; Adriana M. Pimentel, MD, PhD; Jacqueline S. Miranda, MD; Bárbara E. de Jesus Abufaiad, MD; C. Michael Gibson, MD; Christopher B. Granger, MD; John H. Alexander, MD, MHS; Olga F. de Souza, MD, PhD; for the BRACE CORONA Investigators

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 despereteley 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!

Renato D Lopes, MD MHS PhD
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Duke University Medical Center

Duke Clinical Research Institute

From Thought Leadership to Clinical Practice