Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Continuing versus suspending angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: Impact on adverse outcomes in hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–The BRACE CORONA Trial

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Background Angiotensin-converting enzyme-2 (ACE2) expression may increase due to upregulation in patients using angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs). Because renin-angiotensin system blockers increase levels of ACE2, a protein that facilitates coronavirus entry into cells, there is concern that these drugs could increase the risk of developing a severe and fatal form of COVID-19. The impact of discontinuing ACEI and ARBs in patients with COVID-19 remains uncertain.

Design BRACE CORONA is a pragmatic, multicenter, randomized, phase IV, clinical trial that aims to enroll around 500 participants at 34 sites in Brazil. Participants will be identified from an ongoing national registry of suspected and confirmed cases of COVID-19. Eligible patients using renin-angiotensin system blockers (ACEI/ARBs) with a confirmed diagnosis of COVID-19 will be randomized to a strategy of continued ACEI/ARB treatment versus temporary discontinuation for 30 days. The primary outcome is the median days alive and out of the hospital at 30 days. Secondary outcomes include progression of COVID-19 disease, all-cause mortality, death from cardiovascular causes, myocardial infarction, stroke, transient ischemic attack, new or worsening heart failure, myocarditis, pericarditis, arrhythmias, thromboembolic events, hypertensive crisis, respiratory failure, hemodynamic decompensation, sepsis, renal failure, and troponin, B-type natriuretic peptide (BNP), N-terminal-proBNP, and D-dimer levels.

Summary BRACE CORONA will evaluate whether the strategy of continued ACEI/ARB therapy compared with temporary discontinuation of these drugs impacts clinical outcomes among patients with COVID-19. (Am Heart J 2020;226:49-59.)

In December 2019, the first cases of a novel infectious viral respiratory illness, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), were reported in Wuhan, China. The highly contagious coronavirus disease (COVID-19) caused by SARS-CoV-2 spread rapidly to more than 100 countries and was declared a global pandemic by the World Health Organization on March 11, 2020.[1] This new and threatening situation led to a rapid response by the medical and scientific community to identify the main characteristics of the disease and interventions to improve the outcomes of patients with COVID-19.

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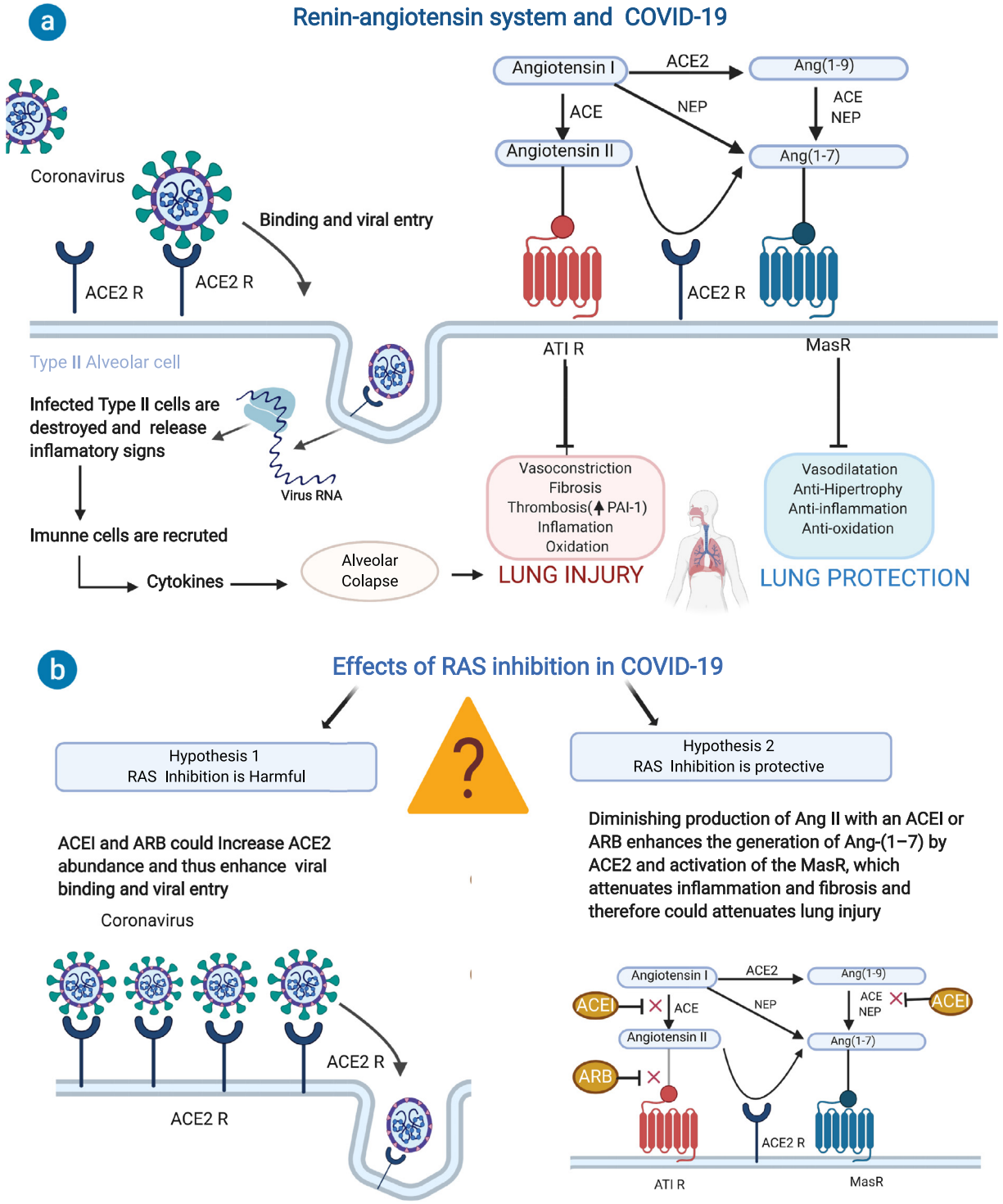
Figure 1



In infectious disease emergencies, such as the ongoing COVID-19 pandemic, trials of interventions need to be implemented as part of the efforts to control the spread of the disease and to improve patient outcomes.[2] Randomized clinical trials are the most reliable approach to evaluate the effects of these interventions.[3] In the

context of public health emergencies, conducting a randomized clinical trial can be even more challenging.[4] The shortfalls of the contemporary clinical trial system include the increasingly prohibitive costs, local and national regulatory requirements, delays in approval, and unnecessary trial processes.[5] Over the past decade, innovations in trial design have been deployed to facilitate trial conduct. An attractive solution is registry-based randomized clinical trials.[6] By including randomization in a clinical registry with unselected consecutive enrolment, the advantages of a prospective randomized trial can be aligned with the strengths of a large-scale, all-comers clinical registry.[7] Prospective registry-based randomized trials may be a powerful tool for conducting studies efficiently and cost-effectively, particularly in an urgent situation like the current COVID-19 pandemic.

Study rationale

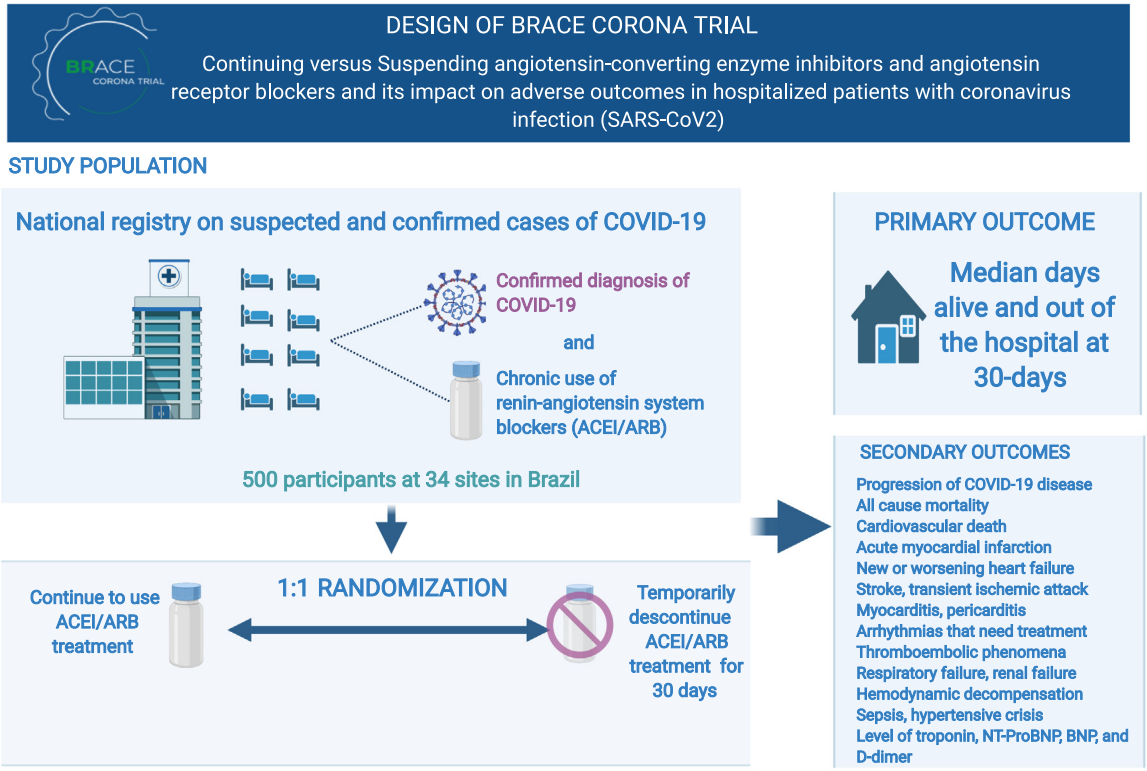
Patients with COVID-19 and comorbidities have a worse prognosis than those with no underlying medical issues. However, other well-known cardiovascular risk factors commonly identified in these patients could also explain the higher risk of this population.[8,9] Renin-angiotensin system blockers are commonly used in patients with cardiovascular comorbidities since this group of drugs is routinely indicated for patients with heart failure, hypertension, and coronary heart disease. Angiotensin-converting enzyme-2 (ACE2) expression may increase due to upregulation in patients using angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs). Since SARS-CoV-2 (and other human pathogenic coronaviruses) binds to target cells through ACE2,[10] the worse prognosis in patients with cardiovascular disease could be related to the interaction with drugs commonly used in these patients that may facilitate virus aggression.[11]

On the basis of data indicating that ACE2 is an effective receptor for SARS-CoV-2, healthcare professionals and researchers are assessing the possible impact of ACEI and ARBs in patients with COVID-19.[12] The ACE2 receptor is found on the surface of type II alveolar epithelial cells in the lungs as well as cells in the heart, kidney, liver, and gastrointestinal tract. There is uncertainty surrounding renin-angiotensin system inhibition in patients with COVID-19, with some hypothesizing that ACEI/ARB use may increase propagation of the virus and others hypothesizing that there may be a protective effect (Figure 1).[13]

SARS-CoV-2 gains entry into the cell by binding to ACE2. The use of an ACEI or ARB could enhance ACE2 abundance and consequently increase susceptibility to viral entry. In theory, this effect could increase the risk for or severity of COVID-19. On the other hand, an increase in the expression of angiotensin II drives lung injury by activating the type 1 angiotensin receptor (AT1R), producing inflammation and fibrosis. Decreasing the production of angiotensin II with an ACEI or blocking angiotensin II–AT1R activity with an ARB enhances the production of angiotensin (1–7) from angiotensin II and activates the Mas receptor, which attenuates inflammation and fibrosis resulting in a decrease in lung damage.[14] Indeed, the use of recombinant human ACE2 has been tested as a promising therapy for patients with severe

A) Renin angiotensin system and COVID-19: The spike proteins covering the coronavirus bind to ACE2 receptors primarily on type II alveolar cells, allowing the virus to inject its RNA. The host cell is destroyed in this process. After infection, type II cells release inflammatory signals to recruit immune cells. When the immune system attacks the area of infection it also kills healthy alveolar cells. This may result in alveolar collapse due to loss of surfactant from type II cells and acute lung injury. In the renin-angiotensin-aldosterone system (RAAS), angiotensin I (Ang I) is converted to angiotensin II (Ang II) by ACE. Ang II mediates vasoconstrictive, pro-inflammatory, pro-oxidative and pro-thrombotic effects (possibly by increasing levels of PAI-1) through agonism of the Ang II type 1 receptor (AT1R). ACE2 converts Ang II to angiotensin (1–7), which finally binds to Mas receptor (MasR) and mediates many beneficial actions, including vasodilation and anti-inflammatory, anti-oxidant and anti-apoptotic effects. Thus, ACE2/Ang (1–7)/MasR axis has opposite actions to ACE/Ang II/AT1R axis. ACE2 limits the adverse vasoconstrictor and profibrotic effects of Ang II through its degradation and by counteracting its actions through the formation of Ang (1–7). SARS-CoV-2 binding to ACE2 may attenuate residual ACE2 activity as a consequence of increased internalization and shedding of ACE2 from the cell surface further tipping the ACE/ACE2 balance to a predominant ACE/Ang II/AT1 axis signaling, in which Ang II may then foster pulmonary vasoconstriction and inflammatory and oxidative organ damage, ultimately progressing towards acute lung injury. (B) Effects of RAAS inhibition in COVID-19: There are different postulated mechanisms by which inhibition of the RAAS with an ACEI or ARB might be dangerous or protective in COVID-19. *Hypothesis 1 — RAAS inhibition is harmful in COVID-19 (left).* ACEI and ARBs could theoretically increase the risk of SARS-CoV-2 infection and more severe COVID-19 owing to the role of ACE2 as the viral binding site. Although ACEI and ARBs do not directly affect ACE2 activity, this premise is based in part on the findings in some studies that ACEI and ARBs may increase ACE2 levels and thus enhance viral entry. *Hypothesis 2 — RAAS inhibition is protective in COVID-19 (right).* ACEI and ARBs may mitigate COVID-19 by attenuating Ang II-mediated acute lung impairment. Decreasing production of Ang II with an ACEI or blocking Ang II–AT1R actions with an ARB may reduce the levels of prothrombotic substances (such as PAI-1) and intensify the formation of Ang (1–7) by ACE2 and activation of the MasR, which attenuates inflammation and fibrosis and consequently may attenuate lung damage. Abbreviations: ACE = angiotensin-converting enzyme; ACE2 = angiotensin-converting enzyme-2; ACEI = ACE inhibitor; Ang (1–7)=angiotensin 1–7; Ang I = Angiotensin I; Ang II = angiotensin II; AT1R = Ang II type 1 receptor; AT2 = type II alveolar cells; ARBs = angiotensin receptor blockers; COVID-19 = coronavirus disease 2019; MasR = Mas receptor; PAI-1 = plasminogen activator inhibitor 1; RAAS = renin-angiotensin-aldosterone system; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Figure 2



Design of the BRACE CORONA trial.

acute respiratory distress syndrome.[15] Finally, renin-angiotensin system inhibition protects the cardiovascular system by lowering blood pressure, avoiding ventricular remodeling, and reducing plasminogen activator inhibitor-1.[16] Thus, withdrawal of these agents could be harmful since there is a potential risk of disease complications related to discontinuation of established therapies already proven effective in preventing cardiovascular events. As a result, there are data supporting a potential benefit and also data indicating potential risk in maintaining these agents during COVID-19 infection, which reinforces the need of a prospective randomized study to address this clinical question.

There are several possible interactions between these medications commonly prescribed for cardiovascular disease and COVID-19 that might influence the prognosis of these patients. When the totality of evidence is taken into account, there is true equipoise between the maintenance or suspension of ACEI/ARB therapy in patients with COVID-19. To date, there is no high quality clinical evidence to confirm any of the theories and this question can only be clarified through a randomized clinical trial.[13] Our initial hypothesis is that continuing ACEI/ARBs will be beneficial for the overall course of the COVID-19 infection compared with withdrawing these agents.

Methods

Study overview

BRACE CORONA (ClinicalTrials.gov: NCT04364893) is an academically led, investigator-initiated, pragmatic, phase IV, multicenter, registry-based randomized trial. The study will be open-label with blinded endpoint assessment (PROBE) and will include approximately 500 patients on ACEI/ARB therapy with a confirmed diagnosis of COVID-19.

The BRACE CORONA trial is embedded in a registry of all patients with COVID-19 admitted at 34 sites in Brazil. Of these patients, the first 500 eligible for the trial will be approached to be randomized for maintenance or discontinuation of renin-angiotensin system inhibition. All of the data necessary for documenting baseline characteristics and outcomes, including ACEI and

Table I. Inclusion and exclusion criteria for BRACE CORONA trial

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

ARB doses, will have been collected already by the registry (Figure 2).

The study protocol was approved by the National Commission for Research Ethics (CONEP) from the Brazilian Ministry of Health. The study will be conducted in compliance with the protocol and adheres fully to the ethical principles of the Declaration of Helsinki, specifications of the International Council for Harmonization, and Good Clinical Practice. The protocol requires that each patient must provide informed consent before any study procedure is initiated.

Primary objective

The primary objective of the trial is to determine whether continued use versus discontinuation of ACEI/ARB therapy increases days alive and out of the hospital over 30 days in patients on renin-angiotensin system inhibition hospitalized with COVID-19.

Secondary objectives

The secondary objectives are to compare the impact of continued use versus discontinuation of renin-angiotensin system inhibition on COVID-19 disease severity, all-cause mortality, cardiovascular death, acute myocardial infarction, new or worsening heart failure, hypertensive crisis, transient ischemic attack, and stroke at 30 days. In addition, the incidence of myocarditis, pericarditis, arrhythmias requiring treatment, thromboembolic phenomena, respiratory failure, hemodynamic decompensation, sepsis, and renal failure will be compared between groups at 30 days. Cardiovascular biomarkers related to COVID-19 (troponin, B-type natriuretic peptide [BNP], N-terminal-proBNP, and D-dimer) will also be assessed.

Study population

All patients hospitalized with a suspected diagnosis of COVID-19 will be included in the registry and followed until the diagnosis is confirmed or refuted. Patients ≥18 years of age with a confirmed diagnosis of COVID-19 who are on chronic renin-angiotensin system inhibitor (ACEI/ARB) therapy are potentially eligible for the BRACE CORONA trial. Based on international data, over 90% of the patients included in BRACE CORONA will have the diagnosis of hypertension and less than 10% will have the diagnosis of heart failure.[17,18] Patients using sacubitril/valsartan for heart failure will not be included in the trial. Patients using more than three antihypertensive agents and those hospitalized for heart failure in the last 12 months are not eligible for the trial. Patients with a clinical indication to stop ACEI/ARB therapy, such as those with hypotension, acute kidney injury, and/or shock, will be excluded. Full inclusion and exclusion criteria are shown in Table I.

Randomization and allocation

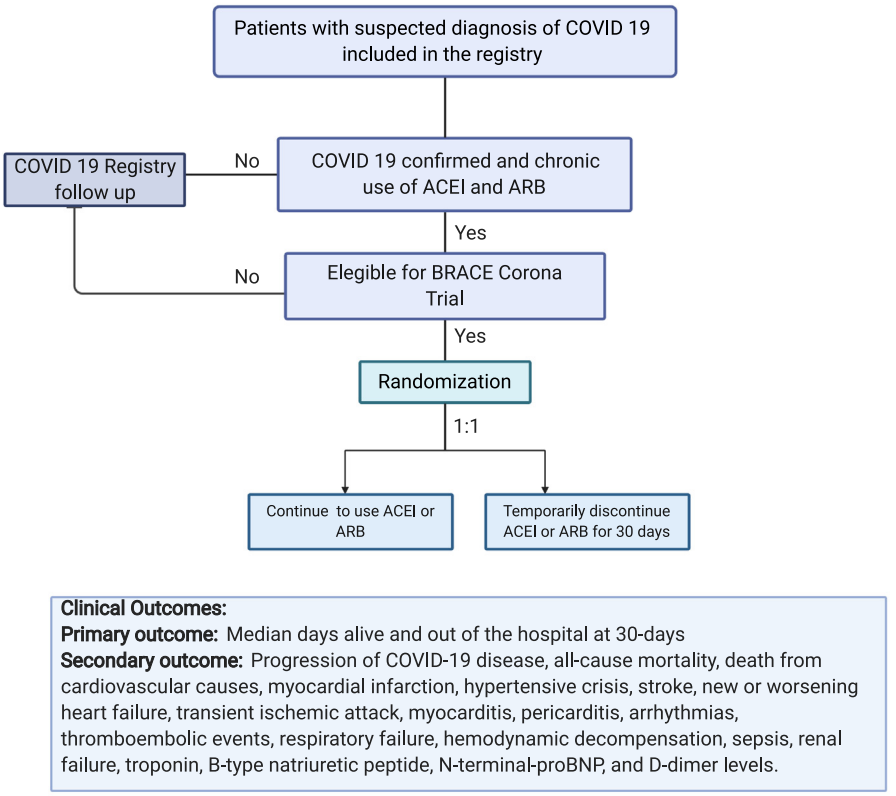
Eligible patients will be randomized using a 1:1 allocation ratio to either continue ACEI/ARB therapy (Group 1) or discontinue ACEI/ARB therapy for 30 days (Group 2).

Trial interventions

Patients randomized to Group 1 will not change their renin-angiotensin system blocker therapy as a result of COVID-19. Dose adjustments and concomitant therapies will be at the discretion of the treating physician.

Patients randomized to Group 2 will discontinue their ACEI or ARB therapy for 30 days. These agents should be replaced by other drugs as needed and at the discretion of the treating physician. β-Blockers should be maintained in those patients who are already using them for heart failure and the study protocol does not recommend any treatment modification beyond renin-angiotensin blockers. The use of hydralazine and nitrates is preferred in patients with heart failure, as they are commonly used and are the preferred treatment for those who cannot tolerate ACEI or ARB therapy. Patients with heart failure who deteriorate after medication withdrawal will be managed based on the hemodynamic profile with the use of diuretics and vasodilators in type B profile. Among vasodilators, the preference in the acute phase will be for short half-life medications with the possibility of using parenteral agents such as nitrates associated with hydralazine or not. The reintroduction of ACEI can be

Figure 3



Study flowchart.

done after clinical compensation, preferably 30 days after randomization with stable renal function. For patients with hypertension, the study protocol recommends thiazide, calcium channel antagonists, or hydralazine as the preferred options (if patients are not already using one of these classes). Other anti-hypertensive agents may be used based on patient and physician preferences (eg, β-blockers commonly used in patients with ischemic heart disease or heart failure). Thus, β-blockers are not recommended as first-line agents unless in the presence of heart failure or ischemic heart disease.[19] In these cases, they should be used regardless of blood pressure control.

The study team will assist treating physicians during the process of drug replacement and decisions will be based on current guidelines.

Concomitant therapies

Since BRACE CORONA is a pragmatic study, the types of ACEI or ARBs used will be defined according to local practice following international guidelines.[19-21] Details around different types of renin-angiotensin system blockers will be reported in the publication of the results.

Since there is currently no specific intervention proven to be beneficial in the treatment of COVID-19, patients will be treated according to current local standards of supportive care without systematic use of experimental therapies.

Study treatment compliance will be assessed based on medical prescription during hospitalization and after discharge.

Study procedures

Data will be collected systematically for patients included in both the COVID-19 registry and BRACE CORONA trial. The data collected will include demographics, cardiovascular risk factors, relevant medical and surgical histories, clinical characteristics, concomitant medications, and laboratory data. A comprehensive biomarker substudy, including proteomic and metabolomic analyses will also be performed. Data collection will be performed during hospitalization until discharge and a phone call at 30 days will be conducted to capture clinical events after discharge. The flowchart including both registry and clinical trial populations is presented in Figure 3. The detailed information collected during

each study visit is provided in the Supplementary Appendix.

Clinical outcomes

The primary outcome of the study will be days alive and outside of the hospital (DAOH) at 30 days. This endpoint will be calculated for each patient and the calculation will be from the date of randomization to 30 days post-randomization. The DAOH endpoint represents the follow-up time (30 days) subtracted from the hospitalization days and/or the days between death and the end of follow-up. This pragmatic endpoint encompasses not only the time to death but also all of the potential non-fatal complications that could lead to a prolonged hospitalization. A sensitivity analysis using a hierarchical approach between death (receiving zero DAOH) and length of hospitalization will also be performed. The main cardiovascular complications that could prolong hospitalization or lead to death will be assessed individually as secondary outcomes.

An independent clinical events committee, whose members are unaware of randomization assignment, will adjudicate the following secondary clinical outcomes: death from cardiovascular causes, myocardial infarction, new or worsening heart failure, stroke, and transient ischemic attack at 30 days. All potential events detected in the electronic case report forms for patients included in the trial will trigger the adjudication process. Detailed definitions of the secondary outcomes are described in the Supplementary Appendix.

Sample size calculation

The initial expected sample size for BRACE CORONA will be around 500 patients; however, this number may increase or decrease according to the recruitment rate, event rate, and data safety monitoring board (DSMB) assessments for efficacy, safety, and futility. Assuming a standard deviation of 4 days and DAOH of 24 days (based on the ongoing COALIZAO I study in Brazil [NCT04322123]), 500 patients will have 90% power to detect a mean ratio of at least 1.10. We estimate the full cohort of patients will be enrolled in 3 to 4 months; however, this may be extended depending on the recruitment rate. There are currently no randomized studies in this field with reported outcomes and event rates to allow an accurate calculation of the sample size.

Statistical analysis

In order to maintain the benefits of randomization, the primary analysis will follow the intention-to-treat principle. Continuous variables will be described as medians (25th, 75th percentiles) or mean ± standard deviation according to the distribution. Medians will be compared using the Kruskal-Wallis test and means will be compared using the t-test. Categorical variables will be described by absolute and relative frequencies and the proportions will be compared using the Chi-square test. P-values <0.05 will be considered statistically significant.

As the primary outcome will be measured as DAOH at 30 days, the analysis will be based on the median of this outcome. The analysis of the distribution of DAOH at 30 days will be presented as histograms for the two groups (with and without discontinuation of renin-angiotensin system inhibitors) and the median and 25th and 75th percentiles of the general population and of each group will be calculated. The comparison between the groups will be made using a Quasi-Poisson model. Results will be presented as mean ratios between study groups with the respective 95% confidence intervals. Interaction tests will be performed for specific subgroups, including sex (male vs. female); age (>65 vs. ≤65 years); days of symptoms (divided into tertiles); history of myocardial infarction (vs. no); history of stroke (vs. no); history of heart failure (vs. no); history of hypertension (vs. no); use of ACEI vs. use of ARB; and length of ACEI or ARB use prior to enrollment.

Secondary endpoints of mortality at 30 days and cardiovascular events at 30 days will be compared by log binomial models, and relative risks with the respective 95% confidence intervals will be reported.

All analyses will be performed using R software in its most current version.

Organizational structure

Funding and trial oversight

This is an investigator-initiated study with financial support from D'Or Institute for Research and Education (IDOR). No extramural funding was used to support this work. The study is being coordinated by IDOR and the Brazilian Clinical Research Institute (BCRI). Both institutions will coordinate data management; IDOR will manage the database and the BCRI will manage the clinical events adjudication process. The Executive and Steering Committees, together with the operational teams from IDOR and BCRI, will oversee the medical, scientific, and operational conduct of the study. The Executive and Steering Committee members are responsible for the reporting of the results and the drafting and editing of this and forthcoming manuscripts. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

An independent DSMB will monitor safety and efficacy data on an ongoing basis with access to unblinded data. The DSMB will review the primary outcome of the study as well as the secondary outcomes through weekly evaluations and also through 2 formal interim analyses, including the heart failure group. The DSMB will use a p-value <0.001 in the interim analyses to declare a statistically significant difference in outcomes between

study groups to guide their recommendations.[22,23] An overall $P < .05$ will be used to declare statistical significance at the end of the study.

An independent clinical events classification committee will adjudicate the causes of death and the clinical outcomes described as secondary outcomes, such as myocardial infarction, stroke, hypertensive crisis, and new or worsening heart failure.

Discussion

The majority of patients affected by COVID-19 will have favorable clinical outcomes during the acute phase of the infection.[24] Nevertheless, the risk of severe forms of the infection increases significantly according to age and the presence of chronic comorbidities.[25,26] Among these comorbidities, cardiovascular diseases are particularly important because of the intrinsic risk of adverse outcomes and the prevalence of these conditions in the global population.[25,26] Hypertension, diabetes, heart failure, and coronary heart disease are common comorbidities associated with worse prognosis among patients with COVID-19; however, the higher risk detected in this group could also be due to other related factors that may facilitate infection and increase propagation of the virus.[27]

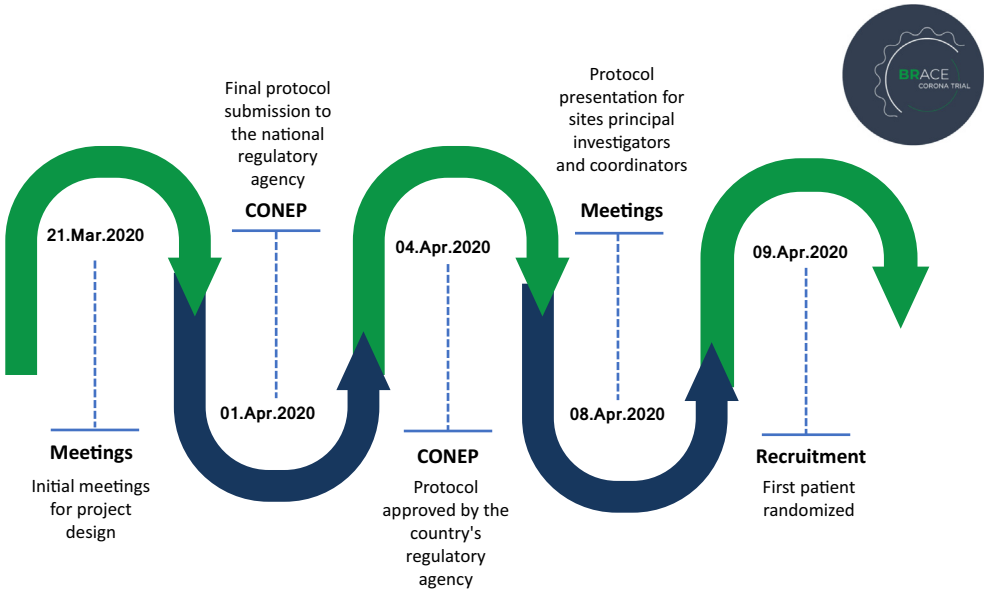
Renin-angiotensin system inhibitors are routinely used for common cardiovascular conditions.[19-21] The benefits in reducing cardiovascular events are well established, mainly in long-term analyses of patients with chronic use of these therapies.[28,29] However, in some acute clinical conditions, these drugs are temporarily discontinued due to an imminent risk higher than the potential short-term benefit of these therapies.[30] There is currently an intense debate about the suspension or maintenance of chronic ACEI/ARB therapy in patients with COVID-19.[12,13,27,31,32]

The BRACE CORONA trial was designed to test the impact of discontinuation compared with maintenance of chronic ACEI/ARB therapy in patients with COVID-19. This is one of several questions that physicians are facing in the setting of COVID-19 and data are needed from randomized clinical trials like BRACE CORONA. Because renin-angiotensin system inhibitors increase levels of ACE2, a protein that facilitates coronavirus entry into cells, there are concerns that these drugs could increase the risk of developing a severe and fatal form of COVID-19.[15] The presence of ACE2 in alveolar epithelial cells makes the lungs a preferred site of entry for the virus, which explains the respiratory manifestations in patients with COVID-19. This hypothesis of worse outcomes associated with the use of ACEI or ARBs in patients with COVID-19 was recently shown in observational studies.[25,26] However, a cause-effect relation between the use of ACEI or ARBs and adverse events in COVID-19 cannot be established since many confounding factors could explain a worse or better prognosis for these patients in observational analyses. In a recent retrospective study of hospitalized COVID-19 patients, all-cause mortality was lower among patients on ACEI/ARB therapy when compared with those not using ACEI/ARBs.[33] An observational analysis from a single-center study showed that ACEI/ARB use was not associated with severity of COVID-19 infection or worse outcomes in hospitalized patients with hypertension.[34] Nonetheless, the effect of renin-angiotensin system inhibition on ACE2 is uncertain and the potential harm related to this mechanism is not well defined.[31,32] In addition, the use of ACEI or ARBs could be beneficial not only due to the well-known cardiovascular protection,[32] but also because of the potential respiratory system protection in patients affected by severe respiratory disease.[15,27] Considering that these high-risk patients with cardiovascular disease and COVID-19 are commonly hospitalized, the decision regarding the best approach for the management of renin-angiotensin system inhibitors is critical. In a scenario of apparent equipoise without high quality scientific evidence, the medical decisions in clinical practice have been heterogeneous. Thus, a randomized clinical trial is necessary to guide practice.

A multicenter randomized clinical trial conducted during a pandemic should follow the same steps commonly adopted in pivotal phase III trials. However, the critical and urgent nature of a pandemic allows the implementation of more efficient research processes, including electronic and verbal informed consent, which hopefully will serve as a legacy to be followed during non-pandemic times. In a new and threatening situation like the COVID-19 pandemic there is no specific evidence to guide medical therapy, yet there is an urgent need to quickly answer the clinical questions that arise in order to guide treatment of the hundreds of thousands of people infected with a potentially lethal disease. Collaborative pragmatic studies are one of the best solutions in this scenario.[5] BRACE CORONA took less than 3 weeks from protocol development to first patient randomized, including national ethics board review and approval, which is unprecedented in Brazil (Figure 4). The COVID-19 registry is already collecting the key clinical variables and outcomes that will be used for the randomized trial. Adding randomization to this structure allows for an efficient process, which can provide the scientific community with a streamlined approach to answer a relevant clinical question with less bureaucracy and at lower cost. In addition, clinicians on the frontline, who are already very interested in answering this medical question, will be highly engaged with the trial.

Source documents from potential events will be adjudicated by a clinical events classification committee. Since many different complications could occur due to the interaction between COVID-19, baseline cardiovascular condition, and therapies used by these patients, the primary study outcome chosen for BRACE CORONA (DAOH at 30 days) was also very pragmatic and captures all relevant in-hospital complications. Therefore, DAOH

Figure 4



Study timelines.

will ultimately represent a meaningful patient-centered outcome. The efficient model of a registry-based randomized trial, which is the first of its kind in Brazil, has already been applied successfully in other countries [35,36] and represents a unique opportunity during the global crisis of COVID-19 that could serve as a relevant legacy to the medical community.

Conclusion

BRACE CORONA is a multicenter randomized trial in patients hospitalized with COVID-19 on renin-angiotensin system blockers that aims to determine whether discontinuation compared with maintenance of these drugs increases days alive and out of the hospital. The results of this study will help guide medical decision making regarding the best management of a high-risk population of patients infected with SARS-CoV-2. Most of all, BRACE CORONA reinforces the importance of pragmatic randomized clinical trials, which are effective models to provide rapid answers to inform clinical practice, especially in situations that require appropriate, rapid, and high-quality evidence to guide medical practice.

Declaration of competing interests

RDL: Research support from Bristol-Myers Squibb, GlaxoSmithKline, Medtronic, Pfizer; Consulting fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Medtronic, Merck, Pfizer, Portola.

AVSM: Consulting fees from Pfizer, Bayer, Novartis, Daiichi-Sankyo, Zodiac and Roche. PGMBS: Fees and Research support from Pfizer.

RJM-B: No conflicts of interests.

AF: Consulting fees Pfizer, Bayer, Daiichi-Sankyo, Boehringer, Servier.

GASA: Consulting fees from Pfizer and Servier.

ASS: No conflict of interest.

DCA: Research support from Boehringer Ingelheim. Consulting fees Pfizer, Bayer, Daiichi-Sankyo, Boehringer, Servier.

LM: No Conflict of interest.

MFS: No Conflict of interest.

NZS: No Conflict of interest.

CMG: No conflict of interest.

CBG: Research Grants: AstraZeneca, FDA, NIH, GSK, Medtronic, Novartis, Apple, Boehringer Ingelheim, BMS/ Pfizer, Janssen. Consulting: AstraZeneca, Espero, GSK, Medtronic, Novartis, Boehringer Ingelheim, Boston Scientific, BMS/ Pfizer, Daiichi Sankyo, Merck, Roche, Eli Lilly, Janssen.

JHA: Research support from Boehringer Ingelheim, Bristol-Myers Squibb, CryoLife, CSL Behring, GlaxoSmithKline, US Food and Drug Administration, US National Institutes of Health, XaTek; Consulting fees or honoraria from AbbVie, Bayer, Bristol-Myers Squibb, CryoLife, CSL Behring, Novo Nordisk, Pfizer, Portola, Quantum Genomics, US Veterans Administration, XaTek,

Zafgen. Conflicts of interest disclosures available at http://www.dcri.duke.edu/research/coi.

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Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2020.05.002.

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