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UNIVERSITY OF OTTAWA
HEART INSTITUTE
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Final Technical Report

Project IDRC No. 109553

Improving Outcomes in Individuals with COVID-19 with Renin-Angiotensin System Inhibition: The COVID-RASi Trial

Study Title:

Evaluation of the potential benefit of renin-angiotensin system inhibitors (RASi, ACEi/ARB) in high-risk patients with COVID-19. The COVID-RASi Trial.

Abstract

The COVID-19 pandemic has impacted the health and economy of countries around the world, bringing a major challenge for physicians and healthcare systems, due to the lack of evidence-based therapy. Patients admitted with COVID had a higher risk for worsening conditions requiring ICU, ventilation, or dialysis, and high mortality. At the peak of the pandemic, many patients with COVID-19 infections were older, with pre-existing cardiovascular (CV) conditions (e.g., prior heart attack, stroke, peripheral arterial disease), or had risk factors such as hypertension, obesity, diabetes, or chronic kidney disease. The scientific and clinical implications showed these patients had higher mortality, confirming the major interactions with the cardiovascular system. While the role of renin-angiotensin system inhibitors (RASi) was known to be protective of the cardiovascular system, and the evidence also showed that the SARS-CoV-2 virus uses the Angiotensin-Converting Enzyme 2 (ACE2) receptors, more research was needed to find evidence-based answers to show if RASi medications are protective for patients with COVID-19.

We have conducted a pragmatic, international, randomized trial to evaluate the potential benefit of angiotensin modulators on outcomes of COVID-19 among patients at high-risk for cardiovascular disease. The Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Blockers (ARBs), already used commonly to treat high blood pressure, may be beneficial to patients at high risk for heart disease, with the potential to save many lives and decrease complications and hospital admissions. These types of medications are readily accessible to many patients around the world at very affordable prices and could be used to prevent complications after COVID-19 infections.

The trial investigators worked together with a network of institutions and built an important South-North collaboration between the Brazilian, Mexican, and Canadian teams. The project has recently joined a COVID-19 consortium with investigators and scientists from the United States, Australia, and the United Kingdom, to combine data and draw conclusions on population outcomes.

During the pandemic, the virus has evolved through more variants and a younger population was also affected by complications. Even after the development of targeted COVID vaccines, more people had symptoms that persisted for weeks, even months after a COVID-19 infection. To address the long-COVID syndrome, the project has also focused on studying the residual symptoms of study participants, through standardized quality-of-life questionnaires, aiming to bring answers to the new challenge resulting from the pandemic.

The Research Problem

The rationale for the project was to determine if COVID-19 patients who have conventional indications for ACE inhibitors, would benefit from the introduction of RASi (ACEi or ARB). The investigators' goal was to run a randomized trial to evaluate the potential benefit of angiotensin modulators on outcomes of COVID-19 among patients at high-risk for cardiovascular disease. A positive trial would potentially allow easy application of these readily accessible types of medications to many patients around the world at very affordable prices.

The trial has encountered many challenges with the enrolment of high-risk COVID-19 patients and the evolution of the pandemic over time. While initially, the virus had a higher rate and mortality in older patients with added co-morbidities, over time it started to impact a younger and healthier population. The study investigators have adjusted inclusion/exclusion criteria to allow the recruitment of younger patients affected by the new variants of the virus.

Objectives

The main objectives of the project were to determine

- *if RASi therapeutics, ACEi or ARB, has a beneficial effect in high-risk elderly patients with COVID-19 infections, in terms of ICU admission, ventilator requirement or death.*
- *if there are differences between ACEi vs ARBs, in these populations*

The hypothesis notes that exposure to ACE inhibitors or ARBs will decrease combined endpoints of death, ventilation/dialysis, ICU admission, and major adverse cardiovascular events (MACE, including myocardial infarction, stroke, and heart failure). RASi treatment (either ACEi or ARB) will decrease individual endpoints when compared to no RASi exposure overall. The patients were recruited during hospital admission (inpatients) and as outpatients. If the patient was recruited as an outpatient, the subsequent admission to a hospital was included as a component of the primary endpoint. The secondary endpoints include all-cause hospitalization, cardiovascular hospitalization, and cardiovascular mortality at 30 days, 180 days, and 365 days after recruitment in the study.

We aim to conduct an analysis of the data collected at baseline and follow-up at 24-hours, 7-days, 28 days, 6- months, and one year to assess the endpoints of the trial, including the hierarchically ranked end-points of death, mechanical ventilation, ICU admission, hospitalizations (for outpatients) and cardiovascular MACE (heart failure, stroke, myocardial infarction, renal failure).

With the pandemic evolution, vaccine development, and with the increasing potential of persistent

and recurrent symptoms for many patients who experienced a COVID-19 infection, the investigators also added a new primary endpoint of quality of life at the one-year follow-up, using standardized questionnaires (EQ-5D-5L).

Methodology

The design was a randomized trial to evaluate the potential benefit of angiotensin modulators on outcomes of COVID-19 among patients at high-risk for cardiovascular disease. It was a prospective, randomized trial in RASi naïve patients (not exposed to RASi in the past), randomized to initiation with either ACEi or ARBs or no RASi in a 1:1:1 ratio. The study was multi-center, conducted in major centers treating COVID-19 patients in-hospital and in various outpatient settings. While the patients were followed up by their physician according to the standard of care, the study sites completed research-related telephone interviews at 24 hours, 7 days, and 28 days to assess the patient's clinical status, side effects, and the achievement of clinical endpoints. The patients were encouraged to continue to follow up with their primary physician to determine if they should continue with the assigned medication beyond the initial 28-day period. The study investigators strongly encouraged physicians to continue treatment if there were no side effects. This study did not impose any restrictions on treatments or testing. Physicians were encouraged to follow the established COVID-19 care pathway at each institution for their patients. Chart review and telephone follow-up were conducted at 6 months and 12 months and will provide data on clinical and health outcomes. Due to the evolution of the pandemic, the focus was shifted toward residual symptoms related to the long-COVID syndrome, with follow-up telephone calls up to three years after the COVID-19 infection. To measure the quality of life for study participants with persistent symptoms, standardized questionnaires were included (EQ-5D-5L).

The initial study protocol aimed to enroll participants over the age of 65 years old, with risk factors for heart disease (such as hypertension, diabetes, prior myocardial infarction, or stroke). The table below underlines the changes in the inclusion criteria for the trial, that have been addressed through Research Ethics Board amendments during the pandemic, as new, various variants of the virus have affected a younger and healthier population.

The Inclusion Criteria - Patients with COVID-19 diagnosis with laboratory confirmation within the last 30 days and age as detailed in the table below.

Inpatients	***Outpatients***	***Additional***	***Date***
Age ≥ 65 years	*Age ≥ 65 years*	AND at least one of the following: Hypertension (BP>140/90 mmHg), diabetes, obesity with BMI>30, existing coronary artery disease, prior myocardial infarction, prior stroke, existing peripheral vascular disease, existing heart failure (LVEF>40%), or renal dysfunction (30 ≤ eGFR < 90 ml/kg/min)	*May 8, 2020*
Age ≥40 years	Age ≥ 65 years	*None*	*May 11, 2021*
Age ≥ 18 years	Age ≥ 40 years	*None*	*Nov 30, 2021*

With the new virus variants that have emerged, younger patients, with or without risk factors for cardiovascular disease, had an increased risk of hospital admissions and major complications due to COVID-19. During the hospitalization for SARS-CoV2 infection, investigators considered that ACEi/ARB may have protective effects in younger patients. A younger population that was affected by a moderate disease that did not require hospitalization could also benefit from RASi protection. We have anticipated that the lower age for admitted patients will boost recruitment.

Due to delays in Health Canada approvals and a pretrial special COVID audit, and complex logistics with the startup at sites in South America, the recruitment had a delayed start, on Jan 27, 2021, at the sites in Canada and in April 2021 at sites in Brazil. The recruitment was then relatively brisk with 142 participants by Nov 2021, 266 participants by April 2022. We have achieved total recruitment of 360 participants by November 30, 2022. The originally calculated sample size (1155 participants) could not be reached, due to the many challenges encountered to recruit COVID-19 participants. These included changes in virus characteristics, evolving COVID-19 patient profile, pre-existing medication intake, competing studies, and multiple co-morbidities. To address this concern, the investigators will collaborate with other scientists from around the world, who conducted similar studies with RASi medication for COVID-19 patients and encountered similar challenges. The collaboration and data analyzed from the combined studies will increase the power that could not be reached through individual studies.

Project activities

The interim reports have addressed the project activities and changes in the study timelines due to the pandemic development. The SARS-Cov-2 virus was a novel virus, that posed many challenges to people and healthcare providers and resulted in an unpredicted development of the pandemic, which has affected the trial progression.

While the Research Ethics Board approval was expedited and obtained in July 2020, there were unexpected delays in launching the trial, in Canada and at the international sites, due to complex logistics. The trial required Health Canada approval, as ACEi/ARBs were considered "off-label" when given to COVID-19-positive patients. Health Canada authorization was obtained under the Interim Order for COVID-19 studies, on Oct 16, 2020. Once the sites were activated, many sites encountered challenges with the enrolment of high-risk COVID-19-positive patients. During the past years, with various "waves" of the pandemic and new virus variants, the number of eligible patients has fluctuated, and COVID-19 serious outcomes have affected a younger population. The researchers have modified the study criteria to address these challenges and expand trial eligibility, while additional REB and Health Canada approvals were required.

In Brazil and Mexico, the project leaders worked with Atlantis, a Clinical Research Organization (CRO), to oversee the regulatory process and site monitoring in Brazil. To mitigate the challenges in recruitment, Atlantis set out new initiatives in Brazil, to be able to access more eligible patients, seen at various hospitals and Public Health Units in Sao Paolo. The initiatives required additional funding for implementing the regulatory requirements (additional Legal Ethics Compliance (LEC) and CONEP approvals and approvals for co-participating sites) and for addressing the recruitment at the sites. Additional funding has also been provided to support human resources at sites with a higher number of COVID-19 cases, to boost enrollment at those sites. Since access to RASi medication has been another challenge to recruiting participants at some of the sites in Brazil, funding has similarly been provided to support the use of RASi for these participants.

Project Outputs

The initial estimate of the project duration was 12 months. However, due to the challenges posed by the unpredictable evolution of the pandemic, the project duration has been extended, for a total of 29 months. Since the start of recruitment for the trial was delayed until Jan 27, 2021, we have continued recruitment until Nov 30, 2022. We are in the final stages of data collection for study participants and the study data has not been yet analyzed. The investigators are planning

a longer-term extended follow-up (for up to three years, supported by internal funding) for study participants.

A preliminary analysis of the data collected at baseline and follow-up at 24 hours, 7-days, 28 days, 6- months, and one year will be completed in the ensuing months, to assess the study objectives, as underlined by the initial study protocol: hierarchical achievement of ranked end-points of death, mechanical ventilation, ICU admission, hospitalizations (for outpatients) and cardiovascular MACE (heart failure, stroke, myocardial infarction, renal failure). The additional endpoint, as assessed by persistent symptoms due to long-COVID syndrome and measured by the quality-of-life questionnaires, will be revised after the one-year follow-up for all study participants.

Through the collaboration with the investigators from Brazil and Mexico, a total of 23 active sites from Brazil and 8 sites from Mexico have joined the project and have been enrolling patients in the COVID-RASi trial.

Other investigators conducting COVID-19 projects around the world have also encountered challenges in recruitment. The study investigators have joined a COVID-19 consortium with scientists from the United States, Australia, and the United Kingdom, to combine data from patients in COVID-19 trials, also treated with RASi medication, and draw conclusions regarding the population outcomes. The individual participant data analysis collaboration will aim to address clinically relevant questions about the efficacy and safety of the use of renin-angiotensin blockade for COVID-19 disease that cannot be addressed in single trials and to maximize global learnings on the use of these agents in different settings and population. The collaboration will assess important outcomes that, even though they may be common, may still have limited power in individual trials, while meta-analyzes could provide a better estimate. There will also be analyses by sub-groups, for example by age, gender, or different ethnicities. We are currently collaborating with other national researchers to develop new tools and guidelines to assess long-COVID symptoms. This is a continuous effort that would lead to a better understanding and treatment of the long-COVID syndrome.

During the study recruitment period, the trial was promoted at local research meetings, at The University of Ottawa Heart Institute, at the Ottawa-Toronto Heart Summit, and at the Canadian Cardiovascular Congress, aiming to raise awareness about the study and increase the number of sites participating in the trial. Once the data from the trial will be analyzed and potentially

combined for additional power with the participating studies in the COVID-consortium, the results will also be presented to national and international conferences in Cardiology. The investigators aim to present at the future Canadian Cardiovascular Congress, American Cardiovascular Congress, and European Cardiovascular Congress. The target journals for publication of articles derived from the trial would be Cardiology and basic science focused, such as the Canadian Medical Association Journal (CMAJ), Canadian Journal of Cardiology (CJC), Journal of American College of Cardiology (JAAC), Journal of American Medical Association (JAMA), British Medical Journal (BMJ), European Heart Journal (EHJ) and other relevant peer-reviewed scientific journals and methods papers.

Project outcomes

The trial has adapted to the pandemic evolution, with the emergence of various virus variants and the development of vaccines. Early in the pandemic, most people who developed complications were elderly, with risk factors for heart disease, or with compromised immunity due to other conditions. The researchers' main goal was to treat the COVID-19 disease and prevent the short-term complications related to the coronavirus, through the potential protective effect of RASi medication. Later in the pandemic, the trial was still relevant, as more and more people contacting the virus were younger, without risk factors for heart disease or compromised immunity, and have developed long-term symptoms after a COVID infection. Through data analysis, we will assess the potential benefit of the treatment with RASi medication on long-term outcomes. Even if the vaccines have become widely available, currently there is no treatment for long-term consequences related to COVID. The study team continues to follow up with study participants to find answers regarding the long-term impact of COVID and the changes in quality of life (problems performing daily activities, anxiety, and depression, persistent fatigue or shortness of breath, to list some of the symptoms that can linger after a COVID-19 infection). While standardized, validated questionnaires (EQ-5D-5L) have been used as part of the follow-up of study participants, a new questionnaire, to include the potential long-term symptoms, has been developed through the study and translated into Spanish and Portuguese, to be used during the trial. The participants enrolled in the study, randomized to the treatment group, have been treated with RASi medication for 28 days and encouraged to continue the medication for long-term id they did not experience side effects. The long-term potential benefit of the RASi medication will be assessed at the time of each follow-up visit.

For this relevant project, the study investigators have collaborated with scientists in North and South America during the multiple waves of the pandemic and after the vaccination campaigns.

In Brazil, we have collaborated with Dr. Jose Nicolau, from Instituto de Coraçao (INCOR) in Sao Paolo. He contributed to the project as the lead investigator for all the sites in Brazil, bringing collaboration with local investigators from across the country. Those included hospitals in Sao Paolo, Goiania, Itabuna, Belo Horizonte, Campo Grande, Passo Fundo, Natal, Reboucas, Curitiba, Canoas, Campinas, Recife, Maceio, Porto Alegre, Fortaleza.

In Mexico, we have collaborated with Dr. Jorge Escobedo, from the Instituto Mexicano del Seguro Social (IMSS), in Ciudad de Mexico. He contributed to the project as the lead investigator for the sites in Mexico, bringing collaboration with local investigators from hospitals in Ciudad de Mexico, El Marques (Queretaro), La Margarita (Puebla), and Xalapa (Veracruz).

We have conducted a successful collaboration with participating sites from South America and will contribute to making a global impact in treating this new and evolving disease. We will conclude the study with important results that will help the researchers better understand the virus, its variants and various health complications, and the effect of COVID-19 on the long-term health of the people affected by the infection.

The international collaboration with scientists from South America, specifically from Brazil and Mexico, has strengthened the relationships between the investigators, who will support each other on additional projects in cardiology in the upcoming years, to address new health challenges in their field.

Overall Assessment and Recommendations

As mentioned in the Methodology section, the originally calculated sample size (1155 participants) could not be reached, due to the many challenges encountered to recruit COVID-19 participants. These included changes in virus characteristics, evolving COVID-19 patient profile, pre-existing medication intake, competing studies, and multiple co-morbidities. To address this concern, the investigators will collaborate with other scientists from around the world, who conducted similar studies with RASi medication for COVID-19 patients and encountered similar challenges. The collaboration and data analyzed from the combined studies will increase the power that could not be reached through individual studies.

The international collaboration with scientists from Brazil and Mexico has strengthened the relationships between the investigators, who will support each other on additional projects in cardiology in the upcoming years, to address new health challenges in their field. A national collaboration between Canadian scientists on long-COVID syndrome projects has been developed and will continue to bring answers to this new condition.

The COVID quarantine and isolation requirements have led to more virtual communication, not only with the study team from various sites but also with the study participants, as face-to-face communication has been reduced during the pandemic. We have learned that a novel disease brings additional anxiety, becomes overwhelming for patients, and brings reluctance to participate in research. We have understood that COVID-19 not only brought severe health, economic and societal challenges but also patient vulnerabilities and consequences that have been experienced disproportionately across various populations.

The study has brought awareness that today we face the double challenge of not only trying to prepare for the next pandemic, but also dealing with the chronic nature and sustained sequelae of the current pandemic with repeat waves of infection, residual long-term symptoms (long-COVID), and increased cardiovascular disease risks, which reduces population resilience for future viruses.

We will need to expand on new trials that address ongoing gaps in knowledge, to be able to provide resources, infrastructure, networks, and capable people to rapidly respond to emerging health threats and opportunities. We need ongoing answers to important long-term questions with the current pandemic and rapidly re-deploy to address novel vaccines or treatments for a new emerging pandemic.