COVID-ARB Protocol Cover Page

Study Title: Randomized Open Label study of Standard of Care Plus an Angiotensin II Receptor Blocker Compared to Standard of Care Alone to Minimize the Progression to Respiratory Failure in SARS-CoV-2 Infection

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Title:
Randomized Open Label study of Standard of Care Plus an Angiotensin II Receptor Blocker Compared to Standard of Care Alone to Minimize the Progression to Respiratory Failure in SARS-CoV-2 Infection

Primary Objective:

To identify whether or not Angiotensin Receptor Blockers (ARB) can halt the progression to respiratory failure requiring transfer into the intensive care unit (ICU) and mechanical ventilation in subjects with mild to moderate hypoxia due to COVID-19.

Secondary Objectives:

1. To identify whether or not the use of Angiotensin Receptor Blockers (ARB) in mild to moderate COVID-19 subjects decreases the transfer from a non-ICU bed to an ICU bed.
2. To identify whether adding an ARB to the standard of care (SOC) for mild to moderate disease will reduce days requiring oxygen therapy.

Hypothesis: We hypothesize that the addition of an ARB will be beneficial in abating acute lung injury in subjects in early stages of SARSCoV-2 induced hypoxia. This abatement may decrease utilization of high-level ICU services including mechanical ventilation.

Background: The Coronavirus has been a known pathogen in animals since the early 1970's that resulted in gastrointestinal symptoms. Bats have been identified as the main carrier and cats have been identified as the primary means of transmission to other animals. In late 2019, the Coronavirus evolved to infect the human respiratory system (SARS-CoV-2) as seen in the outbreak in Wuhan, China. The World Health Organization named the SARS-CoV-2 epidemic COVID-19.

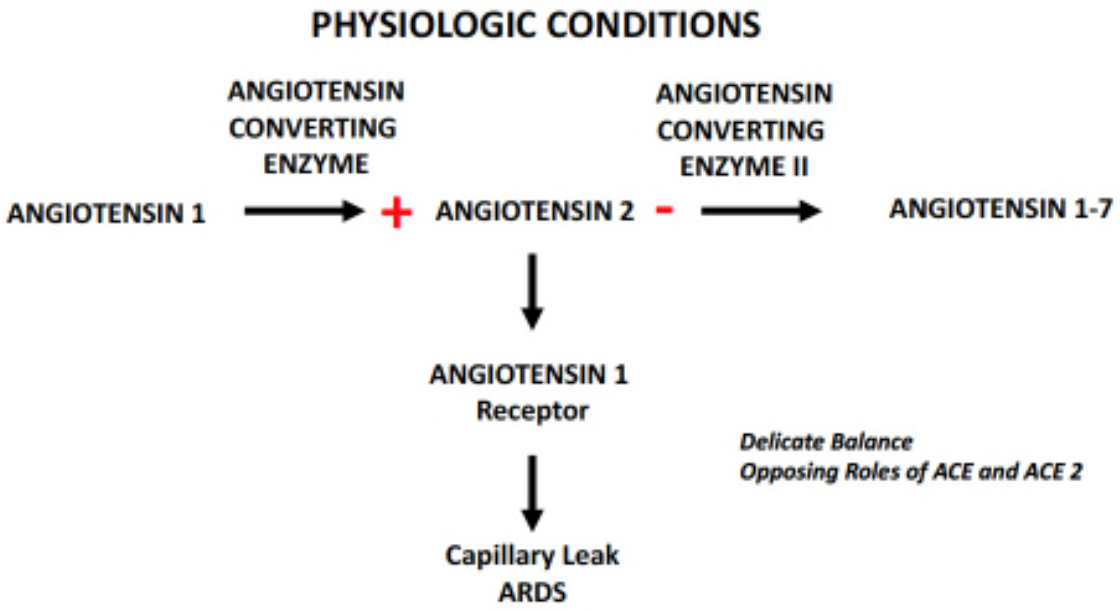
The current mortality rate (17MAR2020) is not well described because of the shortage of laboratory testing assays worldwide. Using WHO data on the cumulative number of deaths to March 1, 2020, mortality rates would be 5.6% (95% CI 5.4–5.8) for China and 15.2% (12.5–17.9) outside of China (Baud et al. Lancet Inf Dis; Mar, 12, 2020, https://doi.org/10.1016/ S1473-3099(20)30195-X).

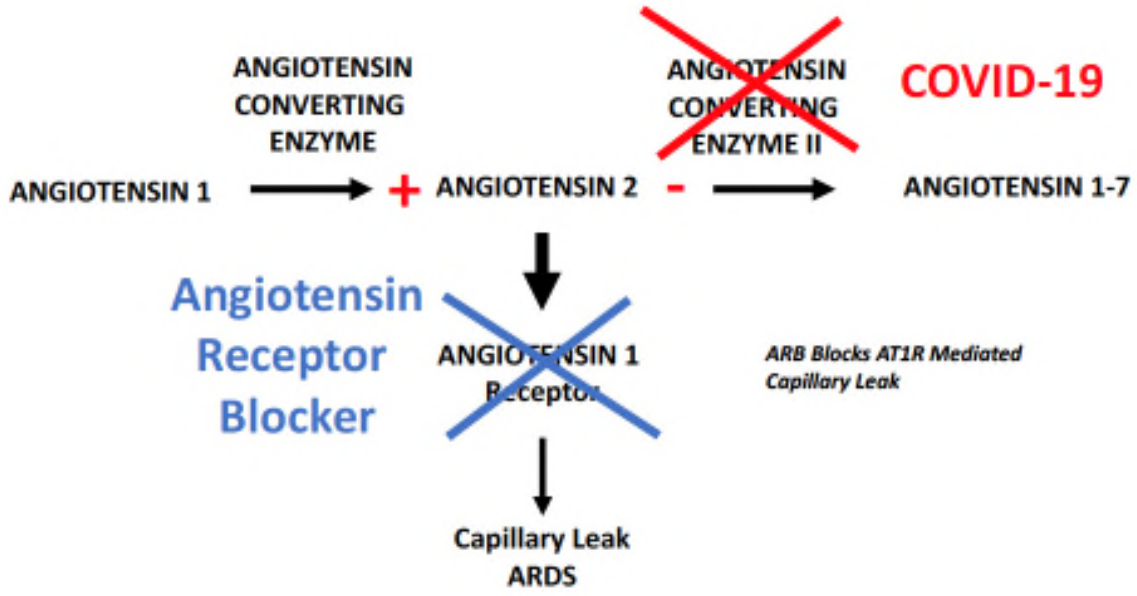
At this moment (17MAR2020), grave concerns are raised about the ability of the US healthcare system to handle the demand of subjects affected by the COVID-19 pandemic. Specifically, there is concern raised by the ability to handle sick subjects and those requiring mechanical ventilation. There are an estimated 160,000 ventilators in the US. Therefore, if only 5% of the 320 million US population were infected with COVID-19, and only 2% of those required ventilation, surge capacity to provide this lifesaving supportive care would be overwhelmed.

Therefore, while the spread of virus continues to escalate logarithmically, the ability to abort subjects away from the path of acute lung injury requiring mechanical ventilation would be a huge service to healthcare. The average time from hypoxia to mechanical ventilation is nine days. Theoretically, the opportunity to effectively intervene with an ARB is soon after admission for hypoxia induced by SARS-CoV-2 and many days prior to Acute Respiratory Distress Syndrome (ARDS).

To date (17MAR2020), there have been very few human studies analyzing the effects of utilizing ARBs in the critical care setting where subjects have confirmed COVID-19 infection. The COVID-19 epidemic has already claimed more human lives than SARS and MERS combined (WHO website MAR-2020). The majority of fatalities from COVID-19 have resulted from respiratory failure.

Data has accumulated since the 2002 SARS epidemic that use of angiotensin receptor blockers may be beneficial in reducing SARS-induced respiratory failure, as summarized recently (Gurwitz, *Drug Dev Res* 04MAR2020).





It is currently believed that 80% of COVID-19 subjects will require no medical treatment, 15% will require non-ICU medical care, and 5% may require ICU admission. The goal of this study is to decrease the rate of subjects requiring ICU hospitalization and decrease the demand for mechanical ventilation.

ARBs may prevent respiratory complications for two reasons. First, ARBs compete with the coronavirus's binding site in the lung. That, in turn, has been shown to decrease the damage to the lung. Second, the ARBs decrease the inflammatory response in the lung that the coronavirus causes. By these two mechanisms, the ARBs decrease the lung damage and allows the body (host) to effectively and naturally fight against the virus.

Number of Subjects: 200

Inclusion Criteria:

1. Confirmed COVID-19 positive test result.
2. Mild to moderate respiratory symptoms of COVID-19. Systolic blood pressure ≥ 100 mmHg.
3. Screen within 3 days of a positive COVID-19 test.
4. Age ≥18 years old.
5. Access to a phone in the hospital room or an electronic device that is capable of receiving phone or video calls.
6. Able to read/write/speak English or Spanish fluently.
7. Subjects must have the capacity to provide consent or an appropriate LAR to provide informed consent
8. Negative pregnancy test for women of childbearing potential and subject is randomized to the study arm.

Exclusion Criteria:

1. Severe allergy to any ARB, including angioedema and ACE inhibitor-induced angioedema
2. In the intensive care unit at screening.
3. Home meds include any kind of ACE inhibitor or ARB
4. Acute Kidney Injury (50% reduction in GFR from baseline at admission to any time during treatment in the study treatment arm)
5. Hyperkalemia >5.0 mmol/L at baseline or any time during treatment in the study treatment arm
6. Creatinine Clearance < 30 ml/min at baseline or any time during treatment in the study treatment arm

Age of Subjects: ≥ 18 yrs of age

Gender of Subjects: Either male or female

Racial and Ethnic Origin: Non-specific

Vulnerable Subjects: Hospitalized subjects

Study Design: Investigator initiated, open label, multicenter, two arm, randomized study to compare the impact of adding an ARB to the Standard of Care (SOC) to the SOC without an ARB. Randomization ratio will be 1:1.

Procedures and Study Visits:

1. The PI will be notified of a COVID-19 tested positive patient via hospital generated alert.
2. The PI or designee will prescreen the patient using the inclusion and exclusion criteria within 3 days of patient testing positive to COVID-19.
3. PI will contact the study team, if the patient passes prescreening.
4. The CRC will obtain an informed consent from the subject or legally authorized representative (LAR) either electronically utilizing DocuSign® or with a paper copy utilizing an impartial witness:
    a. Sharp Healthcare will utilize DocuSign® for the signing of the consents in order to be compliant with the infection control measures taken place for Highly Infectious Diseases. Below are the steps of the DocuSign® procedure:
        i. Upon receiving confirmation of the subject passing prescreening, the CRC will call the subject/LAR to assure the consent process is being conducted in a private place and manner and obtain a valid email address. If the subject does not have a valid email address, instructions will be provided to help them set up an email address account. The CRC will also ask the subject/LAR if he or she would prefer to have the consenting process conducted via video call if this technology is available at the setting of consent.
        ii. If the subject/LAR agrees to participate the CRC will send the DocuSign® instructions via email to the subject.

iii. The CRC will send out Consent via DocuSign® to the subject/LAR (it will appear in their email inbox).
iv. Subject/LAR will use any electronic device that is able to access DocuSign® email and open consent. Subjects/LARs may be instructed to place their phone on speaker mode (while maintaining privacy) to ensure that they can see the consent during the process.
v. The CRC will consent subjects via phone. CRC will ask the subject/LAR to verbally confirm that he or she is alone in the room to ensure privacy and confidentiality. If the subject/LAR wishes to include a significant other during the informed consent discussion, the subject/LAR may add this person to the call.
vi. Subject/LAR will sign consent using any electronic device that is compatible with DocuSign®. Once they are finished, the consent will go to CRC's email inbox and the CRC will sign the consent electronically or print the consent to sign with a wet signature.
vii. Subject/LAR will have a digital copy of the signed consent accessible through DocuSign®. The subject/LAR may also request a printed copy of the signed consent to be mailed to their home address.
viii. After the consenting process, the CRC will download an electronic copy of the consent from DocuSign® (or scan a copy of the consent if the CRC provided a wet signature). The CRC will email the subject/LAR an electronic copy of the consent and print out a copy for the subject's research binder. After this, the CRC will delete the stored copy in DocuSign®. The CRC will also delete the subject/LAR contact information stored in DocuSign®.

b. If the subject/LAR is unable or unwilling to use DocuSign®, an impartial witness will be present during the consenting process and a paper copy of the informed consent will be signed by the subject/LAR.
    i. Upon receiving confirmation of the subject passing prescreening, a nurse or investigator will provide a paper copy of the consent to the subject/LAR. The CRC will call the subject/LAR to assure the consent process is being conducted in a private place and manner. The CRC will also ask the subject/LAR if he or she would prefer to have the consenting process conducted via video call if this technology is available at the setting of consent. An impartial witness will be added to the phone or video call. If the subject/LAR wishes to include a significant other during the informed consent discussion, the subject/LAR may add this person to the call.
        1. The CRC will review the informed consent with the subject/LAR and respond to any questions the subject may have.
        2. The impartial witness will confirm that the subject's/LAR's questions have been answered.

3. The CRC will confirm that the subject/LAR is willing to participate in the trial and sign the informed consent document while the witness is listening on the phone.
4. The subject/LAR will verbally confirm that they would like to participate in the trial and that they have signed and dated the informed consent document that is in their possession.

ii. If feasible, the subject/LAR or hospital staff or CRC (if on a video call) will take a picture of the informed consent document signature pages to be saved with the copy of the consent signed by the CRC in the study records. If this is not feasible, the CRC will sign the consent and the witness and CRC will provide a dated attestation to be saved in the study records confirming that the subject/LAR agreed to participate in the study and signed the informed consent. The CRC will email the participant a copy of the consent that the CRC signed, including the witness and CRC attestation (if applicable). The CRC will also email the participant the photograph of the signature pages that the participant signed, if pictures were taken.

c. If feasible, the LAR may be consented in person in a private setting by the CRC.

5. The designated research team member will randomize the subject. The randomization will be computer generated using this website in blocks of 4 (https://www.sealedenvelope.com/simple-randomiser/v1/lists).
6. If the subject is randomized to the "study arm", then the Research Pharmacy will enter in the order for the chosen ARB starting dose and will not charge the subject. If the subject is randomized to the SOC arm, there is no additional work to be completed by the Research Pharmacy.
7. If the subject is randomized to the "study arm" and already on established anti-hypertensive therapy other than ACE inhibitors or ARB (which would be exclusionary), it will be up to the treating physician's discretion to hold or reduce the dose of this treatment(s) in order to allow tolerability of ARB intervention depending on the blood pressure.
8. If the subject is randomized to the "study arm" a pregnancy test will be ordered as necessary for subjects of childbearing potential who have passed all the other screening criteria.

a. **Dosing Schemata LOSARTAN is the first choice of ARB in this study and will continue based on availability. ARB alternatives are listed below:** 10 days of treatment with losartan
   i. Dose 1 and 2*: Losartan 12.5mg PO BID for all subjects. The first AM dose can be given up to 1:00pm on Day 1.
   ii. Dose 3 and 4 :
      1. PI or delegee has the option to increase losartan dose to 25mg PO BID for subjects with a calculated creatinine clearance of >40ml/min provided the clinician is confident that the subject will

tolerate the higher dose based on the individual trends in blood pressure, renal function and potassium levels.

2. For subjects with a calculated creatinine clearance of 30-40ml/min, there is no option to increase the dose of losartan on Day 2..

iii. Doses 5 - 20:

1. PI or delegee has the option to increase losartan dose to 50mg PO BID for subjects with a calculated creatinine clearance of >40ml/min provided the clinician is confident that the subject will tolerate the higher dose based on the individual trends in blood pressure, renal function and potassium levels.

* The first AM dose of ARB may be given as late as 1300 because of the low dose. The second dose would still be given at 2100.

7. For subjects with a calculated creatinine clearance of 30 - 40ml/min, there is an option to increase the dose of losartan on Day 3 to 25mg PO BID provided the clinician is confident that the subject will tolerate the higher dose based on the individual trends in blood pressure, renal function and potassium levels.Drug Shortage Plan 1: In the event of a drug shortage for losartan, olmesartan will be given at equivalent dosages
    a. Losartan 12.5mg PO BID = Olmesartan 2.5mg PO BID
    b. Losartan 25mg = Olmesartan 5mg PO BID
    c. Losartan 50mg = Olmesartan 10mg PO BID
8. Drug Shortage Plan 2: In the event of a drug shortage for losartan AND olmesartan, valsartan will be given at equivalent dosages
    a. Losartan 12.5mg PO BID = Valsartan 20mg PO BID
    b. Losartan 25mg = Valsartan 40mg PO BID
    c. Losartan 50mg = Valsartan 80mg PO BID

Hold Parameters for Study Arm subjects on ARB:

1. Hold dose for SBP <100, re-check SBP in 10 min. If SBP remains <100, hold dose and call MD.
2. Hold dose and call MD, if potassium level increases >5.0.
3. Hold dose and call MD, if creatinine clearance drops below 30ml/min during treatment.

Parameters to meet to discontinue ARB study treatment for subjects on ARB:

1. Progression to mechanical ventilation.
2. Occurrence of acute renal impairment any time during treatment. This is defined as a 50% reduction in GFR from baseline.

Procedure Classification: Aside from a pregnancy test for subjects of childbearing potential, there are no other extra tests, imaging scans or procedures that will be performed as part of the study.

Potential Hazards and Precautions: There are no perceivable potential hazards to the subject.

Study Timeframe: The study time frame would be from IRB approval date to the end of the pandemic or until our sites reach 200 subjects, whatever comes first.

The end of study for each individual subject will be the date of discharge from the Sharp Healthcare hospital. The subject will not be followed if there is a transfer to a non-Sharp hospital or any sub-acute care setting (i.e. SNF, LTAC, rehabilitation center). If the subject is discharged prior to the 10th day of treatment of the ARB, the ARB is not to be continued after the subject is discharged from the Sharp Healthcare hospital.

Method of Subject Identification and Recruitment: The PI or Sub-I will be notified of a COVID-19 confirmed positive patient via hospital generated alert as part of the Infectious Disease Team at each hospital.

Subject Capacity: Subjects who do not have the capacity or an appropriate LAR to provide written informed consent will not be enrolled in the study.

Subject/Representative Comprehension: Subjects/LARs must have the ability to understand the requirements of the study, provide informed consent, and provide authorization of use and disclosure of personal health information. Subjects with impaired cognitive or decision-making capacity (based on the clinical judgment of the PI or designee) must have an appropriate LAR to provide consent on their behalf.

Documentation of Consent/Assent: Consenting will be conducted as described above in the Procedures and Study Visits section. Consents will be printed and stored in the subject's research binder in a secure location.

Reimbursements or Payments: None

Costs to the Subject: None

Data Sources: Sharp HealthCare electronic medical records (EMR) for hospital inpatients who meet inclusion criteria at acute care facilities.

Data Collection/ Assessment Instruments: The Case Report Form will include the following data elements: Demographics (age, gender, race/ethnicity, insurance), medical status (pre-existing comorbid conditions (based on the Charlson Comorbidity Index). The tool used to calculate the Charlson Comorbidity Index can be found here https://www.mdcalc.com/charlson-comorbidity-index-cci#next-steps). Other data to be collected includes vital signs, serum creatinine, calculated creatinine clearance (Cockroft and Gault equation), white blood cell count, platelet count, maximum body temperature in the past 24 hours, serum potassium level, serum sodium level, oxygen demand rate, and BSA. Receipt of interventions will include use of mechanical ventilation and duration, oxygen requirements, whether or not there is an admission to the ICU, any concomitant antimicrobials including azithromycin, doxycycline, hydroxychloroquine, chloroquine, and remdesivir. Measures of

healthcare service utilization will include length of stay, number of days in ICU, number of days requiring oxygenation, discharge disposition and mortality.

Data Collection Resources: The Study Coordinator will complete the Case Report Forms, with assistance from Sharp's Clinical Analytics team to extract information from the EMR.

Data Analysis: Descriptive statistics will be conducted to describe frequencies of demographics and clinical characteristics including the following: age at discharge, gender, race/ethnicity, payer, comorbid conditions based on the Charlson Comorbidity Index, receipt of medical interventions (mechanical ventilation, medications) and healthcare service utilization (ICU admission and Length of Stay in the hospital). Frequencies and descriptive statistics will be conducted using chi-square or 2-tailed Fisher exact statistics depending on the final sample size for categorical data and t-tests for continuous data.

Privacy of Subjects: There will be limited access to the subject due to standard of care isolation protocols. The Informed Consent process will emphasize the personal nature and privacy concerns related to communications regarding the subject's condition and infectious disease test results.

Confidentiality of Data and Storage: All binders will be stored and secured at Sharp's Center for Research office in accordance with all regulatory and organizational requirements, and will be accessed only by authorized personnel. No subject-specific data will be reported. Sharp medical record number will be used to link subject records across data systems and hospital visits. Protected Health Information (PHI) will be safeguarded as specified by Sharp HealthCare policy. There is a risk of disclosure of PHI from inappropriate access to the study database. All efforts will be made to protect PHI, including password protecting the database with access only allowed to study members who are Sharp HealthCare employees. All datasets will be de-identified prior to any statistical analyses conducted by the Statistician. Identifiers will be destroyed two years after study end date, once data has been aggregated for reporting.

Data Monitoring: Study data will be monitored by the PI and physicians on the study team for frequency of hypotension, hyperkalemia, acute renal impairment, liver dysfunction, rates of ICU transfer, rates of respiratory failure requiring mechanical ventilation. The following team will review the data at intervals of 25%, 50%, and 75% target enrollment:

- Ravina Kulla, PharmD, MPH (Biostatistics/Epidemiology)
- Anuja Vyas, MD (Critical care)
- Venkata Naga Dintyala, MD (hospitalist)
- Mitra Ghafourian, MD (hospitalist)

If disproportionate higher rate of complications is observed in one arm of the study over the other at any interval based on the clinical review, a biostatistician will be consulted for confirmation. If such disproportionality is considered biostatistically significant, study enrollment will cease.

Benefits to Individual Subjects: Potential reduction in ICU hospitalization, potential avoidance of mechanical ventilation and potential decrease in length of stay in the hospital.

Potential Benefits (Value) to Society: Any data collected will be a benefit to society whether we prove or disprove the hypothesis. However, if it is determined that the studied intervention indeed does reduce demand for mechanical ventilation and ICU care, it may provide significant relief to a medical care system that is anticipated to be overwhelmed at pandemic peak. The benefits will most likely be realized in the next SARS-CoV-2 epidemic. There are potential benefits to each institution that participates in this study to reduce the demand of mechanical ventilation and reduce the demand for isolated negative pressure ICU rooms.

Risk Category: Greater than minimal risk

Potential Risks: Hypotension and hyperkalemia would be the main risks of adding an ARB to the SOC.

Protection Against Risks:

Hold Parameters for Study Arm subjects on ARB:

1. Hold dose for SBP <100, re-check SBP in 10 min. If SBP remains <100, hold dose and call MD.
2. Hold dose and call MD, if potassium level increases >5.0.
3. Hold dose and call MD, if creatinine clearance drops below 30ml/min during treatment.

Parameters to meet to discontinue ARB study treatment for subjects on ARB:

1. Progression to mechanical ventilation.
2. Occurrence of acute renal impairment any time during treatment. This is defined as a 50% reduction in GFR from baseline.

Other protections against risks:

Monitoring of hypotension and hyperkalemia will be conducted by the patient care team in accordance with routine standard of care processes.

If the subject experiences side effects that are suspected to be due to the ARB for subjects in the study group, it will be up to the discretion of the treating clinician/critical care team/PI whether to continue the ARB or not. If the subject prematurely stops study treatment, the study team will continue to collect data until discharge.

Subjects who develop acute renal impairment whether or not the ARB is the causative agent during study treatment will be withdrawn from the study. Subjects may also be withdrawn if they develop liver dysfunction, based on physician's discretion.

For subjects who experience disease progression due to the coronavirus and are transferred into the critical care setting, it is up to the discretion of the critical care team and the PI whether or not to continue the ARB.