



**Table 1: Research Priorities for Coronavirus Disease 2019 (COVID-19) and the Renin-Angiotensin System (RAS)**

Unanswered Questions	Suitable Study	Key Epidemiologic Considerations
<p>Are cardiovascular disease, hypertension, or diabetes independently associated with COVID-19 mortality? What subtypes of cardiovascular disease does this apply to?</p> <p>Are these associations mediated through acute respiratory distress syndrome, cardiomyopathy, or both?</p> <p>Is RAS blockade associated with COVID-19 outcomes?</p> <p>Is the association positive or negative?</p> <p>Are these class effects? Is there any effect of neprilysin inhibition or mineralocorticoid receptor antagonism?</p> <p>What duration of exposure or discontinuation matters?</p> <p>Does this association differ for mortality, acute respiratory distress syndrome, or cardiomyopathy?</p>	<p>Observational</p> 	<p>Retrospective hospital cohort feasible with electronic record, greater selection bias towards null</p> <p>Prospective community cohort less biased, but longer time to results</p> <p>Clustering may exist by country, region, or hospital</p> <p>Case definition based on + test: maximizes specificity, reduces sensitivity, will also bias to null</p> <p>Covariate effects may be nonlinear (e.g., age, interaction between hypertension and RAS blockade)</p> <p>Clear comorbidity definitions necessary to minimize misclassification bias</p>
<p>Can addition or removal of RAS blockade modify COVID-19 outcomes?</p> <p>Is this effect acute (within days) or chronic (over weeks to months)? Is it effective to start/stop medications once COVID-19 is already present or must it be prophylactic?</p> <p>What is the relative effect of addition or withdrawal of RAS blockade in different conditions compared to COVID-19?</p>	<p>Randomized Controlled Trial</p> 	<p>Direction of trials (starting or withholding RAS blockade) should be informed by existing observational data</p> <p>Optimal outcomes: <u>Primary</u> (all-cause mortality)</p> <p><u>Secondary</u> (respiratory failure, fulminant myocarditis, need for intensive care)</p>