BMJ Open

Study protocol for a multicentre, prospective cohort study of the association of angiotensin II type 1 receptor blockers on outcomes of coronavirus infection

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ABSTRACT

Introduction The COVID-19 epidemic grows and there are clinical trials of antivirals. There is an opportunity to complement these trials with investigation of angiotensin II type 1 receptor blockers (ARBs) because an ARB (losartan) was effective in murine influenza pneumonia.

Methods and analysis Our innovative design includes: ARBs; alignment with the WHO Ordinal Scale (primary endpoint) to align with other COVID-19 trials; joint longitudinal analysis; and predictive biomarkers (angiotensins I, 1–7, II and ACE1 and ACE2). Our hypothesis is: ARBs decrease the need for hospitalisation, severity (need for ventilation, vasopressors, extracorporeal membrane oxygenation or renal replacement therapy) or mortality of hospitalised COVID-19 infected adults. Our two-pronged multicentre pragmatic observational cohort study examines safety and effectiveness of ARBs in (1) hospitalised adult patients with COVID-19 and (2) out-patients already on or not on ARBs. The primary outcome will be evaluated by ordinal logistic regression and main secondary outcomes by both joint longitudinal modelling analyses. We will compare rates of hospitalisation of ARB-exposed versus not ARB-exposed patients. We will also determine whether continuing ARBs or not decreases the primary outcome. Based on published COVID-19 cohorts, assuming 15% of patients are ARB-exposed, a total sample size of 497 patients can detect a proportional OR of 0.5 (alpha=0.05, 80% power) comparing WHO scale of ARB-exposed versus non-ARB-exposed patients.

Ethics and dissemination This study has core institution approval (UBC Providence Healthcare Research Ethics Board) and site institution approvals (Health Research Ethics Board, University of Alberta; Comite d'etique de la recerche, CHU Sainte Justine (for McGill University and University of Sherbrook); Conjoint Health Research Ethics Board, University of Calgary; Queen's University Health Sciences & Affiliated Hospitals Research Ethics Board; Research Ethics Board, Sunnybrook Health Sciences Centre; Veritas Independent Research Board (for Humber River Hospital); Mount Sinai Hospital Research Ethics Board; Unity Health Toronto Research Ethics Board, St. Michael's Hospital). Results will be disseminated by peer-review publication and social media releases.

Strengths and limitations of this study

► We have four strengths: first, our innovative design includes evaluation of use of angiotensin receptor blockers (ARBs) and aligns with the WHO Ordinal Scale (primary endpoint) to align with other COVID-19 trials.

► Second, we will use adjusted ordinal logistic regression to assess the primary outcome (COVID-19 WHO Ordinal Scale) and adjusted regression analysis for the secondary outcomes.

► Third, we measure and evaluate several biomarkers (angiotensins I, 1–7, II and ACE1 and ACE2) that are predictive of outcomes and response to ARBs in COVID-19.

► Fourth, our two-pronged multicentre pragmatic observational cohort study will determine the safety and effectiveness of ARBs in[1] (1) hospitalised adult patients with COVID-19 and[2] (2) out-patients, already on or not on ARBs.

► The limitations are that the study is not randomised and not blinded.

Trial registration number NCT04510623

INTRODUCTION

The coronavirus (COVID-19) epidemic grows, mortality rate is 2% (lower than Severe Acute Respiratory Syndrome (SARS) (10%) and Middle East Respiratory Syndrome (MERS) (36%)) but is 10% in hospitalised and 24%–62%[1] in ICU-admitted patients in China.[2–4] Interventions to date include quarantine, isolation and usual clinical care. There are no proven vaccines and just one antiviral—remdesivir[5]—is approved for COVID-19. However, the critical illness complications of COVID-19—septic shock, acute respiratory distress syndrome (ARDS) and acute kidney

injury (AKI)—are caused in part by the host response. We have a unique opportunity to complement these trials of antivirals with investigation of modulation of the host response to improve outcomes of COVID-19.[6 7]

Publications at the time of our grant submission were used to derive power and sample size. Of 278 COVID-19 hospitalisations in China[2–4] at that time, 7% had septic shock, 20% ARDS, 9% needed intubation and ventilation, 3% needed extracorporeal membrane oxygenation, 7% had AKI, 5% needed renal replacement therapy (RRT) and 8% died. Critically ill patients with COVID-19 have similar mortality as sepsis and ARDS. Mortality of ICU-admitted patients with COVID-19[3 4] was 2%–62%,[8] similar to or higher than sepsis mortality (24% in 101 064 patients in Australia)[9] and ARDS mortality (30% in a systematic review).[10] Clearly there are opportunities to improve these outcomes.

COVID-19 binds ACE2[11] and so the ACE axis is central to septic shock, ARDS and COVID-19.[12] SARS-CoV-2's spike glycoprotein binds ACE2 10–20 times more avidly than does SARS1[11] and inactivates ACE2.[13] Patients already on ARBs have lower sepsis mortality and do not have worse haemodynamic status (blood pressure[14]) than patients not on ARBs.[15–17]

The underlying mechanisms leading to the acute lung injury after viral infection mediated by an increase in angiotensin II[18] (ie, microvascular damage, increased vascular permeability, secondary production of inflammatory cytokines, accelerated apoptosis, fibrosis). Local activation of the renin-angiotensin-aldosterone system may mediate lung and cardiac injury responses to SARS-CoV-2. SARS-CoV-2 infection increases lung and coronary microvascular thrombosis and coagulation (increased D-dimers), which is associated with increased COVID-19 mortality[19 20]. ATII binds the ATII receptor 1 (AGTR1) which increases expression of tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1).[21] Losartan decreases TF[22] and PAI-1.[22 23] ARBs may also modulate ACE2 activity[24] upregulating ACE2 in cardiac tissue[25] and that could be an adverse effect of ARBs in COVID-19.

The most severe cases of COVID-19 that require ICU care have ARDS, septic shock and AKI. We also have had success in discovery of off-target drugs: proprotein convertase subtilisin/kexin type 9 inhibition[26–28] and cholesteryl ester transfer protein inhibition[29–31] for sepsis. Determining whether plasma angiotensin I, 1–7 and II and ACE and ACE2 levels predict response to ARBs is based on our genomics and protein biomarker research in which we identified predictive biomarkers (ie, predictive of response to angiotensin II,[32] vasopressin,[33] and norepinephrine[34]).

There is clinical equipoise regarding safety and effectiveness of ARBs in COVID-19.[35–37] At the time of our study design and implementation there was only one study that separated ARBs use from ACE inhibitor (ACEi) use[38 39] (n=362) finding no associations of ARBs or ACEi with mortality.[38] A recent meta-analysis found that use of ARBs or ACEi use was associated with decreased mortality of COVID-19.[40] ARBs or ACEi use in patients with COVID-19 with hypertension (n=1128) was associated with decreased mortality (9.8% vs 3.7%, RRR 60%, p = 0.03) compared with patients not on ARBs/ACEis in one study[41] but not in Feng and colleagues.[42] Li and colleagues[38] found no differences in use of ACEis (9.1% vs 9.8%; p = 0.85), ARBs (19.5% vs 23.9%; p = 0.42), or the composite ACEis/ARBs (27.3% vs 33.0%; p = 0.34) between non-survivors and survivors.

Losartan (an ARB) decreases viral replication and lung injury in murine influenza pneumonia.[8] ARBs are inexpensive clinically-available drugs used in hypertension and heart failure that could decrease morbidity and mortality of COVID-19. Angiotensin II worsens lung injury in influenza models[2–4] because ACE2 is downregulated in H1N1, H5N1, H7N9 and SARS[2–4 43] leading to increased angiotensin II. Angiotensin II levels are increased in COVID-19[44] and human influenza and are associated with influenza viral load, disease progression and mortality.[45] Losartan limits lung injury in murine influenza H7N9(8), viral titre and RNA and lung injury. ARBs could limit viral titre and organ injury.

Hypertension guidelines recommend ARBs if ACEis are not tolerated,[46] are very commonly prescribed (59% of hypertension[47]), 35% of hypertensive patients with chronic kidney disease (CKD)[48] and 32% of diabetics.[49] ARBs are recommended first line therapy in Canadian heart failure guidelines.[50] In Alberta, Canada, ARBs or ACEis were used in 50%–70% of patients with heart failure[51] and 58% of patients in Nepal[52] and 52%[53] of US patients with heart failure.

If ARBs protect patients from COVID-19 because they are less sick and are not hospitalised, we may detect this in our study of hospitalised COVID-19. Thus, once hospitalised, ARB-exposed patients may not fare better than patients not on ARBs (ie, ARBs may protect them from getting sick enough to be admitted). To address that possibility, we collaborate with SM and his study of community COVID-19 (COVID-19: Improving the Evidence to Treat an Emerging Infection) to determine whether ARB treatment compared with not being on ARBs decreases the risk of hospitalisation.

Initially when we designed our study (ie, before the amendment), we sought to evaluate ARBs treatment versus no ARBs treatment but not ACEis because the available evidence in previous animal studies used ARB for attenuation of acute lung injury. We added an amendment to similarly evaluate ACEi treatment versus no ACEi treatment and ARBs/ACEi versus no ARBs/ACEi.

Overall purpose

This is a multicentre pragmatic cohort study of hospitalised patients with COVID-19 that leverages cutting-edge longitudinal data analysis methods. We will assess ARBs (losartan, irbesartan, candesartan, telmisartan, valsartan, eprosartan and alzilsartan used to treat hypertension and heart failure) for safety and effectiveness in decreasing need for vital organ support and mortality of hospitalised
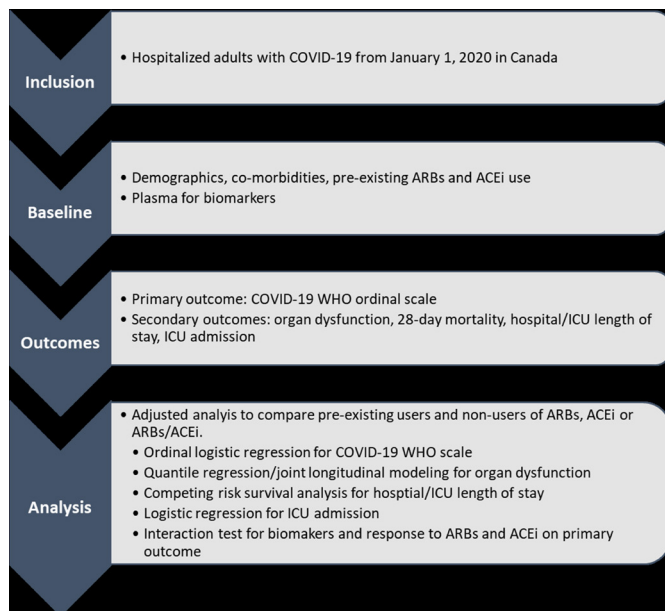
Figure 1 Flow chart of patients. ARBs, angiotensin receptor blockers, ACEi, ACE inhibitor; ARB, angiotensin receptor blockers.

adults with COVID-19. There were two amendments after receiving Canadian Institutes of Health Research (CIHR) funding: to add other ACE pathway biomarkers and to evaluate ACEis (online supplemental file 1). There is a flow chart of ARBs Corona I shown in figure 1.

Objectives

► To accrue and retrospectively record clinical characteristics and outcomes of COVID-19 hospitalised patients.
► To classify patients as ARB-exposed or not ARB-exposed.
► To measure serum angiotensin II levels at hospital admission and compare to the primary outcome COVID-19 WHO Ordinal Scale as well as comparing ARB-exposed to ARB-non-exposed patients (and ACEi-exposed vs not ACEi-exposed) and the association of these treatments with the outcomes.
► To do adjusted ordinal logistic regression for the primary outcome COVID-19 WHO Ordinal Scale and adjusted regression analysis for the secondary outcomes comparing ARB-exposed to not ARB-exposed hospitalised COVID-19 patients.
► To do joint longitudinal analyses of organ dysfunction (as evaluated by the Sequential Organ Failure Assessment (SOFA) Score) over time comparing ARB-exposed to not ARB-exposed hospitalised patients with COVID-19.
► To do ordinal logistic regression and interaction tests for the primary outcome COVID-19 WHO Ordinal Scale to determine whether and at what level plasma angiotensin II levels are associated with improved WHO Ordinal Scale in ARB-exposed patients with COVID-19.

► To do logistic regression for the rates of hospitalisation of ARB-exposed to not ARB-exposed patients in the community (in collaboration with SM (COVID-19: Improving the Evidence to Treat an Emerging Infection).
► To do ordinal logistic regression subgroup analysis in patients already on ARBs when they are hospitalised to determine whether continuing ARBs (or not) decreases WHO COVID-19 Ordinal Outcome Scale.

Our main hypothesis is that modulation of ACE2 by angiotensin receptor blockers is associated with decreased WHO COVID-19 Ordinal Outcome Scale (that evaluates the severity, need for ventilation, vasopressors, extracorporeal membrane oxygenation or RRT and mortality) of hospitalised COVID-19 infected adults.

Secondary biomarker hypothesis

Plasma angiotensin II levels are associated with effectiveness of ARBs in hospitalised COVID-19 adults. *Secondary HospitalisationHypothesi*: odulation of ACE2 by angiotensin receptor blockers is associated with decreased rate of hospitalisation for COVID-19. *Secondary Continuing ARBs Hypothesis*: In patients already on ARBs when they are hospitalised continuing ARBs is associated with decreased WHO COVID-19 Ordinal Outcome Scale.

METHODS AND ANALYSIS
Design, participants and timeframe of enrollment and visits

Our pragmatic multicentre cohort study comparing ARB use to no ARB use in COVID-19 is relatively simple, inexpensive, will be done quickly and thus addresses the urgency of COVID-19 research. We will compare outcomes of hospitalised adult patients with COVID-19 (1) who have use of any ARB within 24 hours of onset of COVID-19 symptoms with (2) patients who were not exposed to ARBs. At hospital admission we will obtain discarded blood from the routine blood work[33 34 54] to measure plasma ACE pathway levels (see online supplemental file 1 regarding amendment) and do ordinal logistic regression of the interaction of plasma ACE pathway levels and ARB-exposed or not. For the hospitalisation hypothesis, we will obtain relevant data from SM's CIHR-funded study: 'COVID-19: Improving the Evidence to Treat an Emerging Infection' and do logistic regression for the rates of hospitalisation of ARB-exposed to not ARB-exposed patients in out-patients. For the continuing ARBs or ACEi hypothesis, we will do ordinal logistic regression subgroup analysis in patients on ARBs (or ACEi) when hospitalised to determine whether continuing ARBs (or ACEi, or not) decreases WHO COVID-19 Ordinal Outcome Scale.

Inclusion criteria are individuals over 18 years of age who have confirmed COVID-19 infection (according to local hospital or provincial laboratories clinically approved laboratory testing for COVID-19). ARBs-exposed and ACEi-exposed patients are defined for inclusion by being on ARB or ACE prior to and at the time of

Table 1 Numbers of patients and per cent of patients who had WHO Ordinal Scale of 6, 7 or 8 (needed ventilation, vasopressors, RRT, ECMO or who died) in three publications[2–4] regarding hospitalised patients in China who had COVID-19 used to derive sample size estimates to detect a one point or greater decrease of the WHO scale of ARB-exposed hospitalised patients compared with a control group of hospitalised patients with no ARB exposure

Publication	Admitted to hospital	WHO=6	WHO=7	WHO=8	WHO 6–8
Chen—Lancet	99	4	4	11	19
Wang—JAMA	138	17	13	6	36
Huang—Lancet	41	4	3	6	13
Totals	278	25	20	23	68
%		9.0	7.2	8.3	24.5

RRT, renal replacement therapy.

the hospital admission for COVID-19. There are no exclusion criteria. We will enrol from 1 January 2020 until the conclusion of the COVID-19 epidemic at the centres in Canada (expected mid to end 2021).

Recruitment and power—sample size estimation

We used published cohorts of hospitalised adults with COVID-19 in China[2–4] to determine expected severity and sample size. About 32% have WHO Ordinal Scale criteria 6–8 (vasopressors, ventilation, ECMO, RRT or death). Since about 30% of patients with COVID-19 had cardiovascular disease or hypertension[2–4] it is conceivable that a significant proportion of the population could be on ARBs. Assuming that 50% of the 30% with cardiovascular disease are on an ARB, then about 15% of patients of the total cohort would be on an ARB. Ordinal logistic regression will be used to compare the primary outcome—WHO Ordinal Scale for COVID-19—in ARB-exposed versus non-ARB-exposed hospitalised patients. Based on data from three publications (tables 1 and 2), assuming 15% of the patients were ARB-exposed, a total sample size of 497 can detect a proportional OR of 0.5 (table 2, translated change in proportion in each category of the scale) at alpha=0.05 with 80% power for the comparison of WHO scale in five categories (WHO Ordinal Scale categories:

3–4, 5, 6, 7 and 8). The current sample size was selected for feasibility as there was no existing information available to determine the potential effect of ARB exposure on the WHO Ordinal Scale. Calculation was performed using *posamsize* in the *Hmisc* package of R 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Exam/visit components, measurements of exposure and disease and other measurements

Our Case Report Form is adapted from the ISARIC WHO Novel Coronavirus (nCoV) Acute Respiratory Infection Clinical Characterisation Data Tool (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/early-investigations) because measurements are clinically available and our data will align with other studies of COVID-19.

We will record baseline characteristics (age, gender, heart rate, respiratory rate, temperature, blood pressure, SaO_2, respiratory (PaO_2/FiO_2), creatinine and bilirubin, use of oxygen, vasopressors, ventilation and RRT. Use of ARBs is defined by taking an ARB up to within 24 hours of onset of COVID-19 symptoms. We will also record whether ARBs are continued after onset of symptoms and for how long.

Table 2 Sample size by proportional OR of ARB-exposed versus non ARB-exposed (five categories for WHO scale)

	Proportion of patients					Mean score	Total sample size* (by % ARB exposed)			
	WHO 3–4	WHO 5	WHO 6	WHO 7	WHO 8	All patients†	10%	15%	20%	50%
Non-ARB exposed	0.604	0.151	0.090	0.072	0.083	4.577				
ARB exposed										
OR=0.7	0.685	0.129	0.071	0.054	0.060	4.330	2656	1875	1494	956
OR=0.6	0.718	0.119	0.064	0.048	0.052	4.237	1295	914	729	466
OR=0.5	0.753	0.107	0.056	0.041	0.043	4.137	704	**497**	396	253
OR=0.4	0.792	0.093	0.047	0.033	0.035	4.030	403	284	227	145
OR=0.3	0.836	0.076	0.037	0.026	0.026	3.914	233	165	132	84

*Total size sample referred to the total of ARB exposed and non-ARB exposed.
†Assuming patients were evenly distributed across the WHO 3–4 categories.

Table 3 WHO 2019-nCoV Ordinal Outcome Scale (J Marshall, personal communication, and Cao and colleagues[73])

Uninfected	0 points
Ambulatory—no limitation of activities	1 point
Ambulatory—limitation of activities	2 points
Hospitalised—no oxygen (mild)	3 points
Hospitalised—oxygen (mild)	4 points
Hospitalised (severe) non-invasive ventilation or high-flow oxygen	5 points
Hospitalised (severe) intubation and ventilation	6 points
Hospitalised (severe) ventilation and additional organ support (vasopressors, RRT, ECMO)	7 points
Death	8 points

nCoV, novel coronavirus; RRT, renal replacement therapy.

The primary outcome is the COVID-19 WHO Ordinal Scale (table 3, J Marshall, personal communication).

Secondary outcomes are SOFA score[55] (for joint longitudinal modelling), 28-day mortality, hospital length of stay, proportions admitted to ICU, ICU length of stay, need for ventilation, vasopressors and RRT (ie, days alive and free of ventilation, vasopressors and RRT within 14 days[56]) and severe adverse effects of ARBs. Comparison of ARB-exposed versus non ARB-exposed will be done by ordinal logistic regression analysis for the primary outcome and by logistic regression for binary secondary outcomes. Time to death and hospital length of stay will be analysed simultaneously using competing risk survival analysis. Given the heavily skewed distribution for days alive and free of ventilation/vasopressors/RRT, the comparison of these outcomes will be done based on quantile regression. Patients who die within the first 14 days will be assigned a value of 0 to maximise penalty for non-survival. No adjustment for multiplicity of inferences will be made for the secondary outcomes given the hypothesis generating nature of these analyses.

Adequacy of ARB intervention timing on COVID-19

ARB intervention in our study will have been for months–years before COVID-19 infection, optimising beneficial effects of ARB on COVID-19 replication, inflammation and permeability. In murine models, the ARB losartan was effective when given 30 min before H7N9[8]; recombinant ACE2 was effective when given 3 hours prior, 8 hours and 3 days after murine H5N1.[57] Clinicians are often uncertain whether to continue ARBs in patients hospitalised for non-cardiovascular conditions. Thus, in a subgroup analysis of patients already on ARBs when hospitalised, we will evaluate whether continuing ARBs or ACEi (the ARB or ACEi they were already on) or not decreases WHO COVID-19 Ordinal Outcome Scale.

Data management and statistical analyses

DAF vasopressors, ventilation and RRT will be calculated separately by subtracting the number of days on vasopressors, ventilation or RRT from the lesser of 14 or the number of days to death, scored as 1 if the patient is alive and free of vasopressors, ventilation or RRT[56] and zero (0) if the patient had vasopressors, ventilation or RRT or is not alive (to maximise non-survival penalty).[56]

We will evaluate ARB-exposed versus not ARB-exposed and ACEi-exposed and not ACEi-exposed. The ACEi-exposed versus not ACEi-exposed patient analyses will be done exactly as described for the ARBs-exposed versus not ARBs-exposed patients. There will be a third analysis which compares ARB/ACEi versus no ARB/ACEi. All analyses will be adjusted for potential confounders (age, biological sex, blood pressure, and presence of heart failure, hypertension, renal failure and diabetes (the most common comorbidities of 2019 nCoV[2–4] associated with increased risk of ICU admission[4]) using regression techniques rather than matching (eg, Propensity Score) because of the potential limited sample size and the possibility of discarding valuable data due to unmatched cases).

About 25% of patients with COVID-19 have organ dysfunction requiring critical care support. Comparisons of organ dysfunction are susceptible to bias from informative censoring (death, discharge, other competing risks[58–61]). Joint models handle data that is biassed from informative censoring by simultaneous estimation of two separate regression models with a shared random effect.[62 63] Joint modelling of the longitudinal and survival processes allows each model to inform (ie, adjust) the other to mitigate potential biases caused by missing outcomes (eg, death). Joint longitudinal modelling of SOFA requires estimation of an unobserved SOFA trajectory, estimating the SOFA trajectory if there was no informative censoring. The most common joint models are longitudinal (eg, repeated measures or mixed-effects models) and time-to-event (survival) models.

We will compare ARB-exposed to not ARB-exposed patients' SOFA score by fitting (i) a traditional linear mixed-effects model (ie, longitudinal model with a participant random-intercept) and (ii) several joint longitudinal and survival models of SOFA scores over time.[64] Time-to-event survival data will be modelled using a Cox proportional hazards model for death; discharge and day 14 will be considered censoring events in death-specific Cox model. Shared random effects will be used to capture the association between the longitudinal and time-to-event models. We will explore multiple model specifications for the joint model by varying the functional form of time in both the fixed effects in the longitudinal component and the shared random effects specifications. For instance, we will test linear and quadratic effects, and spline terms with an increasing number of knots (up to 7 and 2 for the fixed effect and random effect of time, respectively). We will select the final model according to the Akaike Information Criterion and Bayesian Information Criterion.

Standard errors for the coefficients of the joint model will be estimated via 1000 bootstrap replications, resampling at a participant level. We will test for the modification of treatment by study time by including an interaction term in the longitudinal submodel and by testing its significance using the Wald test. Finally, we will perform several sensitivity analyses to assess the robustness of our findings including fitting a joint model accounting for the competing risk of discharge. All models will be estimated using the *joineRML* package V.0.4.2 in the statistical software R.[65] Joint models for longitudinal and survival data can also be implemented in other statistical software such as Stata[66] and SAS.[67]

We collate in real time and evaluate the the most common severe adverse effects of ARBs: hypotension (systolic pressure <90 mm Hg or mean arterial pressure <65 mm Hg), hyperkalemia (potassium >6 mmol/L) and AKI (creatinine >200 mmol/L) comparing ARB-exposed with not ARB-exposed patients.

We will examine missing data fields to identify the type of missing data mechanisms. Most data will be missing at random; thus, as a sensitivity analysis, we will use multiple imputation technique to impute the missing data.[68 69] Some data will be 'informatively' missing due to clinically relevant events: for example, death, discharge so we will examine statistical models to account for missing not at random (eg, joint longitudinal and time-to-event models,[63] and inverse probability of censoring weighting[70]).

We will evaluate ARB-exposed versus not ARB-exposed, ACEi-exposed versus not ACEi-exposed and ARB/ACEi-exposed vs not ARB/ACEi-exposed in[1] (1) heart failure and hypertension RRT and[2] (2) patients who do or do not have ARB continued after hospital admission for the primary outcome and DAF vasopressors, ventilation and RRT. Sensitivity analyses will be carried out with adequate adjustments for missing data using multiple imputations technique as described above. The potential bias is that ARBs are not assigned randomly but are given for treatment of hypertension or heart failure thus having a poorer COVID-19 prognosis. We mitigate this bias by doing ordinal logistic regression adjusted analyses to control for confounding by indication and control for variables that increase risk of poor outcomes. We will do analyses that assess the potential of unmeasured confounding (eg, E-value and other recently developed techniques[71 72]).

Quality assurance and control plans

We will monitor 15% of eCRFs against key primary data. We have a weekly 2-hour Management Committee meeting in which data quality and control is a regular agenda item.

Patient and public involvement

The development of the research question, outcome measures and design was not informed by patients' priorities, experience and preferences. Patients were not involved in the recruitment to and conduct of the study because this is an inpatient hospital-based cohort study. Patients will be included without consent and all data are anonymised so that patients cannot be informed of the results of the study. Patients will be included in the interpretation and dissemination of results through a relationship with the British Columbia Support Unit.

There are limitations of our study. In this association study we cannot determine causation but will add further evidence regarding ARBs or ACEi use in COVID-19 as a foundation for future RCTs in COVID-19 and other viral epidemics caused by viruses that bind ACE2. Another potential limitation is inadequate sample size. The use of ARBs by COVID-19-infected patients may not be adequately large; yet, 50% of hospitalised patients with COVID-19 had comorbidities[56] 40% cardiovascular or cerebrovascular disease[2] in which ARBs are commonly prescribed. There is potential bias regarding ARB confounding by indication that we limit by doing[1] (1) ordinal logistic regression analyses,[2] (2) sensitivity analyses and[3] (3) subgroup analyses to examine consistency of effects of ARBs on COVID-19 outcomes.

RCT(s) of ARBs in COVID-19 are now warranted and we are pleased to indicate that we have been funded by the CIHR for a multicentre randomised controlled trial of an ARB in COVID-19.

ETHICS AND DISSEMINATION

This study has core institution approval by the Providence Healthcare and University of British Columbia Human Research Committee and individual site institutional approvals. Results will be disseminated by peer-review publication and social media releases.

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related to the use of vasopressin in septic shock and a patent owned by Ferring for use of selepressin in septic shock. JR is an inventor on these patents. JR was a founder, Director and shareholder in Cyon Therapeutics Inc. and is a shareholder in Molecular You Corp. JR reports receiving consulting fees in the last 3 years from: (1) Asahi Kesai Pharmaceuticals of America (AKPA) (was developing recombinant thrombomodulin in sepsis). (2) SIB Therapeutics LLC (developing a sepsis drug). (3) Ferring Pharmaceuticals (manufactures vasopressin and developing selepressin). JR is no longer actively consulting for the following: (4) La Jolla Pharmaceuticals (developing angiotensin II; JR chaired the DSMB of a trial of angiotensin II from 2015–2017). (5) PAR Pharma (sells prepared bags of vasopressin). JR reports having received an investigator-initiated grant from Grifols (entitled 'Is HBP a mechanism of albumin's efficacy in human septic shock?') that was provided to and administered by UBC.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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