JIM Original Article

doi: 10.1111/joim.13202

ACE inhibitors, angiotensin receptor blockers and endothelial injury in COVID-19

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Abstract. Tetlow S, Segiet-Swiecicka A, O'Sullivan R, O'Halloran S, Kalb K, Brathwaite-Shirley C, Alger L, Ankuli A, Baig MS, Catmur F, Chan T, Dudley D, Fisher J, Iqbal MU, Puczynska J, Wilkins R, Bygate R, Roberts P (University College Hospital, Bloomsbury, London, UK; Medical University of Warsaw; Cardinal Stefan Wyszynski Institute of Cardiology, Warszawa, Poland; Lewisham and Greenwich NHS Trust; Newham University Hospital NHS Trust, Newham University Hospital, London, UK). ACE inhibitors, angiotensin receptor blockers and endothelial injury in COVID-19. *J Intern Med* 2021; **289**: 688–699.

Background. COVID-19 is caused by the coronavirus SARS-CoV-2, which uses angiotensin-converting enzyme 2 (ACE-2) as a receptor for cellular entry. It is theorized that ACE inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs) may increase vulnerability to SARS-CoV-2 by upregulating ACE-2 expression, but ACE-I/ARB discontinuation is associated with clinical deterioration.

Objective. To determine whether ACE-I and ARB use is associated with acute kidney injury (AKI), macrovascular thrombosis and in-hospital mortality.

Methods. A retrospective, single-centre study of 558 hospital inpatients with confirmed COVID-19 admitted from 1 March to 30 April 2020, followed up until 24 May 2020. AKI and macrovascular thrombosis were primary end-points, and in-hospital mortality was a secondary end-point.

Results. AKI occurred in 126 (23.1%) patients, 34 (6.1%) developed macrovascular thrombi, and 200 (35.9%) died. Overlap propensity score-weighted analysis showed no significant effect of ACE-I/ARB use on the risk of occurrence of the specified end-points. On exploratory analysis, severe chronic kidney disease (CKD) increases odds of macrovascular thrombi (OR: 8.237, 95% CI: 1.689–40.181, $P = 0.009$). The risk of AKI increased with advancing age (OR: 1.028, 95% CI: 1.011–1.044, $P = 0.001$) and diabetes (OR: 1.675, 95% CI: 1.065–2.633, $P = 0.025$). Immunosuppression was associated with lower risk of AKI (OR: 0.160, 95% CI: 0.029–0.886, $P = 0.036$). Advancing age, dependence on care, male gender and eGFR < 60 mL min^{-1}/1.73 m^2 increased odds of in-hospital mortality.

Conclusion. We did not identify an association between ACE-I/ARB use and AKI, macrovascular thrombi or mortality. This supports the recommendations of the European and American Societies of Cardiology that ACE-Is and ARBs should not be discontinued during the COVID-19 pandemic.

Keywords: ACE inhibitors, critical care, thrombosis, renal failure, infectious disease, endothelial function.

Introduction

COVID-19 is a global pandemic caused by the coronavirus SARS-CoV-2. Since its emergence in the city of Wuhan, China, SARS-CoV-2 has spread rapidly across the world; almost 27 million infections and 900,000 deaths have been reported to the WHO as of 6 September 2020 [1]. SARS-CoV-2 is genetically similar to SARS-CoV-1, the causative organism of the 2003 SARS outbreak, and both organisms use the membrane-bound form of ACE-2 as the cellular receptor for viral

entry [2]. The use of ACE-Is and ARBs has been shown in some experimental models to upregulate ACE-2 expression, and it has been hypothesized that they might therefore increase vulnerability to SARS-CoV-2 infection [3, 4]. Others, however, suggest that they may confer a protective effect, citing evidence that ACE-2 reduces acute lung injury (ALI) [5, 6].

ACE-2 is expressed on endothelial cells of the lung, kidney, myocardium and vasculature [7–9]. SARS-CoV-2 cellular infection results in endotheliitis and cell death [10], whilst ACE-2 receptor endocytosis leads to dysregulation of the renin–angiotensin–aldosterone system and promotes the release of pro-inflammatory cytokines [11, 12]. These processes increase endothelial permeability through disruption of intercellular junctions and the endothelial glycocalyx [13] leading to fluid extravasation, whilst the exposure of pro-coagulant factors carried on the endothelial basement membrane promotes the development of micro- and macrovascular thrombi [11, 14]. Thus, the endothelial injury caused by SARS-CoV-2 infection leads to respiratory failure, myocarditis, renal failure and intravascular thrombosis [15–17].

The hypothesis that ACE-Is and ARBs might increase patients' vulnerability to SARS-CoV-2 infection is based upon experimental models demonstrating that their use increased the expression of the ACE-2 receptor. Both ACE-I exposure and ARB exposure increased ACE-2 expression in rat and mouse kidneys [8, 18], myocardium [9, 19–21] and vasculature [22, 23] although these findings were not replicated in all animal models [24, 25]. Human studies are limited to indirect measures of ACE-2 activity. The use of the ACE-I captopril has been found to increase circulating levels of angiotensin 1-7, which is the product of ACE-2-mediated angiotensin 2 metabolism [26]. ACE-2 mRNA expression was higher in the myocardium [27] and intestinal tissues [28] of ACE-I users, but not in patients taking ARBs. Conversely, urinary ACE-2 levels were found to be elevated in ARB users but not in patients taking ACE-Is [29], and circulating levels of ACE-2 in peripheral blood remain unchanged in patients taking both ACE-Is and ARBs [30–32].

There is clear and consistent evidence that ALI is attenuated by ACE-2 and that ACE-Is and ARBs are protective against the development of ALI. In numerous animal models, ALI was consistently exacerbated by ACE-2 knockout and improved with ACE-2 overexpression and by the administration of soluble ACE-2 [5, 33–35]. ACE-Is [36] and ARBs [5, 6, 33, 34, 37] have been demonstrated to attenuate ALI in a number of rodent models. Finally, soluble ACE-2 has been demonstrated to prevent cellular entry by SARS-CoV-1 [6, 38] and SARS-CoV-2 [39].

The management of the renin–angiotensin–aldosterone system is essential in the treatment of hypertension, CKD, heart failure and myocardial infarction [29, 31]. Abrupt withdrawal of ACE inhibitors or ARBs is associated with worsening of heart failure [40], relapse of dilated cardiomyopathy [41], destabilization of blood pressure control [42] and increased rates of mortality [43]. It is essential to establish whether the theoretical advantages of ACE-I or ARB withdrawal in response to the COVID-19 pandemic outweigh the well-established risks. We therefore decided to explore whether ACE-I or ARB use might exacerbate the endotheliopathic effects of SARS-CoV-2 by examining complications of the disease known to be associated with endotheliopathy. The rates of AKI, major venous or arterial thrombi, and in-hospital mortality were examined in patients admitted to an inner London hospital with laboratory-confirmed SARS-CoV-2. The data were analysed to determine whether ACE-I or ARB use was associated with increased incidence of these end-points.

Methodology

The development of AKI and macrovascular thrombosis was selected as co-primary end-points, and in-hospital mortality was a secondary end-point. All patients aged ≥18 admitted to Queen Elizabeth Hospital London between the 1 March and 30 April 2020 with laboratory-confirmed SARS-CoV-2 infection ($n = 558$) were included in the study. Patients were followed up until the 24 May 2020.

Patients aged < 18 were excluded from the study. Patients with clinically suspected SARS-CoV-2 but without a laboratory-confirmed diagnosis were excluded. One further patient was excluded after being admitted to ICU for postoperative monitoring; they were found incidentally to have SARS-CoV-2 infection and excluded in order to prevent skewing of the ICU subpopulation data. A total number of 557 patients were included in the statistical analysis.

ACE-I or ARB exposure was defined as a history of ACE-I or ARB use prior to hospital admission on pharmacy medicine reconciliation, regardless of whether the medication was continued as an inpatient. Anticoagulant use was defined as pre-admission use of a vitamin K antagonist (VKA) or direct-acting oral anticoagulant (DOAC), regardless of whether this was continued or withheld on hospital admission. SARS-CoV-2 testing was performed by reverse transcriptase PCR of oronasal swab or nonbronchoscopic lavage samples. Macrovascular thrombi were defined as radiological or ultrasound evidence of deep venous thrombi, pulmonary emboli, renal vein thrombi, ischaemic stroke, myocardial infarction and ventricular thrombi. AKI was defined as a rise in blood creatinine level of >50% from baseline, or a drop in eGFR of >50% below baseline value.

Data were retrospectively extracted from the electronic and paper health records of included patients using a standardized data collection tool by a team of clinicians working on the ICU. Patients transferred to other hospitals for specialist care or capacity reasons (n = 42) were followed up through networked electronic patient record systems and by contacting clinicians in the accepting centres.

The project was discussed with the research and development department for the study centre, Lewisham and Greenwich NHS Foundation Trust. The research and development lead advised that Research Ethics Committee approval was not required because the project utilized pre-existing, anonymized patient data. The study was approved and endorsed by the hospital's clinical effectiveness department as a service evaluation project (approval number 6644). The research did not receive any grant or funding.

Statistical analysis

Data were summarized using descriptive statistics. For categorical variables, counts and percentages are reported. Distribution of continuous variables was first tested for normality using the Shapiro–Wilk test; mean and standard deviations are reported for normally distributed variables; and median with 1st and 3rd quartiles was reported for non-normally distributed data. To compare variable distribution between groups, chi-squared or Fisher's exact tests were used for categorical variables, independent-samples Student's t-test was used for normally distributed continuous variables and the Mann–Whitney test was used for non-normally distributed continuous variables.

To assess the effect of ACE-I and ARB use on the occurrence of macrovascular thrombi, AKI or in-hospital mortality, a multivariable conditional logistic regression models stratified on ICU admission adjusted for demographic and clinical data were fitted. Confounders included in the models were demographic data including age, gender, dependence on assistance to perform activities of daily living (ADLs), coexisting conditions (diabetes mellitus, hypertension, hypercholesterolaemia, any cardiovascular disease, any respiratory disease, baseline eGFR < 60 mL min^{-1}/1.73 m^2, baseline eGFR < 15 mL min^{-1}/1.73 m^2, any malignancy, immunosuppression of any cause, autoimmune disease), medications (use of aldosterone antagonists, beta-blockers, calcium channel blockers, statin, any hypoglycaemic drug, antiplatelet drug, anticoagulants; additionally diuretics in case of analysis of AKI risk factors) and laboratory results (platelet count). Odds ratios with 95% confidence intervals and Wald's test p-values were reported.

An overlap propensity score weighting was used to adjust for potential confounding, as patients treated with ACE-Is or ARBs are more likely to have underlying comorbidities and use other medications. A propensity score for use of ACE-Is or ARBs was estimated from a multivariable logistic regression model including selected variables (demographic – age, gender, ADLS; comorbidities – diabetes mellitus, hypertension, hypercholesterolaemia, congestive heart failure, ischaemic heart disease, any cardiovascular disease, obstructive sleep apnoea, eGFR < 60 mL min^{-1}/1.73 m^2; medications – use of anticoagulant, antiplatelet drug, diuretic, statin, any hypoglycaemic drug). The overlap propensity score-weighted method was then applied, and each patient's weight was the probability of being assigned to the opposite group (i.e. taking/not taking ACE-I/ARB). Overlap propensity score-weighted logistic regression models were then built to assess the effect of ACE-Is/ARBs on the probability of selected outcome occurrence, and weighted estimates for relative risks with 95% confidence intervals are reported.

In the next step, as a part of exploratory analysis of risk factors for selected outcomes, variable selection using stepwise regression with minimization of the Akaike criterion procedure was applied on a

multivariable conditional logistic regression models stratified on ICU admission with full set of explanatory variables (specified above). Estimated odds ratios with 95% confidence intervals for fitted reduced multivariable models were reported.

The effect of antiplatelet and anticoagulation treatment on the occurrence of macrovascular thrombi, AKI and in-hospital death was assessed using an overlap propensity score-weighted analysis that was analogous to the procedure described for ACE-I/ARB effect assessment.

Patients with pre-existing end-stage renal failure (eGFR < 15 mL min^{-1}/1.73 m^2, $n = 12$) were excluded from the analysis of risk factors for AKI development, and patients in whom disease outcome was not known at last follow-up (neither discharged from hospital or stepped down from ICU nor died by 24 May 2020, $n = 13$) were excluded from the analysis of risk factors for in-hospital death.

In all analyses, the two-sided significance threshold was set at 0.05. Statistical analysis was performed in R statistical software version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria https://www.R-project.org/).

Results

Between 1 March and 30 April 2020, 557 patients were admitted to hospital with laboratory-confirmed SARS-CoV-2; 171 patients (30.7%) took either ACE-Is (115 patients, 20.6%) or ARBs (55 patients, 9.9%) prior to admission, and one patient took both medications.

Demographic and clinical characteristics are displayed in Table 1. The mean (±SD) age at hospital admission was 68.4 years (±17.0), and 237 (42.5%) participants were female. Of the patients for whom ethnicity data were available ($n = 451$), 276 (61.2%) were recorded as Caucasian, 79 (17.5%) as Black and 59 (13.1%) as Asian. Regarding comorbidities, 288 (51.7%) suffered from hypertension, 173 (31.1%) were diabetic, and 129 (23.2%) had hypercholesterolaemia. Two hundred and seven (37.2%) patients suffered from a premorbid cardiovascular condition, 116 (20.8%) had a pre-existing respiratory illness, and 152 (27.3%) had a baseline eGFR below 60 mL min^{-1}/1.73 m^2.

Patients taking ACE-Is or ARBs were more likely to be male ($P = 0.001$) and had a higher prevalence of diabetes, hypertension, hypercholesterolaemia and cardiovascular disease (all $P = <0.001$). They were also more likely than non-ACE-I/ARB users to take aldosterone antagonists ($P = 0.014$), beta-blockers, calcium channel blockers, diuretics, statins, antiplatelet drugs (all $P = <0.001$) or anticoagulants ($P = 0.021$). They were more often independent in their ADLs ($P = 0.036$). Patients taking ACE-Is or ARBs prior to admission had higher D-dimer levels (median 565.5 vs 461.0 ng mL^{-1}, $P = 0.046$) and lower lymphocyte counts (median 0.8 vs 1.0×10^9 cells L^{-1}, $P = 0.026$) at admission (Table 2).

At last follow-up on the 24 May 2020, 532 (95.5%) of the included patients had either died or been discharged from hospital; 25 were still inpatients. The median length of hospital stay was 8.0 days (IQR: 4.0, 15.2). Of all 557 enrolled patients, two hundred (35.9%) died during the study period, 92 (16.5%) were admitted to ICU, and 89 (16.0%) were invasively ventilated. At last follow-up, 126 (23.1%) had developed an AKI, 34 (6.1%) were diagnosed with macrovascular thrombi, and 13 (2.3%) experienced a major haemorrhage. The use of ACE-Is or ARBs was not associated with any change in the incidence of these end-points on univariate analysis.

The patients admitted to ICU were younger than those not admitted to ICU (mean ± SD age 55.8 ± 11.3 vs 70.9 ± 16.9, $P = <0.001$), more likely to be male and were more frequently from Black or Asian backgrounds. They had comparable rates of diabetes, hypertension and hypercholesterolaemia, but patients who suffered from cardiovascular disease, respiratory disease or dementia, or were dependent on assistance to perform their ADLs were less likely to be admitted to ICU (Figure S1). Patients admitted to ICU stayed in critical care for a median of 18.0 (IQR: 10.0, 27.0) days. Amongst the 92 patients admitted to ICU, 44 (51.2%) died, 48 (53.3%) developed an AKI, and 30 (33.0%) received emergency renal replacement therapy. A macrovascular thrombus was diagnosed in 22 (23.9%), whilst 8 (8.7%) had clinically significant bleeding.

A multivariable conditional logistic regression model stratified on ICU admission was constructed to further examine the relationship between ACE-I and ARB use and the development of macrovascular thrombi, AKI and in-hospital mortality. The results of the full multivariable logistic regression

Table 1. *Demographic and clinical characteristics stratified by ACE-I/ARB use*

Variable	All patients (n = 557)	ACE-I/ARB users (n = 171)	ACE-I/ARB nonusers (n = 386)	P-value
Age (years)				
Mean (SD)	68.4 (17.0)	69.9 (14.7)	67.7 (18.0)	0.325
Range	19–105	19–98	19–105	
Gender				
Male – n (%)	320 (57.5%)	117 (68.4%)	203 (52.6%)	0.001
Female – n (%)	237 (42.5%)	54 (31.6%)	183 (47.4%)	
Ethnicity (n = 451)				
Caucasian – *n* (%)	276 (61.2%)	90 (63.4%)	186 (60.2%)	0.871
Asian – *n* (%)	59 (13.1%)	20 (14.1%)	39 (12.6%)	
Black – *n* (%)	79 (17.5%)	21 (14.8%)	58 (18.8%)	
Mixed – *n* (%)	8 (1.8%)	2 (1.4%)	6 (1.9%)	
Other – *n* (%)	29 (6.4%)	9 (6.3%)	20 (6.5%)	
Comorbidities				
Diabetes – *n* (%)	173 (31.1%)	78 (45.6%)	95 (24.6%)	<0.001
Hypertension – *n* (%)	288 (51.7%)	131 (76.6%)	157 (40.7%)	<0.001
High cholesterol – *n* (%)	129 (23.2%)	66 (38.6%)	63 (16.3%)	<0.001
Cardiovascular disease – *n* (%)	207 (37.2%)	87 (50.9%)	120 (31.1%)	<0.001
Respiratory disease – *n* (%)	116 (20.8%)	36 (21.1%)	80 (20.7%)	1.000
eGFR < 60 mL min^{-1}/1.73 m^2 – *n* (%)	152 (27.3%)	61 (35.7%)	91 (23.6%)	0.004
eGFR < 15 mL min^{-1}/1.73 m^2 – *n* (%)	12 (2.2%)	3 (1.8%)	9 (2.3%)	1.000
Chronic liver disease	11 (2.0%)	6 (3.5%)	5 (1.3%)	0.101
Any malignancy	60 (10.8%)	21 (12.3%)	39 (10.1%)	0.538
Autoimmune connective tissue disease	18 (3.2%)	5 (2.9%)	13 (3.4%)	0.989
HIV	5 (0.9%)	1 (0.6%)	4 (1.0%)	1.00
Immunosuppressant medication	23 (4.1%)	6 (3.5%)	17 (4.4%)	0.796
Recent chemotherapy	1 (0.2%)	0 (0.0%)	1 (0.3%)	1.00
Dementia – *n* (%)	109 (19.6%)	29 (17.0%)	80 (20.7%)	0.359
Assistance required with activities of daily living				
Independent – *n* (%)	328 (58.9%)	114 (66.7%)	214 (55.4%)	0.036
Minor assistance – *n* (%)	75 (13.5%)	21 (12.3%)	54 (14.0%)	
Major assistance – *n* (%)	154 (27.6%)	36 (21.1%)	118 (30.6%)	
Medications				
Aldosterone antagonist	14 (2.5%)	9 (5.3%)	5 (1.3%)	0.014
Beta-blocker	115 (20.6%)	57 (33.3%)	58 (15.0%)	<0.001
Calcium channel blocker	146 (26.2%)	72 (42.1%)	74 (19.2%)	<0.001
Diuretic	93 (16.7%)	51 (29.8%)	42 (10.9%)	<0.001
Statin	222 (39.9%)	115 (67.3%)	107 (27.7%)	<0.001
Antiplatelet drug	116 (20.8%)	56 (32.7%)	60 (15.5%)	<0.001
Anticoagulant	58 (10.4%)	26 (15.2%)	32 (8.3%)	0.021
First blood test results (within 3 days of admission)				
D-dimer ng mL^{-1} – median (IQR) (n = 281)	494.0 (311.0, 961.0)	565.5 (359.8, 1180.2)	461.0 (285.0, 927.0)	0.046

Table 1 (*Continued*)

Variable	All patients (n = 557)	ACE-I/ARB users (n = 171)	ACE-I/ARB nonusers (n = 386)	P-value
Lymphocyte count ×10*9/L – median (IQR) (n = 555)	0.90 (0.70, 1.30)	0.80 (0.60, 1.20)	1.00 (0.70, 1.30)	0.021
PLT count ×10*9/L – median (IQR) (n = 556)	220.0 (164.8, 278.0)	209.0 (163.0, 272.0)	225.0 (169.0, 279.0)	0.332

Table 2. *Outcomes stratified by ACE-I/ARB use*

Outcome	All patients (n = 557)	ACE-I/ARB users (n = 171)	ACE-I/ARB nonusers (n = 386)	P-value
Died in hospital by 24/5/20 – n (%)	200 (35.9%)	70 (40.9%)	130 (33.7%)	0.121
Admitted to ICU – n (%)	92 (16.5%)	28 (16.4%)	64 (16.6%)	1.000
Invasive ventilation – n (%)	89 (16.0%)	28 (16.4%)	61 (15.8%)	0.965
AKI during stay – n (%)	126 (23.1%)	43 (25.6%)	83 (22.0%)	0.421
Acute renal replacement therapy – n (%)	30 (5.4%)	12 (7.0%)	18 (4.7%)	0.355
Macrovascular thrombus detected – n (%)	34 (6.1%)	9 (5.3%)	25 (6.5%)	0.719
Major haemorrhage – n (%)	13 (2.3%)	6 (3.5%)	7 (1.8%)	0.233
ECMO – n (%)	4 (0.7%)	0 (0.0%)	4 (1.0%)	0.318
Length of hospital stay if died or discharged before 24/5/20 (days) (n = 532)				
Median (IQR)	8.0 (4.0, 15.2)	7.0 (3.0, 15.0)	8.0 (4.0, 16.0)	0.174
Range	0–63	0–56	0–63	
Length of ICU stay if died or discharged from ICU before 24/5/20 (days) (n = 85)				
Median (IQR)	18.0 (10.0, 27.0)	18.0 (7.5, 26.5)	18.0 (11.2, 27.5)	0.458
Range	0–49	2–38	0–49	

models for these three end-points are detailed in Figure S2; the results pertaining to the primary end-points are displayed in Table 3. On multivariable analysis, the use of ACE-Is or ARBs was not found to be an independent predictor of the three end-points. Furthermore, an overlap propensity score-weighted analysis found that the risk of developing macrovascular thrombi, AKI and of in-hospital mortality was not significantly different in patients using ACE-Is/ARBs prior to hospital admission (Table 3).

Table 4 reports an exploratory analysis using multivariable conditional logistic regression stratified on ICU admission with variables selected by stepwise regression with minimization of the Akaike information criteria (AIC) for factors associated with thrombosis, AKI and in-hospital mortality. Severe CKD, as defined by a baseline eGFR < 15 mL min^{-1}/1.73 m^2, was associated with an increased risk of macrovascular thrombi (OR: 8.237, 95% CI: 1.689–40.181, P = 0.009), and the use of antiplatelet medications carried a nonstatistically significant risk reduction for macrovascular thrombosis (OR: 0.327, 95% CI: 0.074–1.437, P = 0.139). The risk of developing an AKI increased with each year of advancing age (OR: 1.028, 95% CI: 1.011–1.044, P = 0.001), and diabetic patients were also at increased risk of AKI (OR: 1.675, 95% CI: 1.065–2.633, P = 0.025). Patients who were immunosuppressed (including patients taking immunosuppressive medications, those with HIV and patients who had recently undergone chemotherapy) had a lower risk of AKI (OR: 0.160, 95% CI: 0.029–0.886, P = 0.036). Advancing age, dependence on assistance to perform ADLs, male gender and baseline eGFR < 60 mL min^{-1}/1.73 m^2 were all associated with a greater likelihood of in-hospital mortality.

Table 3. *Results of a multivariable analysis and overlap propensity score-weighted analysis examining the incidence of macrovascular thrombi, acute kidney injury and in-hospital mortality in patients taking ACE-Is or ARBs prior to hospital admission compared with patients not taking these medications*

Dependent variable	ACE-I/ARB users – *n* (%)	ACE-I/ARB nonusers – *n* (%)	Outcome measure	95% CI	*P*-value
Multivariable conditional logistic regression analysis – odds ratio					
Macrovascular thrombus	9 (5.3%)	25 (6.5%)	0.724	0.253–2.066	0.546
AKI	43 (25.6%)	83 (22.0%)	1.039	0.595–1.813	0.839
In-hospital mortality	70 (40.9%)	130 (33.7%)	1.158	0.703–1.907	0.564
Overlap propensity score-weighted analysis – weighted estimate for relative risk					
Macrovascular thrombus	9 (5.3%)	25 (6.5%)	1.05	0.48–2.31	–
AKI	43 (25.6%)	83 (22.0%)	1.04	0.71–1.52	–
In-hospital mortality	70 (40.9%)	130 (33.7%)	1.04	0.80–1.36	–

Table 4. *Reduced multivariable conditional logistic model stratified for ICU admission for macrovascular thrombi, acute kidney injury and in-hospital mortality; variables selected using stepwise regression to minimize the Akaike information criteria*

Dependent variable	Independent variable	Odds ratio	95% CI	*P*-value
Macrovascular thrombus	eGFR < 15 mL min^{-1}/1.73 m^2	8.237	1.689–40.181	0.009
	Antiplatelet drug	0.327	0.074–1.437	0.139
AKI	Age at admission (per year)	1.028	1.011–1.044	0.001
	Diabetes mellitus	1.675	1.065–2.633	0.025
	Any malignancy	1.738	0.885–3.416	0.109
	Immunosuppression	0.160	0.029–0.886	0.036
	Autoimmune connective tissue disease	3.227	0.909–11.458	0.070
In-hospital mortality	Age at admission (per year)	1.050	1.031–1.068	<0.001
	Female gender	0.652	0.424–1.004	0.052
	Any cardiovascular disease	1.608	1.048–2.467	0.029
	eGFR < 60 mL min^{-1}/1.73 m^2	2.093	1.351–3.243	0.001
	Assistance required to perform ADLs	1.682	1.018–2.780	0.043

In view of the observed reduction in the incidence of macrovascular thrombi in patients taking antiplatelets, a further overlap propensity score-weighted analysis was undertaken to examine how the incidence of the selected end-points might be affected by the premorbid use of antiplatelets or anticoagulants (Table 5). The weighted estimator for relative risk of macrovascular thrombi amongst patients using antiplatelets prior to admission was 0.238 (95% CI: 0.0577–0.978), whilst for patients taking anticoagulants it was 0.0692 (95% CI: 0.00674–0.710). The use of antiplatelets and anticoagulants was not associated with a change in the incidence of AKI or in-hospital mortality.

Discussion

By exploring the association between ACE-I/ARB use and the development of AKI and macrovascular thrombi, we provide evidence that these medications do not increase vulnerability to the endotheliopathic effects of SARS-CoV-2. Furthermore,

Table 5. *Results of an overlap propensity score-weighted analysis of the incidence of macrovascular thrombi, AKI, renal replacement therapy and in-hospital mortality in patients taking antiplatelet and anticoagulant medications compared with patients not taking these medications*

Dependent variable	Independent variable	Weighted estimate for relative risk	95% CI
Macrovascular thrombus	Antiplatelet use	0.238	0.0577–0.978
	Anticoagulation	0.0692	0.00674–0.710
AKI	Antiplatelet use	0.827	0.531–1.288
	Anticoagulation	0.515	0.265–1.000
In-hospital mortality	Antiplatelet use	1.108	0.833–1.474
	Anticoagulation	1.118	0.760–1.644

these data also suggest that ACE inhibitors and angiotensin receptor blockers do not increase the risk of in-hospital mortality in SARS-CoV-2 infection. In the exploratory analysis, severe CKD was associated with macrovascular thrombi, and diabetes was found to predispose this patient group to the development of an AKI. Patients who were immunosuppressed, whether through immunosuppressive medication, HIV infection or other conditions causing immunocompromise, were less likely to develop an AKI. Our findings are in agreement with previous reports that advancing age and male gender are important risk factors for mortality in SARS-CoV-2 infection [44], and suggest that CKD might increase mortality in this patient group. Finally, our additional analysis suggests that anticoagulation and antiplatelet use may be protective against macrovascular thrombi in SARS-CoV-2 infection.

The hypothesis that the use of ACE-Is/ARBs is potentially harmful in SARS-CoV-2 infection is based on the observation that these medications have been shown to increase ACE-2 receptor expression in the tissues infected by SARS-CoV-2 [9, 27]. The authors have theorized that increased ACE-2 expression might facilitate the viral cellular infection that is at the base of the SARS-CoV-2 endotheliopathy [3, 4]. If this were the case, we would expect ACE-I or ARB use to promote SARS-CoV-2 endotheliopathy, leading to an increased incidence of AKI, thrombosis and mortality. Our analysis revealed no association between ACE-I/ARB use and mortality, and we also found no signal for a relationship between the use of these medications and the development of AKI or the diagnosis of macrovascular thrombi. Taken together, this suggests that ACE-I/ARB use does not promote SARS-CoV-2-mediated endotheliopathy to any clinically significant extent. These findings are consistent with previous data suggesting that ACE-I/ARB use does not increase susceptibility to SARS-CoV-2 infection [45] or mortality [46]. On the other hand, there is clear evidence that discontinuation of ACE-Is or ARBs is associated with adverse clinical outcomes, including the worsening of cardiac failure and death [40, 43]. Therefore, ACE-Is and ARBs should not be discontinued in response to the SARS-CoV-2 pandemic, and they should not be routinely suspended in patients who contract SARS-CoV-2.

Diabetes is known to cause end-organ failure through adverse vascular remodelling, and many patients with diabetes, even without established organ dysfunction, have subclinical vascular disease and endothelial damage [47]. Given the central role of inflammation and endotheliopathy in SARS-CoV-2 infection, it is perhaps unsurprising that diabetes was found to predispose patients to developing an AKI. The underlying vascular disease and loss of end-organ functional reserve are destabilized by the effects of SARS-CoV-2 infection and by the physiological stress of critical illness, and diabetic patients would therefore be predisposed to developing an AKI. Autoimmune connective tissue disease also approached the significance threshold to predispose AKI, whilst immunosuppression of any cause emerged as a protective factor. We hypothesize that patients with autoimmune connective tissue disease have pre-existing endothelial inflammation that is exacerbated by the effects of SARS-CoV-2, thus promoting end-organ damage, whilst immunosuppression mitigates against the inflammatory effects of viral infection.

Male gender was associated with mortality during the SARS-CoV-1 pandemic of the early 2000s [48], and advancing age is an established risk factor for mortality in seasonal influenza [49].

Similarly, older age and male sex are established risk factors for mortality in SARS-CoV-2 [44]. Immune cell phenotyping has identified that weaker T-cell immunity in males may underlie the observed association between sex and mortality [50]. Intriguingly, research carried out on an Asian population identified higher levels of ACE-2 expression across a variety of tissues in young female patients, whilst older male patients showed lower ACE-2 expression [51]. Chronic kidney disease was identified as a risk factor for mortality in two large data sets of patients in the UK with SARS-CoV-2 [44, 52]. These observations support the associations seen in our data between older age, male gender and CKD with increased mortality.

SARS-CoV-2 infection perfectly creates Virchow's triad of thrombosis. The endothelial damage caused by SARS-CoV-2 exposes clotting factors carried on the endothelial basement membrane, the systemic inflammatory response to SARS-CoV-2 infection leads to hypercoagulability, and the physical immobility of serious illness leads to blood stasis. This results in a high incidence of macrovascular thrombi. In the study centre, the use of prophylactic heparins (enoxaparin, dose adjusted to weight and renal function, or unfractionated heparin in patients with severe renal impairment) is the standard of care in patients who are not otherwise anticoagulated, with no contraindications to prophylactic anticoagulation. Patients taking antiplatelet medications still received prophylactic heparins, whilst patients anticoagulated with VKAs or DOACs did not routinely receive prophylactic heparin. Our overlap propensity score-weighted analysis found that the use of antiplatelet or anticoagulant medications was associated with a reduced incidence of macrovascular thrombi. We theorize that the use of antiplatelet medications protects against thrombosis by reducing platelet aggregation at exposed endothelial basement membranes and that the use of anticoagulants attenuates the systemic prothrombotic effects of SARS-CoV-2 more effectively than prophylactic dose heparin. However, these data are an additional analysis beyond the original intended scope of the project and these results should be considered to be hypothesis-generating only. It should also be noted that the reduced incidence of thrombosis did not translate to any decrease in mortality rates.

The results described must be interpreted in the context of the study's limitations. As this was a retrospective review of patient charts, we must assume the completeness and accuracy of hospital records. It is likely that some confounding will be introduced by variations in treatment strategies between clinicians, and by changes in practice that occurred during the study period in response to emerging evidence on the optimal management of SARS-CoV-2. The retrospective nature of the work also means that the incidence of macrovascular thrombi may be underestimated due to the fact that investigations were undertaken at physicians' discretion rather than systematically, increasing the likelihood of a type II statistical error. Data were not available on the duration of ACE-I/ARB therapy prior to hospital admission, and patient compliance with ACE-modulating therapy was not assessed. The use of ACE-Is and ARBs was highly correlated with the presence of hypertension, diabetes and cardiovascular disease; analyses were adjusted to account for potential confounders, but as this is not a randomized controlled trial we cannot exclude the possibility of results being skewed by collinearity. An exploratory analysis was used to examine the relationship between many variables and the selected end-points without a prespecified hypothesis, increasing the possibility of discovering chance associations. The findings of the exploratory analysis must therefore only be considered as hypothesis-generating. Finally, relatively few patients used antiplatelets (n = 116) and anticoagulants (n = 58) and fewer still developed macrovascular thrombi (n = 34). The analysis of their effects on the incidence of thrombi, even after overlap propensity score weighting, is therefore the least reliable aspect of the analysis. Further randomized controlled trials examining the effects of initiating ACE-Is [NCT04355429] and ARBs [NCT04311177, NCT04312009] in patients with SARS-CoV-2 are currently recruiting participants, and we await their results with great interest.

Conclusion

In this single-centre retrospective analysis of patients hospitalized with SARS-CoV-2, we did not identify any association between ACE-I/ARB use and acute kidney injury, macrovascular thrombi or in-hospital mortality. Abrupt discontinuation of ACE-Is and ARBs is known to be associated with adverse cardiovascular outcomes [40, 43], and as such, our findings support the recommendations of the European [53] and American [54] Societies of Cardiology that ACE-Is and ARBs

should not be routinely discontinued in response to the COVID-19 pandemic or in cases of SARS-CoV-2 infection.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contribution

Simon John Tetlow: Conceptualization (lead); Data curation (lead); Formal analysis (supporting); Investigation (lead); Methodology (lead); Project administration (lead); Writing-original draft (lead); Writing-review & editing (lead). **Agnieszka Segiet:** Formal analysis (lead); Methodology (supporting); Writing-original draft (supporting); Writing-review & editing (equal). **Rebecca O'Sullivan:** Data curation (supporting); Investigation (supporting); Methodology (supporting); Writing-review & editing (supporting). **Sinéad O'Halloran:** Conceptualization (supporting); Data curation (supporting); Investigation (supporting); Writing-review & editing (supporting). **Kelli Kalb:** Data curation (supporting); Investigation (supporting); Writing-review & editing (supporting). **Charlotte Brathwaite-Shirley:** Conceptualization (supporting); Data curation (equal); Investigation (supporting); Writing-review & editing (supporting). **Laura Alger:** Data curation (supporting); Investigation (supporting); Writing-review & editing (supporting). **Akshay Ankuli:** Data curation (supporting); Investigation (supporting); Writing-review & editing (supporting). **Mirza Shaheer Baig:** Data curation (supporting); Investigation (supporting); Writing-review & editing (supporting). **Fergus Catmur:** Data curation (supporting); Investigation (supporting); Writing-review & editing (supporting). **Torbert Chan:** Data curation (supporting); Investigation (supporting); Writing-review & editing (supporting). **Declan Dudley:** Data curation (supporting); Investigation (supporting); Writing-review & editing (supporting). **Joshua Fisher:** Data curation (supporting); Investigation (supporting); Writing-review & editing (supporting). **Muhammad Usman Iqbal:** Data curation (supporting); Investigation (supporting); Writing-review & editing (supporting). **Joanna Puczynska:** Data curation (supporting); Investigation (supporting); Writing-review & editing (supporting). **Ryan Wilkins:** Data curation (supporting); Investigation (supporting); Writing-review & editing (supporting). **Rachael Bygate:** Writing-original draft (supporting); Writing-review & editing (supporting). **Peter Roberts:** Conceptualization (equal); Supervision (lead).

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Baseline characteristics: admitted to ICU vs not admitted to ICU.

Figure S2. Full multivariable conditional logistic models stratified for ICU admission for macrovascular thrombotic events, acute kidney injury and in-hospital mortality.

