The influence of ACE inhibitors and ARBs on hospital length of stay and survival in people with COVID-19

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ABSTRACT

Objective: During the COVID-19 pandemic the continuation or cessation of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) has been contentious. Mechanisms have been proposed for both beneficial and detrimental effects. Recent studies have focused on mortality with no literature having examined length of hospital stay. The aim of this study was to determine the influence of ACEi and ARBs on COVID-19 mortality and length of hospital stay.
Methods: COPE (COVID-19 in Older People) is a multicenter observational study including adults of all ages admitted with either laboratory or clinically confirmed COVID-19. Routinely generated hospital data were collected. Primary outcome: mortality; secondary outcomes: Day-7 mortality and length of hospital stay. A mixed-effects multivariable Cox's proportional baseline hazards model and logistic equivalent were used.
Results: 1371 patients were included from eleven centres between 27th February to 25th April 2020. Median age was 74 years [IQR 61–83]. 28.6% of patients were taking an ACEi or ARB. There was no effect of ACEi or ARB on inpatient mortality (aHR = 0.85, 95%CI 0.65–1.11). For those prescribed an ACEi or ARB, hospital stay was significantly reduced (aHR = 1.25, 95%CI 1.02–1.54, p = 0.03) and in those with hypertension the effect was stronger (aHR = 1.39, 95%CI 1.09–1.77, p = 0.007).

Conclusions: Patients and clinicians can be reassured that prescription of an ACEi or ARB at the time of COVID-19 diagnosis is not harmful. The benefit of prescription of an ACEi or ARB in reducing hospital stay is a new finding.

1. Introduction

Throughout the coronavirus pandemic there has been speculation that recovery from COVID-19 may be influenced by drugs inhibiting the renin-angiotensin-aldosterone system (RAAS) including angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) [1,2]. Risk factors have been identified as predisposing to poor outcome with COVID-19 including: hypertension, cardiovascular disease, chronic kidney disease and diabetes [3–5], all of which have clear indications for ACEi or ARB prescription [6–8]. Due to the numerous indications for these drugs in chronic disease management ramipril has become the fourth most commonly prescribed drug in the UK at 27 million prescriptions [9]. Of inpatients testing positive for SARS-CoV-2 in New York 8.3% and 10.5% were taking an ACEi or ARB respectively [10]. Teasing out the effect on COVID-19 recovery due to these comorbidities, or due to the drugs prescribed for them, has not been straightforward. Opinions on whether to withhold or continue community prescriptions of these medications during the pandemic have both been debated [11,12]. However, due to a paucity of trial or observational evidence, organisations including the European Society of Cardiology and the American College of Cardiology and the American Heart Association have advocated continuing ACEi and ARB therapy to avoid deterioration of a person's underlying health issues [13–15].

Patients receiving these medications have been hypothesised to be detrimentally predisposed to infection; SARS-CoV-2 spike protein attaches to target cells by binding to the ACE2, which is upregulated with ACEi and ARBs in animal models [11,16]. However, this remains controversial in humans, for example in a cohort of patients with heart failure, ACE2 was not found to be altered by ACEi or ARBs [17]. In contrast, beneficial effects of ACEi and ARBs have been proposed mediated via changes in both the innate and adaptive immune responses occurring within the RAAS [18,19].

A New York database study and an Italian registry study have shown no increased rate of admissions in those taking an ACEi or ARB in propensity matched cohorts of admitted patients, inferring that there is no increased predisposition to COVID-19 [10,20]. One Chinese multicentre study has shown a mortality benefit in COVID-19 positive patients who were taking ACEi or ARB for hypertension [21]. A recent meta-analysis including 9890 patients across 10 studies showed a similar risk of dying from COVID-19 in those taking and not taking these drugs [22]. None of these studies have examined the effects of ACEi and ARB on non-mortality process outcomes such as length of stay.

2. Objectives

The primary aim was to investigate the influence of ACEi and ARB on mortality and hospital length of stay in patients diagnosed with COVID-19.

3. Methods

3.1. Study design

These data were obtained as part of a prospective multicentre observational study: the COPE study (COVID-19 in Older People study). Authority in the United Kingdom to conduct the study was granted by the Health Research Authority (20/HRA/1898) and in Italy by the Ethics Committee of Azienda Policlinico Hospital Modena (Reference 369/2020/OSS/AOUMO). Cardiff University acted as study sponsor. This manuscript follows the STROBE statement. The study protocol was written prior to including participants [23]. The hospitals included were part of a remobilised research network investigating frailty in emergency laparotomy - the Older Persons Surgical Outcomes Collaboration (OPSOC) [24].

3.2. Setting

Ten hospitals in the United Kingdom participated (Ysbyty Ystrad Fawr in Caerphilly, Royal Gwent Hospital in Newport, Neville Hall Hospital in Abergavenny, Southmead Hospital in Bristol, Aberdeen Royal Infirmary, Royal Alexandra Hospital Paisley, Inverclyde Royal Hospital, Salford Royal, Glasgow Royal Infirmary, and the University Hospital of Wales in Cardiff) and one in Italy (University Hospital of Modena Policlinico). The study collected routinely generated hospital data which were anonymised prior to analysis. Data were recorded securely at the sites and transferred in anonymised format to King's College London for analysis.

3.3. Participants

Patients ≥18 years old admitted to hospital with laboratory or clinically diagnosed COVID-19 were eligible for inclusion. There were no exclusion criteria. Convenience sampling was undertaken from hospital admission lists which were screened by the local clinical teams. Data were collected from 27th February to 25th April 2020.

3.4. Variables

The primary outcome was inpatient mortality. The time to outcome (death or discharge) was measured from patient admission, or the date of diagnosis (if diagnosis was five or more days after admission to take into account hospital acquired COVID-19). Patients' outcomes of discharged and mortality were censored on the date of each.

Secondary outcomes included: length of hospital stay and Day-7 mortality. Outcomes were assessed up to 25th April 2020 using paper and electronic health records. Demographics collected included age, sex, presence of clinical characteristics documented in the patient's health record: coronary artery disease (CAD), diabetes, hypertension, smoking status, and reduced kidney function. C-reactive protein (CRP) was collected as a marker of disease severity. Both ACEi and ARB medication doses were recorded and categorised into low and high dose (low dose = as per the British National Formulary initial dose or below maintenance dose; high dose = equal or greater than maintenance dose). Doses for hypertension in adults 18–75 years old were used if the British National Formulary (BNF) stated more than one indication or specific age group for a drug [25,26]. Sacubitril–valsartan was classified as an ARB.

3.5. Patient and public engagement

Patients were involved in discussion with the study conception and development of the protocol.

3.6. Bias

A standardised case report form was used at all sites. All study personnel underwent data collection training under the supervision of each site's principal investigator.

3.7. Data analysis

We summarised the baseline variables and outcomes using descriptive statistics. Missing smoking status was imputed in 19 cases as never smokers, and 31 cases of missing CRP were imputed as not elevated CRP. The primary outcome was analysed as the time to mortality. Secondary outcome events included time in days to discharge and Day-7 mortality. Patients who remained in hospital, but had not reached their seventh day of admission by the end of the data collection period, were excluded from the Day-7 analysis. Each time to event analysis was reported with a Kaplan-Meier survival plot.

3.8. Statistical methods

The primary outcome of time to mortality was analysed with a mixed-effects multivariable Cox's proportional baseline hazards model. The analysis was fitted with a random effect for site to account for variation occurring at each hospital, and adjusted for patient age group ($\leq$64, 65–79, $\geq$80 years old), sex, disease severity at presentation (elevated CRP > 40 mg/L); diabetes (yes / no); hypertension (yes / no); CAD (yes / no), and kidney disease (eGFR > 60 ml/min/1.73 m^2 / $\leq$60 ml/min/1.73 m^2). Both a crude hazard ratio (HR), and adjusted hazard ratio (aHR) were estimated. The baseline proportionality assumption was tested visually using log-log residuals.

Secondary outcomes were Day-7 mortality (dead / alive), and the length of hospital stay (measured using time-to discharge). Day-7 mortality was analysed using a mixed-effects multivariable logistic regression model, fitting each site as a random effect to account for variation across hospitals, and adjusted with covariates consistent with the primary outcome. The length of stay was analysed using a multivariable Cox model consistent with the primary outcome. Adjusted odds ratio (aOR), and aHR were estimated alongside associated 95% confidence interval. To explore moderating effects in subgroups, the adjusted multivariable analyses were partitioned by: hypertension; diabetes; CAD; kidney disease; patient age; sex; smoking status. Analysis was carried out using Stata version 15. Kaplan Meier survival plots were visualised in R, with packages survival and survminer.

4. Results

4.1. Participants

We screened 1447 participants from all medical and surgical admissions. 76 participants were excluded due to: no positive laboratory polymerase chain reaction result or clinical diagnosis of COVID-19 found (n = 60), and access not granted to records (n = 16). The study included a total of 1371 participants, of which 1124 (89.0%) patients were from the UK and 150 (11%) from Italy (Table 1). There were 63 patients still in hospital with less than seven days follow-up that were excluded from the Day-7 mortality

analysis. The main study findings have been reported with an analysis looking at frailty in a separate publication [27].

4.2. Descriptive data

The population median age was 74 years old (IQR, 61–83) with a similar number of participants between the age groups. 560 participants were female (40.9%) and 100 (7.3%) were current smokers (Table 1). Of comorbidities collected 706 (51.5%) had hypertension, 493 (36.3%) had kidney disease, 372 (27.2%) had diabetes, and 299 (21.9%) had CAD. Of the included patients 363 (26.5%) died in hospital. The median survival time from admission for those who died in hospital was 6 days (IQR, 3–11 days; longest time to death was 38 days), and for those alive (i.e. those who were discharged or censored, when last known alive, and in hospital) was 12 days (IQR, 6–19 days).

A RAAS drug was prescribed for 392 (28.6%) patients, of which 271 (19.8%) were prescribed an ACEi, and 121 (8.8%) an ARB. The most frequently prescribed ACEi was ramipril for 181 patients and ARB was losartan for 48 patients. When dichotomised by dose, we estimate that approximately 185 patients were prescribed a low dose ACEi or ARB, versus 207 prescribed a high dose (Supplementary Table 1), dose is only presented descriptively.

4.3. Mortality and length of stay

ACEi or ARBs were not associated with inpatient mortality, Day-7 mortality rate (Table 2). However, they were associated with a reduced length of stay. Older age, kidney disease, and elevated CRP were associated with worse outcomes: inpatient mortality, increased Day-7 mortality, and increased length of stay. Presence of CAD was associated with increased Day-7 mortality and increased length of stay. Diabetes mellitus was associated with increased length of stay only. Hypertension and smoking status had no association with any outcome.

In the crude analysis mortality there was no crude association between ACEi or ARB prescription and mortality (HR = 1.01, 95% CI 0.80–1.28, p = 0.91). Of the other covariates, mortality was associated with older age (compared to under 65; 65–79 years old, HR = 3.22, 95%CI 3.27–4.57, p < 0.001; and 80 and older, HR = 4.04, 95%CI 2.86–5.71, p < 0.001; see also Supplementary Figure 1), CAD (HR = 1.60, 95%CI 1.27–2.02, p < 0.001), elevated CRP (HR = 2.38, 95%CI 1.77–3.21, p < 0.001), and kidney disease (HR = 1.93, 95%CI 1.55–2.40, p < 0.001) (Table 3).

In the multivariable analysis there was no independent association between ACEi or ARB prescription and mortality (aHR = 0.85, 95%CI 0.65–1.11, p = 0.23). In the other covariates increased risk of mortality was associated with older age (compared to under 65; 65–79 years old, aHR = 3.19, 95%CI 2.22–64.58, p < 0.001; 80 and older, aHR = 4.02, 95%CI 2.79–5.80, p < 0.001), kidney disease (eGFR < 60 ml/min/1.73 m^2, aHR = 1.55; 95%CI 1.23–1.94), and elevated CRP (aHR = 2.70, 95%CI 2.00–3.64, p < 0.001). There was a suggested association between mortality and CAD (aHR = 1.27, 95%CI 0.99–1.64, p = 0.06).

There was no main effect of ACEi or ARB on Day-7 mortality (aOR = 0.82, 95%CI 0.54–1.23, p = 0.16). Of the other covariates older patients had an increased odds of mortality (Table 3). Compared to those aged under 65, patients aged 65–79 had an increased odds of mortality (aOR = 3.45, 95%CI 2.03–5.88, p < 0.001), as well as those aged 80 years and older (aOR = 5.58, 95%CI 3.26–9.57, p < 0.001). There was an increased odds of Day-7 mortality in patients with CAD (aOR = 1.50, 95%CI 1.02–2.22, p = 0.05), kidney disease (aOR = 1.87, 95%CI 1.31–2.67, p < 0.001), and elevated CRP (aOR = 5.51, 95%CI 3.28–9.24, p < 0.001).

Table 1
Demographic characteristics of the included participants (Note: longest time to mortality was 38 days).

	Inpatient mortality		
Sites	Dead (n = 363)	Alive (n = 1008)	Total (n = 1371)
Hospital A	12 (14.1)	73 (85.9)	85 (6.2)
Hospital B	12 (30.0)	28 (70.0)	40 (2.9)
Hospital C	33 (23.4)	108 (76.6)	141 (10.3)
Hospital D	8 (18.6)	35 (81.4)	43 (3.1)
Hospital E	15 (14.4)	89 (85.6)	104 (7.6)
Hospital F	21 (14.0)	129 (86.0)	150 (10.9)
Hospital G	17 (29.3)	41 (70.7)	58 (4.2)
Hospital H	86 (42.6)	116 (57.4)	202 (14.7)
Hospital I	117 (31.2)	258 (68.8)	375 (27.4)
Hospital J	42 (24.3)	131 (75.7)	173 (12.6)
Age			
Under 65 yrs	45 (10.6)	380 (89.4)	425 (31.0)
65 to 79 yrs	139 (29.8)	328 (70.2)	467 (34.1)
Over 80 yrs	179 (37.4)	300 (62.6)	479 (34.9)
Sex			
Female	142 (25.4)	418 (74.6)	560 (40.9)
Male	221 (27.3)	590 (72.8)	811 (59.2)
Smoking status			
Never smokers	179 (24.7)	546 (75.3)	725 (52.9)
Ex smokers	158 (30.0)	369 (70.0)	527 (39.8)
Current smokers	20 (20.0)	80 (80.0)	100 (7.3)
Missing	6	13	19
Diabetes mellitus			
No	252 (25.3)	743 (74.7)	995 (72.6)
Yes	110 (29.6)	262 (70.4)	372 (27.1)
Missing	1	3	4
Hypertension			
No	162 (24.5)	500 (75.5)	662 (48.3)
Yes	200 (28.3)	506 (71.7)	706 (51.5)
Missing	1	2	3
Coronary artery disease			
No	250 (23.4)	819 (76.6)	1069 (78.0)
Yes	112 (37.5)	187 (62.5)	299 (21.8)
Missing	1	2	3
Elevated CRP > 40 mg/L			
No	44 (12.2)	318 (87.8)	362 (28.7)
Yes	308 (31.5)	670 (68.5)	978 (71.3)
Missing	11	20	31
Kidney disease (eGFR < 60 ml/min/ 1.73 m^2)			
No	173 (20.0)	692 (80.0)	865 (63.1)
Yes	184 (37.3)	309 (62.7)	493 (36.0)
Missing	6	7	13
RAAS drug[&]			
None	257 (26.3)	722 (73.8)	979 (71.4)
Low Dose ACE	36 (28.8)	89 (71.2)	125 (9.1)
High Dose ACE	38 (26.0)	108 (74.0)	146 (10.7)
Low Dose ARB	17 (28.3)	43 (71.7))	60 (4.4)
High Dose ARB	15 (24.6)	46 (75.4)	61 (4.4)

[&] Dosage is presented descriptively only.

The prescription of an ACEi or ARB offered evidence of a protective effect, and was associated with a shorter length of stay (aHR = 1.25, 95%CI 1.02–1.54, p = 0.03). There was a longer length of stay in patients that were: older (65–79 years old, aHR = 0.68, 95%CI 0.56–0.83, p < 0.001; ≥80 years old, aHR = 0.50, 95%CI 0.40–0.64, p < 0.001); had a greater disease severity at presentation (CRP > 40 mg/L, aHR = 0.81, 95%CI 0.68–0.97, p = 0.02); and had diabetes (aHR = 0.82, 95%CI 0.67–1.00, p = 0.05).

Due to our incomplete understanding of the disease, and mixed findings in other literature regarding ACEi and ARB prescriptions, we explored subgroup analyses (Supplementary Figures 2–4). A protective effect was demonstrated for ACEi and ARB prescriptions in hypertensive patients with a shorter length of stay (aHR = 1.39, 95%CI 1.09–1.77, p = 0.007, Supplementary Figure 4). There was a suggested finding of an ACEi or ARB prescription being moderated by the influence of smoking status: length of stay was reduced in ex-smokers prescribed an ACEi or ARB (aHR = 1.46, 95%CI 1.08–1.98, p = 0.015); with a stronger effect seen in current smokers (aHR = 3.26, 95%CI 1.16–9.18, p = 0.025). However, caution is needed when interpreting all subgroup analyses

5. Discussion

5.1. Key results

These data show that ACEi and ARBs were not associated with increased mortality in a hospital population admitted with a diagnosis of COVID-19. Furthermore, patients taking an ACEi or ARB had a reduced length of stay, and this was seen with greater effect in patients with hypertension, independent of age, other comorbidities or disease severity.

5.2. Mortality

Our demonstration of no difference in mortality between the ACEi/ARB and non-ACEi/ARB groups admitted with COVID-19 is in keeping with other studies [28,22]. We have demonstrated a protective effect with a reduction in Day-7 mortality for patients with hypertension taking an ACEi or ARB. This fits with another multi-centre study in China showing similar mortality reductions at 28-day follow-up. However, compared to our study, their reported overall mortality rate was far lower (28.3% vs 8.8% respectively). This may have been due to a due to a younger cohort (median 74 [IQR 61–83] vs 64 [IQR 55–68] respectively) with fewer comorbidities [21], at a different stage of the pandemic.

5.3. Length of hospital stay

We are the first to show that ACEi or ARB prescription has been linked to a reduction in the length of stay. Rapid discharge may represent either a marker of better disease recovery, or improvement in unmeasured factors that facilitate discharge from hospital service such as more rapid normalisation of oxygen saturations. The virus likely causes inactivation of ACE2, as has been see for SARS-CoV, and leads to an increase in angiotensin II (Ang II), which in turn acts via the angiotensin II type 1a receptor (AT1aR) to result in pulmonary vasoconstriction and increased lung endothelial permeability. This precipitates acute lung injury and potentially acute respiratory distress syndrome [29]. The reduced length of stay in all patients may be due to the fact that ACEi decreases Ang II production, by blocking the conversion of Ang I to Ang II, and ARBs block AT1aR preventing Ang II's actions, both theoretically resulting in a lower degree of lung injury, and faster recovery. However, despite this faster hospital recovery the overall physiological

Table 2
Analysis of the time from admission to inpatient mortality.

	Time to mortality			
	Crude Hazard Ratio (HR) (n = 1342)[&&]		Adjusted Hazard Ratio (aHR)[&] (n = 1338) (n = 1326)[&&&]	
	HR, (95%CI)	p-value	aHR, (95%CI)	p-value
ACEi/ARB	1.01, (0.80–1.28)	0.91	0.85, (0.65–1.11)	0.23
Age				
<65 years	Ref			
65–79	3.22, (2.27–4.57)	<0.001	3.19, (2.22–4.58)	<0.001
80 and older	4.04, (2.86–5.71)	<0.001	4.02, (2.79–5.80)	<0.001
Sex (Female)				
Male	1.03, (0.82–1.28)	0.81	1.04, (0.82–1.31)	0.74
Smoking Status (Never)	Ref			
Ex-smoker	1.17, (0.94–1.45)	0.16	0.94, (0.75–1.18)	0.59
Current	0.76, (0.47–1.24)	0.28	0.92, (0.56–1.52)	0.76
Diabetes	1.06, (0.84–1.34)	0.61	1.07, (0.84–1.38)	0.57
Coronary Artery Disease	1.60, (1.27–2.02)	<0.001	1.27, (0.99–1.64)	0.06
Hypertension	1.17, (0.94–1.45)	0.15	0.95, (0.75–1.20)	0.67
Kidney disease (eGFR < 60 ml/min/1.73 m^2)	1.93, (1.55–2.40)	<0.001	1.55, (1.23–1.94)	<0.001
Elevated CRP (>40 mg/L)	2.38, (1.77–3.21)	<0.001	2.70, (2.00–3.64)	<0.001

[&] The multivariable regression were adjusted for: age group; sex; smoking status; CRP; diabetes; CAD; hypertension; kidney disease and ACEi/ARB.
[&&] 29 Cases were not included in the analysis due to patient death on admission.
[&&&] 16 Cases were not included in the analysis due to missing covariate data.

Table 3
Secondary outcomes: Day-7 Mortality and Time to discharge (length of stay).

	Day-7 mortality		Length of stay	
	Adjusted Odds Ratio (aOR)[&] (n = 1291)[&&]		Adjusted Hazard Ratio (aHR)[&] (n = 1338) (n = 1326)[&&&]	
	aOR, (95%CI)	p-value	aHR, (95%CI)	p-value
ACEi/ARB	0.82 (0.54–1.23)	0.34	1.25, (1.02–1.54)	0.03
Age				
<65 years	Ref			
65–79	3.45 (2.03–5.88)	<0.001	0.68, (0.56–0.83)	<0.001
80 and older	5.58 (3.26–9.57)	<0.001	0.50, (0.40–0.64)	<0.001
Sex				
Male	0.91 (0.64–1.30)	0.60	1.01, (0.85–1.21)	0.89
Smoking Status (Never)	Ref			
Ex-smoker	1.11 (0.78–1.59)	0.55	0.91, (0.76–1.08)	0.27
Current	0.90 (0.40–2.03)	0.80	0.95, (0.68–1.32)	0.74
Diabetes	1.20 (0.82–1.76)	0.36	0.82, (0.67–1.00)	0.05
Coronary Artery Disease	1.50 (1.02–2.22)	0.04	1.00, (0.80–1.26)	0.99
Hypertension	0.88 (0.61–1.27)	0.50	1.12, (0.94–1.37)	0.21
Kidney disease (eGFR < 60 ml/min/1.73 m^2)	1.87 (1.31–2.67)	0.001	0.88, (0.72–1.07)	0.19
Elevated CRP (>40 mg/L)	5.51 (3.28–9.24)	<0.001	0.81, (0.68–0.97)	0.02

[&&]The multivariable regression were adjusted for: age group; sex; smoking status; CRP; diabetes; CAD; hypertension; kidney disease and ACEi/ARB.
[&&&]63 cases were excluded as the patient was followed up for less than 7 days and was alive and in hospital, and a further 17 cases were not included due to missing covariate data.
[&&&]29 cases were not included due to patient death on admission, and 16 cases were not included in the analysis due to missing covariate data.

recovery may not be significant enough to counteract mortality from COVID-19.

It is difficult to propose a mechanism that explains the consistent effect of ACEi and ARB improving outcomes for hypertensive patients that is not seen in other comorbidity groups. This may demonstrate better medical optimisation preventing significant inpatient events and so allowing more rapid recovery from COVID-19. In addition, non-prescription of an ACEi or ARB may represent a patient group that has not presented to medical services recently, or has ceased the drug, and therefore has

undiagnosed or poorly optimised comorbidities (e.g. CAD); this study would be unable to detect this difference.

5.4. Strengths and limitations

These data were collected through a collaborative of ten representative hospitals across the UK and included one Italian hospital. Bias of data collection was minimised by the collaborative's established record in collecting multisite observational data [24], as well as delivery of training to new contributing researchers. Patients

were only included in this study if they were admitted to hospital. This would have precluded community cases who never presented to hospital due to COVID-19 being either less severe or fatal. We may have overestimated our COVID-19 population through inaccurately diagnosed clinical disease. However this methodology of inclusion has been used in other COVID-19 studies [30]. Unmeasured factors included socioeconomic status, ethnicity, and escalation decisions including intensive care admission. Data were only collected on the presence of an ACEi or ARB on admission, with no data collected on whether the drug was continued during hospital stay. The study did not collect data on other cardiovascular medications that may influence outcome from COVID-19 which has been borne out in other studies; the use of B-blockers has been associated with lower likelihood of having a positive COVID-19 test, which may have been co-prescribed with ACEi and ARB [10]; being prescribed any antihypertensive drug has been shown to be protective of mortality from COVID-19, without ACEi and ARB being significant [31].

5.5. Interpretation

These results provide reassurance that patients on an ACEi or ARB at the point of COVID-19 diagnosis is not harmful. As with other studies we found factors that predisposed to higher mortality independent of ACEi or ARB prescription, including being over 65 years old, and having either kidney disease or CAD. In addition, clear differences in mortality outcomes were demonstrated between the age groups of <65, 65–79 and >80 years old. Disease severity at presentation as measured by CRP was associated with higher mortality.

5.6. Generalisability

Our results have good generalisability across the UK covering three out of the four comprising countries – England, Wales and Scotland. They also represent a large sample of patients. Our inpatient mortality rate is higher than other studies and requires further examination to determine whether this is in relation to a higher threshold for admission to UK hospitals, patients having higher severity of illness, differences in therapy received, or more predisposing factors e.g. older and more comorbid.

The prevalence of prescription of ACEi and ARBs in our COVID-19 cohort was higher than other reported populations, potentially representing more comorbidity with a greater frequency for ACEi and ARB indication, and prescribing practice associated with differing healthcare systems (COPE: ACEi 19.8%, ARB 8.8%; Italy: ACEi 23.9%, ARB 22.2% [20]; New York: 8.3%, ARB 10.5% [10]; China: ACEi and ARB grouped 5% [21]). These results may not be generalisable to non-hospitalised COVID-19 patients where a community versus hospital based COVID-19 study reported a lower community comorbidity burden and rate of ACEi / ARB prescription [20,32].

6. Conclusion

This study provides reassurance to clinicians to continue ACEi and ARBs despite the risk of exposure to COVID-19. However, those patients that are more likely to receive either an ACEi or ARB - older patients with comorbidity - remain at higher risk of poor outcome from COVID-19. Whilst we have reported a shorter length of stay associated with ACEi or ARB these results do not endorse the universal prescription of an ACEi or ARB as protective drugs in COVID-19.

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