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Association of the patterns of use of medications with mortality of COVID-19 infection: a hospital-based observational study

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ABSTRACT

Objectives SARS-CoV-2 enters cells using the ACE2 receptor. Medications that affect ACE2 expression or function such as angiotensin receptor blockers (ARBs) and ACE inhibitors (ACE-I) and metformin have the potential to counter the dysregulation of ACE2 by the virus and protect against viral injury. Here, we describe COVID-19 survival associated with ACE-I, ARB and metformin use.

Design This is a hospital-based observational study of patients with COVID-19 infection using logistic regression with correction for pre-existing conditions and propensity score weighted Cox proportional hazards models to estimate associations between medication use and mortality.

Setting Medical record data from the US Veterans Affairs (VA) were used to identify patients with a reverse transcription PCR diagnosis of COVID-19 infection, to classify patterns of ACE inhibitors (ACE-I), ARB, beta blockers, metformin, famotidine and remdesivir use, and, to capture mortality.

Participants 9532 hospitalised patients with COVID-19 infection followed for 60 days were analysed.

Outcome measure Death from any cause within 60 days of COVID-19 diagnosis was examined.

Results Discontinuation of ACE-I was associated with increased risk of death (OR: 1.4; 95% CI 1.2–1.7). Initiating (OR: 0.3; 95% CI 0.2–0.5) or continuous (OR: 0.6; 95% CI 0.5–0.7) ACE-I was associated with reduced risk of death. ARB and metformin associations were similar in direction and magnitude and also statistically significant. Results were unchanged when accounting for pre-existing morbidity and propensity score adjustment.

Conclusions Recent randomised clinical trials support the safety of continuing ACE-I and ARB treatment in patients with COVID-19 where indicated. Our study extends these findings to suggest a possible COVID-19 survival benefit for continuing or initiating ACE-I, ARB and metformin medications. Randomised trials are appropriate to confirm or refute the therapeutic potential for ACE-I, ARBs and metformin.

Strengths and limitations of this study

- ► Findings are based on a large hospital-based observational study providing opportunity to examine associations for ACE2 dysregulating medications with mortality after COVID-19 infection, and to conduct sensitivity analyses and evaluation of associations in informative subgroups.
- ► Employment of logistic regression and propensity score weighted Cox proportional hazards models enabled correction of observed associations for pre-existing conditions and treatment assignment.
- ► Residual confounding of associations due to underlying differences between treatment groups could remain, despite adjustment for pre-existing conditions and propensity score weighting.
- ► Electronic health records were the source of information for assignment of treatment group, and determination of COVID-19 infection, mortality and pre-existing conditions, reducing likelihood of misclassification.
- ► Examination of additional coextensive medications (beta blockers and famotidine) provided in situ control groups for the ACE2 dysregulating medications of interest.

INTRODUCTION

COVID-19 caused by SARS-CoV-2 has created a worldwide pandemic. As of 23 December 2020, over 76 million people worldwide have been infected with 1.7 million deaths. SARS-CoV-2 enters cells using the ACE2 receptor and induces the subsequent shedding of ACE2 on cells it infects, contributing to vascular injury and inflammatory tissue damage.[1] The presence of ACE2 receptors on the surface of multiple cell types, including lung alveolar epithelial, heart myocardial and kidney cells, enable the virus to target multiple organ systems.[2] Thus, COVID-19 has many pathophysiologic mechanisms of injury, including thrombosis, inflammation and microvascular dysfunction, resulting in stroke, myocardial infarction, heart and renal failure, pneumonia and ischaemic injury. This plethora of actions suggests that repurposing

approved medications may identify therapies that can improve outcomes.

At present, there are few specific treatments widely available for COVID-19.[3 4] More than 80 approved medications have been proposed as therapies for COVID-19. For example, famotidine because of its proposed interactions with viral enzymes has been proposed as a possible therapy.[5–7] Despite potent in vitro antiviral effects, clinical studies of hydroxychloroquine in COVID-19 have been disappointing.[8] Similarly, the antiviral drug remdesivir has received Emergency Use Authorization from the US FDA but has shown only limited clinical efficacy.[9] Medications that affect ACE expression or function such as angiotensin receptor blockers (ARBs) and ACE inhibitors (ACE-I) have the potential to counter the dysregulation of ACE2 by the SARS-CoV-2 and protect against viral injury.[10] Type 2 diabetes is a risk factor for severe COVID-19, and improved outcomes have been proposed in subjects taking antidiabetic agents such as the biguanidine drug, metformin.[11] Other commonly used medications might also interact with either viral enzymes or viral mechanisms of injury reducing morbidity and mortality.

The current study uses US Veterans Affairs (VA) medical record data to assess the association of patterns of use of common medications on the mortality of COVID-19. It tests the hypothesis that mortality in patients with COVID-19 can be altered by drugs affecting the renin–angiotensin–aldosterone system and by other commonly used medications proposed to alter COVID-19 morbidity and mortality.

METHODS

Setting

This study uses VA curated datasets compiled to facilitate capture of COVID-19 infections using the Corporate Data Warehouse (CDW) medical records data, which includes morbidity, medications, laboratory results, demographics and risk factors, as well as hospital course and mortality data.

Analysis sample

All VA healthcare users with a COVID-19 infection, identified using a reverse transcription PCR (RT-PCR) assay, were eligible for this study. As of 10 December 2020, there were 68 678 VA patients with a positive RT-PCR test result. To define a homogeneous study sample with unbiased capture of medication use and mortality, veterans who were aged 18 years and older and had been followed for 60 days since their positive test result were selected. The sample was further restricted to patients hospitalised for COVID-19 primarily to examine associations among the more severe COVID-19 cases. These criteria resulted in a final sample of 9532 veterans.

Medication use

Patients were analysed by patterns of medication use employing four categories. (1) Not used: which was defined as a patient who did not use a medication in 2 years prior to or in 60 days after a positive COVID-19 RT-PCR test result. (2) Taken before only: which was defined as a patient who used a medication within the period of 2 years before a positive COVID-19 test result but not in 60 days after. (3) Taken after only: which was defined as a patient with no use in 2 years prior to the diagnosis but who was administered a medication within the period of 60 days after a positive COVID-19 test result. (4) Taken before and after: which was defined as a patient who took a medication in the period of 2 years prior to and during 60 days after a positive COVID-19 test result. In-patient and outpatient prescriptions were analysed for medication use. In hospital, administration of medications was analysed through VISTA in-patient medication orders and the VA Bar Code Medication Administration data set, which includes in-hospital administration data, allowing confirmation of the administration of medications. VA outpatients receive medications through the VA Consolidated Mail Outpatient Pharmacy, which provides comprehensive data on outpatient medication data. A 2-year interval was used to classify medication use before COVID-19 infection in order to maximise data capture of medication use. Because admission to the hospital is an indicator of severity of COVID-19 disease and a point where medications are frequently changed, analyses were restricted to hospitalised patients.

Covariates

Pre-COVID-19 diagnosis and demographic data were calculated for the population. These included known risk factors for COVID-19 morbidity and mortality: age, body mass index, Charlson Comorbidity Index (CCI),[12] race, overweight at diagnosis, current smoking, past smoking, type 2 diabetes, cardiovascular disease, hypertension, coronary atherosclerotic heart disease, congestive heart failure, chronic obstructive pulmonary disease, bronchitis, acute respiratory failure, asthma, chronic lung disease and emphysema. Data on pre-COVID-19 diagnoses are stored in the CDW by International Classification of Diseases, Nineth and Tenth Revisions (ICD-9 and ICD-10) coding. All comorbidities were classified as diagnosed in the medical record at any time within 2 years of COVID-19 infection.

Outcome

Death from any cause within 60 days of positive RT-PCR test result was the outcome under observation. Death is derived using data from a combination of Master Veteran Index, Vital Status files and patient medical records (in that hierarchical order). These sources include deaths that occurred both inside and outside VA.

Statistical analysis

Statistical significance was determined by a two-tailed p value of <0 05. Tests of differences by medication group for continuous covariates were performed using the analysis of variance (ANOVA) F-test and for categorical

Table 1 (A) ACE-Is and ARBs in hospitalised VA patients with COVID-19 followed for 60 days. (B) Metformin and beta blockers in hospitalised VA patients with COVID-19 followed for 60 days. (C) Famotidine and remdesivir in hospitalised VA patients with COVID-19 followed for 60 days

	Medication use by timing of COVID-19 positive test result								
Medication/outcome*	**Not used**		**Taken before only†**		**Taken after only‡**		**Taken before and after§**		
(A) ACE-Is and ARBs in hospitalised VA patients with COVID-19 followed for 60 days									
ACE-I	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**P value¶**
Age	5896	67.1 (15.9)	1365	70.6 (11.7)	351	70.7 (13.2)	1920	69.2 (11.2)	<0.0001
BMI (kg/m^2)† at diagnosis	5803	29.3 (7.2)	1364	29.7 (7.5)	342	29.8 (7.3)	1919	30.5 (7.1)	<0.0001
CCI	5896	2.7 (2.7)	1365	4.4 (3.0)	351	1.9 (2.5)	1920	3.4 (2.5)	<0.0001
	N	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**P value****
Male gender	5423	92	1320	97	326	93	1861	97	<0.0001
Black	2074	35	543	40	80	23	683	36	<0.0001
Hispanic	524	9	103	8	26	7	167	9	0.3509
Overweight	425	7	129	9	34	10	187	10	0.0005
Smoker at diagnosis	573	12	159	12	19	9	255	14	0.0500
Past smoker	2416	50	678	53	100	48	928	51	0.2398
Pre-index type 2 diabetes††	2219	38	888	65	134	38	1262	66	<0.0001
Pre-index CVD††	2618	44	924	68	125	36	1136	59	<0.0001
Pre-index HTN††	3574	61	1277	94	193	55	1807	94	<0.0001
Pre-index CAHD††	1467	25	588	43	81	23	684	36	<0.0001
Pre-index CHF††	811	14	428	32	25	7	390	20	<0.0001
Pre-index heart disease††	1953	33	772	57	95	27	869	45	<0.0001
Pre-index heart failure††	994	17	487	36	36	10	457	24	<0.0001
Pre-index COPD††	1391	24	434	32	45	13	497	26	<0.0001
Pre-index bronchitis††	573	10	158	12	22	6	211	11	0.0091
Pre-index acute respiratory failure††	380	6	180	13	10	3	149	8	<0.0001
Pre-index asthma††	367	6	91	7	17	5	116	6	0.6345
Pre-index chronic lung disease††	2182	37	660	48	72	21	808	42	<0.0001
Pre-index emphysema ††	160	3	46	3	2	1	50	3	0.0377
Death	1284	22	411	30	34	10	283	15	<0.0001
ARB	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**P value¶**
Age	7730	67.8 (151)	545	71.6 (10.9)	218	70.6 (11.5)	1039	69 (11.0)	<0.0001
BMI (kg/m^2)† at diagnosis	7633	29.34 (7.2)	545	30.0 (7.4)	212	30.0 (6.4)	1038	31.5 (7.3)	<0.0001
CCI	7730	2.8 (2.7)	545	4.8 (3.0)	218	2.3 (2.5)	1039	3.9 (2.7)	<0.0001
	N	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**P value****
Male gender	7216	93	530	97	198	91	986	95	0.0003

Continued

Table 1 Continued

Medication/outcome*	Medication use by timing of COVID-19 positive test result								
	Not used		Taken before only†		Taken after only‡		Taken before and after§		
Black	2664	35	233	43	34	34	408	39	<0.0001
Hispanic	685	9	32	6	19	9	85	8	0.1087
Overweight	584	‡‡8	51	9	13	6	127	12	<0.0001
Smoker at diagnosis	832	13	63	12	26	17	85	9	0.0008
Past smoker	3259	50	264	51	72	47	527	53	0.1946
Pre-index type 2 diabetes††	3317	43	364	67	100	46	722	69	<0.0001
Pre-index CVD††	3639	47	400	73	87	40	677	65	<0.0001
Pre-index HTN††	5197	67	521	96	149	68	984	95	<0.0001
Pre-index CAHD††	2057	27	274	50	52	24	437	42	<0.0001
Pre-index CHF††	1128	15	209	38	27	12	290	28	<0.0001
Pre-index heart disease††	2718	35	339	62	74	34	558	54	<0.0001
Pre-index heart failure††	1364	18	234	43	36	17	340	33	<0.0001
Pre-index COPD††	1799	23	206	38	46	21	316	30	<0.0001
Pre-index bronchitis††	726	9	69	13	18	8	151	15	<0.0001
Pre-index acute respiratory failure††	529	7	89	16	9	4	92	9	<0.0001
Pre-index asthma††	434	6	52	10	14	6	91	9	<0.0001
Pre-index chronic lung disease††	2861	37	295	54	68	31	498	48	<0.0001
Pre-index emphysema ††	193	3	28	5	3	1	34	3	<0.0001
Death	1607	21	212	39	28	13	165	16	<0.0001
(B) Metformin and beta blockers in hospitalised VA patients with COVID-19 followed for 60 days									
Metformin	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**P value¶¶**
Age	6970	68.4 (15.5)	1208	69.7 (10.5)	151	65.0 (14.1)	1203	66.7 (10.8)	<0.0001
BMI (kg/m^2)† at diagnosis	6877	28.9 (7.1)	1207	31.2 (7.3)	142	32.0 (7.3)	1202	32.1 (7.1)	<0.0001
CCI	6970	2.8 (2.9)	1208	4.1 (2.6)	151	1.9 (2.1)	1203	3.3 (2.4)	<0.0001
	N	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**P value****
Male gender	6482	93	1159	96	136	90	1153	96	<0.0001
Black	2413	35	455	38	54	36	458	38	0.0400
Hispanic	584	8	120	10	14	9	103	9	0.3546
Overweight	467	7	136	11	23	15	149	12	<0.0001
Smoker at diagnosis	756	13	125	11	9	8	116	10	0.0065
Past smoker	2917	51	600	52	53	50	552	48	0.1901
Pre-index type 2 diabetes††	2064	30	1176	97	86	60	1177	98	<0.0001
Pre-index CVD††	3409	49	727	60	47	31	620	52	<0.0001

Continued

Table 1 Continued

Medication/outcome*	Medication use by timing of COVID-19 positive test result								
	Not used		Taken before only†		Taken after only‡		Taken before and after§		
Pre-index HTN††	4641	67	1075	89	91	60	1044	87	<0.0001
Pre-index CAHD††	1977	28	443	37	27	18	373	31	<0.0001
Pre-index CHF††	1194	17	266	22	15	10	179	15	<0.0001
Pre-index heart disease††	2622	38	564	47	36	24	467	39	<0.0001
Pre-index heart failure††	1443	21	298	25	18	12	215	18	<0.0001
Pre-index COPD††	1756	25	312	26	24	16	275	23	0.0177
Pre-index bronchitis††	671	10	126	10	11	7	156	13	0.0028
Pre-index acute respiratory failure††	528	8	111	9	6	4	74	6	0.0128
Pre-index asthma††	414	6	79	6	14	9	84	7	0.1896
Pre-index chronic lung disease††	2688	39	525	44	40	27	469	39	0.0001
Pre-index emphysema ††	205	3	29	2	1	1	23	2	0.0668
Death	1536	22	366	30	7	5	103	9	<0.0001
Beta blockers	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**P value¶**
Age	4247	64.3 (16.6)	683	70.3 (13.0)	1041	70.9 (12.7)	3561	71.6 (10.8)	<0.0001
BMI (kg/m^2)† at diagnosis	4174	29.6 (7.2)	683	27.9 (7.0)	1012	29.6 (7.5)	3559	30 (7.2)	<0.0001
CCI	4247	2.0 (2.3)	683	4.2 (2.9)	1041	2.1 (2.2)	3561	4.3 (2.9)	<0.0001
	N	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**P value****
Male gender	3866	91	645	94	984	94	3435	96	<0.0001
Black	1479	35	270	39	351	34	1280	36	0.0590
Hispanic	477	11	49	7	61	6	234	7	<0.0001
Overweight	337	8	35	5	87	8	316	9	0.0108
Smoker at diagnosis	426	12	80	12	88	12	412	12	0.9895
Past smoker	1556	46	340	52	367	50	1859	55	<0.0001
Pre-index type 2 diabetes††	1499	35	361	53	421	40	2222	62	<0.0001
Pre-index CVD††	1211	28	492	72	350	34	2750	77	<0.0001
Pre-index HTN††	2379	56	598	88	608	58	3266	92	<0.0001
Pre-Index CAHD††	447	10	302	44	166	16	1905	54	<0.0001
Pre-index CHF††	187	4	194	28	66	6	1207	34	<0.0001
Pre-index heart disease††	672	16	395	58	241	23	2381	67	<0.0001
Pre-index heart failure††	249	6	233	33	96	9	1406	39	<0.0001
Pre-index COPD††	724	17	222	33	178	17	1243	35	<0.0001
Pre-index bronchitis††	378	9	74	11	65	6	447	13	<0.0001
Pre-index acute respiratory failure††	146	3	81	12	43	4	449	13	<0.0001

Continued

Table 1 Continued

Medication/outcome*	Medication use by timing of COVID-19 positive test result								
	Not used		Taken before only†		Taken after only‡		Taken before and after§		
Pre-index asthma††	257	6	55	8	48	5	231	6	0.0265
Pre-index chronic lung disease††	1302	31	341	50	287	28	1792	50	<0.0001
Pre-index emphysema ††	84	2	30	4	22	2	122	3	<0.0001
Death	695	16	202	30	316	30	799	22	<0.0001
(C) Famotidine and remdesivir in hospitalised VA patients with COVID-19 followed for 60 days									
Famotidine	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**P value¶**
Age	7521	68.0 (14.7)	459	68.1 (13.3)	1129	68.5 (13.6)	423	70.0 (12.4)	0.0376
BMI (kg/m^2)† at diagnosis	7430	29.6 (7.3)	459	28.7 (6.8)	1116	30.0 (7.4)	423	29.6 (7.0)	0.0145
CCI	7521	2.9 (2.8)	459	4.7 (3.3)	1129	2.6 (2.6)	423	4.2 (2.8)	<0.0001
	N	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**P value****
Male gender	7032	94	439	96	1060	94	399	94	0.2851
Black	2692	36	168	36	364	32	156	37	0.1064
Hispanic	605	8	44	10	136	12	36	9	0.0001
Overweight	608	8	25	5	110	10	32	‡‡8	0.0358
Smoker at diagnosis	791	12	68	16	108	12	39	10	0.0663
Past smoker	3197	50	234	54	483	52	208	53	0.1951
Pre-index type 2 diabetes††	3508	47	258	56	484	43	253	60	<0.0001
Pre-index CVD††	3673	49	330	72	523	46	277	65	<0.0001
Pre-index HTN††	5302	71	390	85	791	70	368	87	<0.0001
Pre-index CAHD††	2157	29	200	44	304	27	159	38	<0.0001
Pre-index CHF††	1257	17	147	32	157	14	93	22	<0.0001
Pre-index heart disease††	2828	38	262	57	393	35	203	49	< 0.0001
Pre-index heart failure††	1497	20	166	36	196	17	115	27	<0.0001
Pre-index COPD††	1789	24	180	39	244	22	154	36	<0.0001
Pre-index bronchitis††	715	10	72	16	109	10	68	16	<0.0001
Pre-index acute respiratory failure††	501	7	98	21	75	7	45	11	<0.0001
Pre-index asthma††	449	6	40	9	55	5	47	11	<0.0001
Pre-index chronic lung disease††	2832	38	268	58	389	34	233	55	<0.0001
Pre-index emphysema ††	196	3	21	5	26	2	15	4	0.0420
Death	1436	19	99	22	379	34	98	23	<0.0001
Remdesivir‡‡	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**P value¶**
Age	6800	38.1 (14.8)			2732	68.3 (13.5)			0.6342
BMI (kg/m^2)† at diagnosis	6710	29.1 (7.1)			2718	31.1 (7.5)			<0.0001

Continued

Table 1 Continued

Medication/outcome*	Medication use by timing of COVID-19 positive test result								
	Not used		Taken before only†		Taken after only‡		Taken before and after§		
CCI	6800	3.2 (2.9)			2732	2.7 (2.5)			<0.0001
	N	(%)	N	(%)	N	(%)	N	(%)	P value**
Male gender	6349	93			2581	94			0.0449
Black	2619	38			761	28			<0.0001
Hispanic	512	8			309	11			<0.0001
Overweight	480	7			295	11			<0.0001
Smoker at diagnosis	802	14			204	‡‡8			<0.0001
Past smoker	2833	49			1289	53			0.0012
Pre-index type 2 diabetes††	3119	46			1384	51			<0.0001
Pre-index CVD††	3506	52			1297	47			0.0003
Pre-index HTN††	4818	71			2033	74			0.0005
Pre-index CAHD††	2066	30			754	28			0.0071
Pre-index CHF††	1268	19			386	14			<0.0001
Pre-index heart disease††	2733	40			956	35			<0.0001
Pre-index heart failure††	1505	22			469	17			<0.0001
Pre-index COPD††	1678	25			689	25			0.5789
Pre-index bronchitis††	674	10			290	11			0.3032
Pre-index acute respiratory failure††	518	8			201	7			0.6633
Pre-index asthma††	395	6			196	7			0.0124
Pre-index chronic lung disease††	2639	39			1083	40			0.4513
Pre-index emphysema ††	175	2			83	‡			0.2063
Death	1362	20			650	24			<0.0001

*Outcome is death from any cause occurring within 60 days of positive COVID-19 test result.
†Taken before only includes ever use within the period of 2 years before the positive COVID-19 test result.
‡Taken after only includes any record of use within the period of 60 days after the positive COVID-19 test result.
§Taken before and after includes any use in the period of 2 years prior and during 60 days after a positive COVID-19 test result.
¶P value resulting from analysis of variance (ANOVA) F-test for continuous variables.
**P value resulting from χ^2 test of differences in the distributions across categories.
††Pre-index conditions are coded if ever present in 2 years preceding positive COVID-19 test result.
‡‡Remdesivir was given only after COVID-19 diagnosis; therefore, data are presented only for categories: 'Not used' and 'Taken after only'.
ACE-Is, ACE inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; CAHD, coronary atherosclerotic heart disease; CCI, Charlson Comorbidity Index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HTN, hypertension; VA, Veterans Affairs.

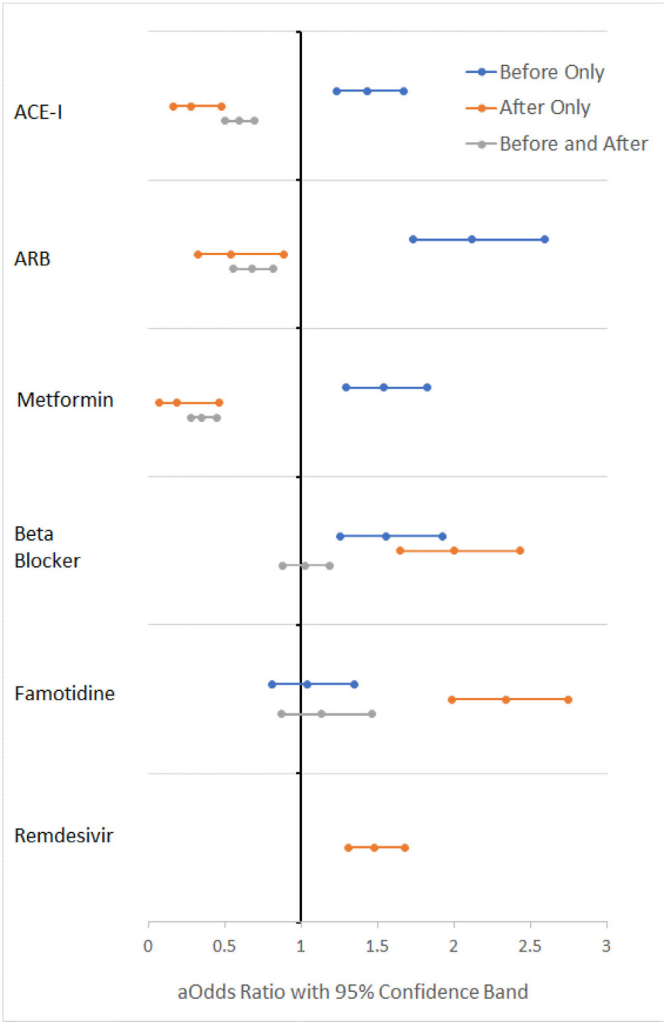

Figure 1 Associations of mortality with patterns of medication use among hospitalised VA patients with COVID-19 followed for 60 days, estimated from logistic regression models adjusted for adjusted for age, race, ethnicity, sex, overweight, smoking status and pre-existing morbidity. ACE-I, ACE inhibitor; ARB, angiotensin receptor blocker; VA, Veterans Affairs.

variables using the χ^2 test. ORs for risk of death were estimated from logistic regression and HRs from Cox proportional hazards models adjusted for: age, race, ethnicity, overweight and smoking status at index date, and for the presence of the following pre-existing conditions within 2 years of positive COVID-19 test: diabetes, cardiovascular disease, hypertension, coronary atherosclerotic heart disease, congestive heart failure, mention of heart disease, mention of heart failure, chronic obstructive pulmonary disease, bronchitis, acute respiratory failure, asthma, mention of chronic lung disease, mention of emphysema and for the CCI. Associations of death with patterns of medication use are presented as adjusted ORs (aORs) and adjusted HR (aHRs) bounded by 95% CIs. Adjusted HRs were estimated using inverse propensity score weighted Cox proportional hazards models. To address non-random assignment to treatment groups, propensity scores estimating the conditional probability of being in a given treatment group were calculated using a multinomial logistic regression that included morbidity associated with indication for treatment. Survival time was estimated as length of hospital stay terminating in discharge or death. The assumption of proportional hazards was tested both graphically using Kaplan-Meier survival curves and log(−log(survival)) curves, and by testing scaled Schoenfeld residuals. Product terms between each medication group×log(−log(survival time)) were used to test whether medication groups were time varying. Where statistically significant time dependence was observed, proportional hazards models were stratified by survival time based on examination of survival curves and on calculating contrasts at 5-day intervals for medication categories with statistically significant time dependence.

Sensitivity and supplementary analyses

Sensitivity analysis examined the persistence of associations among patients who were and were not ventilated. The specificity of associations for ACE-Is, ARBs and metformin were compared with beta blockers and famotidine to examine whether associations were a result of pre-existing morbidity or more severe disease, or discontinuation of medication because of imminent death. In supplementary analyses, we also examined whether multiple medication use influenced associations. Medication associations with death were also examined among those not admitted to the hospital in supplementary analysis to determine whether associations were different for hospitalised versus non-hospitalised patients.

Statistical analyses were performed using SAS Enterprise Guide V.7.1 (SAS Institute).

RESULTS

Table 1 reports pre-COVID-19 characteristics and incidents of death for hospitalised patients (n=9532) by pattern of medication use for each medication. In particular, patients not using ARB, ACE-I, metformin or beta blockers were younger and less likely to have higher risk morbidity at time of COVID-19 diagnosis.

Figure 1 provides the adjusted aORs and upper and lower CIs for associations of COVID-19 death with patterns of medication use for each medication. Figure 2 shows corresponding survival curves for each medication and medication group, and are consistent with associations estimated from models. Discontinuation of ACE-I was associated with an increased risk of death (aOR: 1.44; 95% CI 1.24–1.67). Initiating (aOR: 0.28; 95% CI 0.17–0.48) or continuous (aOR: 0.59; 95% CI 0.50–0.69) ACE-I was associated with a reduced risk of death in hospitalised patients (figures 1 and 2). The pattern was similar for ARB, which was also associated with increased risk with discontinuation (aOR: 2.12; 95% CI 1.73–2 .59) and reduced risk with addition (aOR: 0.54; 95% CI 0.33–0 .89) or continuous use (aOR: 0.68; 95% CI 0.56–0.82) use (figures 1 and 2).

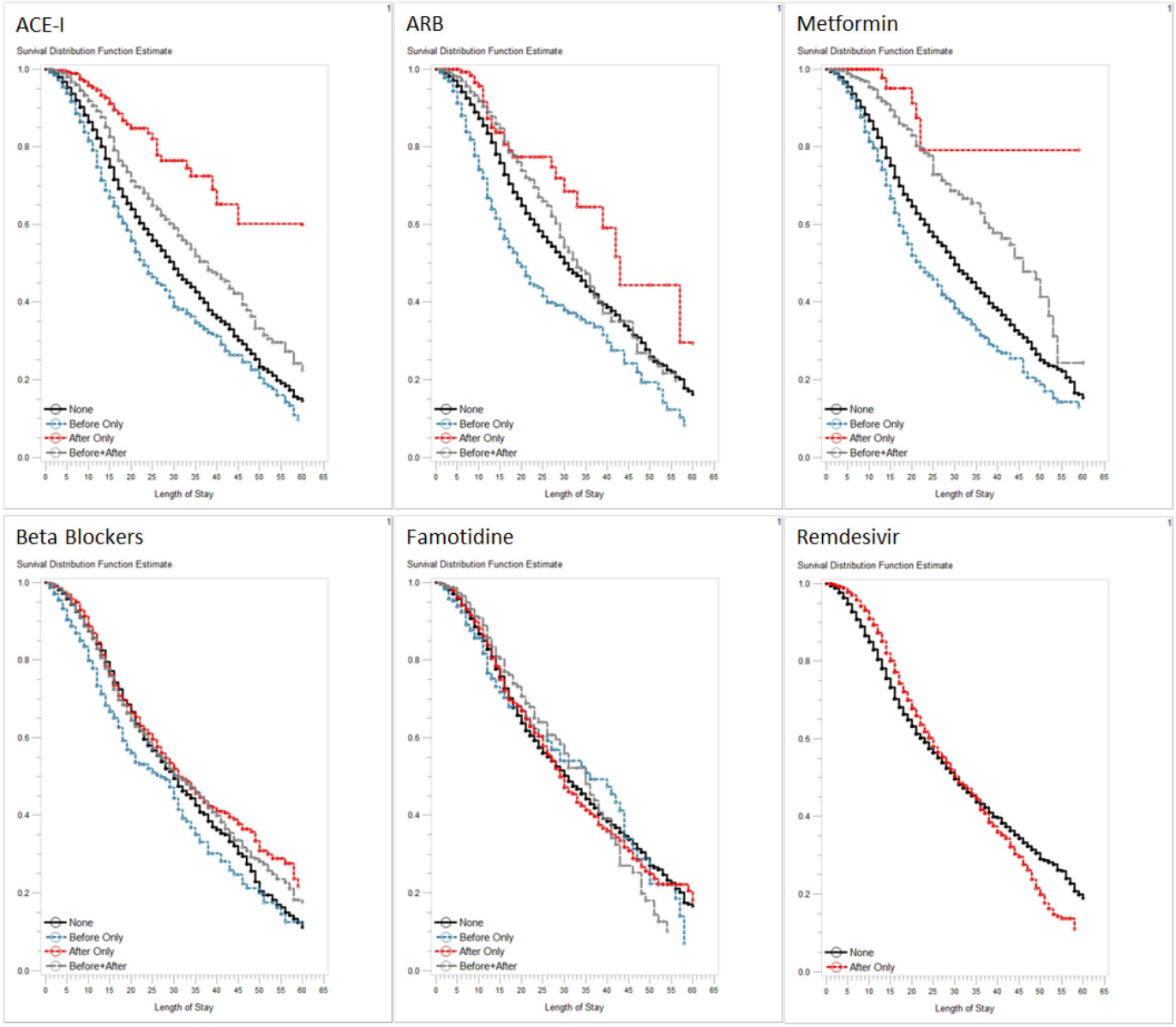

Figure 2 Survival curves by patterns of medication use among hospitalised VA patients with COVID-19 followed for 60 days. ACE-I, ACE inhibitor; ARB, angiotensin receptor blocker; VA, Veterans Affairs.

Associations for patterns of use for metformin were similar to those for ACE-I and ARB (figures 1 and 2). Withdrawal of metformin was associated with an increased risk of death (aOR: 1.54; 95% CI 1.30–1.82) Initiating metformin (aOR: 0.19; 95% CI 0.07–0.47) or continuous use (aOR: 0.35; 95% CI 0.28–0.45) was associated with reducing risk of death.

The results for remdesivir were not encouraging (figures 1 and 2). Use of remdesivir was associated with an increased risk of death (aOR: 1.48; 95% CI 1.31–1.68). The differential associations for ACE-I, ARB and metformin compared with those famotidine and beta blockers (figures 1 and 2) suggest specificity and imply that the protective effects observed for ACE-I, ARB and metformin are not likely to be solely attributed to pre-COVID-19 morbidity, or other unexplained reasons for non-random treatment assignment.

Associations for patterns of ACE-I, ARB and metformin use were not perturbed by whether or not patients received mechanical ventilation (table 2), lending further evidence that the observed estimates do not appear to be explained or confounded by disease severity.

Examining patterns of ACE-I, ARB and metformin use among patients who discontinued their beta blocker medication compared with those who used it continuously (table 3) showed associations that were comparable to those among all patients. These results are consistent with the notion that observed risk patterns for ACE-I, ARB and metformin were not impacted by withdrawal of beta blockers and a consequent loss of possible therapeutic benefit from the beta blocker medication.

Table 4 presents results for ACE-I, ARB and metformin estimated from inverse propensity score weighted Cox proportional hazards models. Results show that

Table 2 Associations of mortality with patterns of medication use among hospitalised VA patients with COVID-19 followed for 60 days according to mechanical ventilation status

	Received ventilation* (n=1315)		Did not receive ventilation* (n=6847)	
	OR†	95% Confidence limits	OR†	95% Confidence limits
ACE-I				
Before only	1.29	0.94 to 1.77	1.22	1.00 to 1.51
After only	0.18	0.07 to 0.48	0.33	0.17 to 0.65
Before and after	0.57	0.42 to 0.78	0.55	0.44 to 0.69
ARB				
Before only	2.95	1.86 to 4.67	1.55	1.17 to 2.07
After only	0.74	0.30 to 1.83	0.44	0.21 to 0.93
Before and after	0.88	0.59 to 1.31	0.75	0.58 to 0.97
Metformin				
Before only	1.47	1.04 to 2.08	1.03	0.80 to 1.33
After only	0.23	0.02 to 2.30	0.30	0.11 to 0.86
Before and after	0.29	0.18 to 0.45	0.44	0.32 to 0.61

*Models are stratified by whether or not patients received mechanical ventilation within the 60 days following positive COVID-19 test result.
†ORs and 95% confidence limits are estimated from logistic regression models adjusted for age, race, ethnicity, sex, overweight and smoking status at index date, and for the presence of the following pre-existing conditions within 2 years of positive COVID-19 test: diabetes (type 2), CVD, HTN, CAHD, CHF, mention of heart disease, mention of heart failure, COPD, bronchitis, acute respiratory failure, asthma, mention of chronic lung disease and emphysema, and for the CCI.
ACE-I, ACE inhibitor; ARB, angiotensin receptor blocker; CAHD, coronary atherosclerotic heart disease; CCI, Charlson Comorbidity Index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HTN, hypertension; VA, Veterans Affairs.

Table 3 Associations of mortality with patterns of medication use among hospitalised VA patients with COVID-19 followed for 60 days according to beta blocker use

	Discontinued beta blocker* (n=651)		Continuous beta blocker* (n=3361)	
	OR†	95% Confidence limits	OR†	95% Confidence limits
ACE-I				
Before only	0.90	0.58 to 1.40	1.53	1.25 to 1.89
Before and after	0.46	0.27 to 0.79	0.64	0.51 to 0.80
ARB				
Before only	2.22	1.29 to 3.83	2.06	1.57 to 2.69
Before and after	0.74	0.38 to 1.44	0.68	0.52 to 0.87
Metformin				
Before only	1.23	0.72 to 2.11	1.37	1.08 to 1.73
Before and after	0.51	0.22 to 1.16	0.33	0.24 to 0.47

*Models are stratified by whether or not patients discontinued or continued their beta blocker medication in the 60 days following positive COVID-19 test result.
†ORs and 95% confidence limits are estimated from logistic regression models adjusted for age, race, ethnicity, sex, overweight and smoking status at index date, and for the presence of the following pre-existing conditions within 2 years of positive COVID-19 test: diabetes (type 2), CVD, HTN, CAHD, CHF, mention of heart disease, mention of heart failure, COPD, bronchitis, acute respiratory failure, asthma, mention of chronic lung disease and emphysema, and for the CCI.
ACE-I, ACE inhibitor; ARB, angiotensin receptor blocker; CAHD, coronary atherosclerotic heart disease; CCI, Charlson Comorbidity Index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HTN, hypertension; VA, Veterans Affairs.

associations persisted after efforts to adjust for the probability of treatment assignment, and also that associations were time varying. For continued use of both ACE-I and ARB, there appears to be a diminution of the protective effect over time, suggesting that prompt resumption of these medications is critical.

Supplementary analysis examining associations controlled for multiple medication use showed similar findings for ACE-Is, ARBs and metformin. Supplementary analysis examining associations among non-hospitalised show similar patterns of associations for ACE-I, ARB, metformin and remdesivir with death to those observed among hospitalised cases (online supplemental figure 1). The consistency in results for both groups lends validity to observed results among hospitalised cases and suggests that associations are not a result of an artefact or underlying characteristic related to being hospitalised.

DISCUSSION

The current study presents associations of mortality with the patterns of use of medications in patients with COVID-19 using a large national database. Although large observational trials cannot demonstrate causality, they can help generate testable hypotheses and focus or refine subsequent interventional studies of potential COVID-19 treatments. Previous analysis of this large database recently demonstrated the lack of efficacy and risks of hydroxychloroquine for the treatment of COVID-19 within the VA.[8] In the current study, medications affecting the renin–angiotensin system and the anti-diabetic drug metformin were identified as potentially protective in COVID-19 survival.

The relationship between ACE2-mediated viral entry and the anti-inflammatory effects of ACE2 form the basis for controversy surrounding the use of renin–angiotensin–aldosterone system's antagonists in COVID-19. SARS-CoV-2 enters cells using the ACE2 enzyme, which acts as a viral receptor on the cell surface. Like ACE1, ACE2 is a carboxypeptidase that converts angiotensin II to vasoactive angiotensin peptides and is expressed in multiple tissues, including lungs, heart and kidneys.[13 14] Despite their structural homology, ACE1 and ACE2 appear to play counterbalancing roles on vascular function and

Table 4 Associations of mortality with patterns of medication use among hospitalised VA patients with COVID-19 followed for 60 days, estimated from propensity score weighted proportional hazards models

	aHR*	95% Confidence limits
ACE-I		
Before only	1.39	1.24 to 1.57
After only	0.24	0.14 to 0.39
Before and after†		
≤40 days	0.73	0.63 to 0.84
>40 days	0.79	0.50 to 1.24
ARB		
Before only‡		
≤25 days	1.97	1.67 to 2.32
>25 days	1.17	0.73 to 1.88
After only	0.53	0.33 to 0.84
Before and after§		
≤20 days	0.65	0.52 to 0.81
>20 days	1.42	1.09 to 1.83
Metformin		
Before only¶		
≤25 days	1.53	1.32 to 1.77
>25 days	1.88	1.43 to 2.47
After only	0.20	0.07 to 0.54
Before and after	0.28	0.21 to 0.37

*aHRs are estimated using inverse propensity score weighted Cox proportional hazards models adjusted for: age, race, ethnicity, sex, overweight and smoking status at index date, and for the for the presence of the following pre-existing conditions within 2 years of positive COVID-19 test: diabetes (type 2), CVD, HTN, CAHD, CHF, mention of heart disease, mention of heart failure, COPD, bronchitis, acute respiratory failure, asthma, mention of chronic lung disease and emphysema, and for the CCI, and fitted with time dependent terms for medication categories, where statistically indicated. Propensity scores were derived from multinomial logistic regression predicting probability of being in a medication treatment category using morbidity that would indicate clinical need for treatment. Death is death from any cause within 60 days of COVID-19 positive test result. Time dependence was tested using product terms for each medication category×log (–log(survival time)) at p <0.05. For time dependent medication categories, risk was estimated from models stratified by survival time. The stratification time points were selected based on examination of survival curves, log(–log survival)) curves and by calculating contrasts at 5-day intervals to determine where estimated associations became non-statistically significant or diverged.
†$P_{(\text{ACE-I: before and after}\times\log(-\log(\text{survival})))}$=0.0451.
‡$P_{(\text{ARB: before only}\times\log(-\log(\text{survival})))}$=0.0267.
§$P_{(\text{ARB: before and after}\times\log(-\log(\text{survival})))}$<0.0001.
¶$P_{(\text{metformin: before only}\times\log(-\log(\text{survival})))}$=0.0002.
aHRs, adjusted HRs; CAHD, coronary atherosclerotic heart disease; CCI, Charlson Comorbidity Index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HTN, hypertension; VA, Veterans Affairs.

inflammation. Unlike ACE1, ACE2 primarily converts angiotensin II to the angiotensin(1–7) heptapeptide, a ligand for the Mas1-G-protein coupled receptor, which counteracts the vasoconstrictive and inflammatory effects of ACE1-derived peptides.[15] Angiotensin(1–7)/Mas1 binding downregulates the expression of numerous inflammatory cytokines, including interleukin 6 (IL-6), interferon (IFN) γ, tumour necrosis factor α, CCL2, IL-12 and IL-5.[15] Unlike ACE1, ACE2 exhibits promiscuous proteolytic activity against additional specific inflammatory mediators des-Arg[9]-bradykinin, neurotensin, dynorphin A(1–13) and the inflammatory adipokine apelin-13.[15 16] After viral entry, SARS-CoV-2 triggers ACE2 shedding from infected cells through induction of the ADAM17 protease during SARS-CoV-2 replication.[17] Virally induced ACE2 shedding likely exacerbates viral pathogenesis. ACE2 has known protective effects on lung injury due to numerous respiratory viruses, including RSV, H5N1 influenza and SARS-CoV-1.[18 19] Infusion of soluble recombinant ACE2 in human acute respiratory distress syndrome (ARDS) can reduce levels of cytokines and inflammatory markers and can have a protective effect in human ARDS.[20 21] Moreover, ACE2 in the heart is required for normal cardiac activity, as ACE2 deficiency in mice leads to severe left ventricular dysfunction.[22]

Comparison with previous studies

These studies suggest that increasing levels of ACE2 might play an important role protecting patients from severe cardiopulmonary morbidity and death in COVID-19. ARBs and ACE-Is selectively block ACE1 and can affect the balance between ACE1 and ACE2. Both ACE-I and ARBs can increase ACE2 viral receptors in animal models, providing a theoretically mixed effect on COVID-19 severity. But even the directionality of the effects is debated: higher ACE2 levels may be protective once infection is established, but might increase the susceptibility of an individual to new infection.[10 23] Potential concern about ACE-I and/or ARB use on COVID-19 severity have been reported in early studies.[24] Evidence recently reported from the Randomized Elimination and Prolongation of ACE Inhibitors and ARBs in Coronavirus 2019 Trial (REPLACE COVID)[25] and the Angtiotensin Receptor Blockers and Angiotensin-converting Enzyme Inhibitors and Adverse Outcomes in Patients with COVID-19 (BRACE-CORONOA)[26] randomised clinical trials and from a 'living' systematic review by Mackey *et al*[27] demonstrates that continuation of renin–angiotensin system inhibitors did not negatively impact the severity or duration of hospitalisation in patients with COVID-19. The present study further suggests beneficial effects due to continued or newly initiated ACE-I or ARB treatment in patients with COVID-19, and demonstrates adverse effects due to ACE-I and/or ARB discontinuation.

Continued use or initiation of metformin were associated with reduced COVID-19 mortality in our analysis. These data support a previous study implicating protective effects of metformin in acute COVID-19.[11] Metformin is used to treat the Metabolic Syndrome, a low-grade systemic inflammatory condition characterised by obesity, hypertension, insulin resistance, type 2 diabetes and atherosclerosis. Since aspects of the Metabolic Syndrome are known risk factors for severe COVID-19, agents such as metformin might logically be

expected to diminish COVID-19 severity. There may be a more compelling mechanistic explanation, however. The Metabolic Syndrome results from an expanded population of inflammatory type-1 macrophages (M1), rather than alternatively activated, or anti-inflammatory type-2 macrophages (M2).[28] Currently available data suggest that severe COVID-19 pneumonia is characterised by lymphopenia, hyperferritinaemia, cytokine storm and haemophagocytosis—features of a unique, corticosteroid responsive condition known as the Macrophage Activation Syndrome.[29 30] It is plausible that basal M1 macrophage activation in the Metabolic Syndrome provides a fertile milieu for the Macrophage Activation Syndrome and severe COVID-19 pneumonia. In addition to metformin conceivably acting to reverse M1 polarisation, a recent publication reports that metformin can increase ACE2 in animals through a variety of cellular mechanisms.[31 32] These observed metformin effects suggest that increased ACE2 or other metformin specific effects might be mechanistically crucial to COVID-19 protection.

Strengths and limitations

The current study is an observational analysis of medical record data from the VA; it can demonstrate associations but cannot be used to demonstrate causality. Epidemiologic analysis of administrative electronic healthcare records can quickly identify associations of potential therapies with improved outcomes but cannot establish safety or efficacy or causality. The associated reductions in mortality with continuation and/or starting ACE-I or ARB may be an indicator of a possible therapy or simply identify patients who were doing better clinically or could be a marker for better care. The increases in the risk of death with discontinuation of ACE-I and ARB may indicate that discontinuation of these medications in COVID-19 infections truly did increase risk, or it may indicate that patients that were doing poorly clinically required discontinuation of the medication to maintain haemodynamic stability. Although reasons for discontinuation were not routinely captured, any changes in medications after a diagnosis of COVID-19 were coded at the time of hospitalisation. Therefore, it is unlikely that the discontinuation was a response to acute clinical deterioration but rather discontinuation on admission to the hospital with subsequent deterioration. Risk adjustment by pre-existing conditions, and the CCI, by propensity score weighting of associations, or stratification of results by ventilation status may be inadequate to correct for the severity of COVID-19 illness and reverse causation. However, the persistence of associations among patients who were and were not ventilated and the specificity of associations in comparison with beta blockers and famotidine suggests that they are not merely a result of pre-existing morbidity or more severe disease, or discontinuation of medication because of imminent death. Ongoing randomised clinical trials will be definitive.

Policy implications

We have identified at least 24 prospective clinical trials of currently available agents in COVID-19, including immunoglobulin, IFNs, chloroquine, hydroxychloroquine, arbidol, remdesivir,[4] favipiravir, lopinavir, ritonavir, oseltamivir, methylprednisolone, bevacizumab and traditional Chinese medicines.[33] Despite the testing of multiple antiviral[4] and/or anti-inflammatory drugs,[3] no proven treatment is widely available for the current COVID-19 pandemic. Thus, we suggest that the current study may provide time-sensitive relevance to clinical decisions that must be made before definitive clinical trials can be completed. Our findings not only support continuation of ACE-I, ARB and metformin medication among hospitalised patients with COVID-19, but suggest benefit for initiation in patients with indication for therapy. We also found evidence consistent with benefits for the same strategy in patients with COVID-19 who are not hospitalised. However, we consider the evidence for non-hospitalised patients less rigorous because a filled prescription out of hospital is not as reliable a measure of medication use as in-hospital administration of medication.

Conclusions

Findings support a possible COVID-19 survival benefit for continuing or initiating ACE-I, ARB and metformin medications. Furthermore, discontinuation of these medications in patients with COVID-19 infection was associated with an increase in risk of death. The results for remdesivir were not encouraging—use of remdesivir was associated with an increase in risk of death. Our study not only reinforces the safety of ACE-I, ARB and metformin use among patients with COVID-19 where indicated but suggests therapeutic benefit.

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Contributors AWW originated the idea to investigate ACE-I, angiotensin receptor blocker and type 5 phosphodiesterase inhibitors (PDE-I) drugs in the context of ARDS and microvascular dysfunction in patients with COVID-19. AWW, PMC, NYK, AB and BAC assisted with securing funding for this project. AWW, PMC and NYK directly accessed and verified the data. PMC undertook statistical analyses and created the tables and figures. AWW, JCR and PMC wrote the manuscript. NYK, AB and BAC reviewed, commented on and critically revised the manuscript for important intellectual content. AWW and PMC are guarantors of this work. All authors helped to interpret the data, approved the final version of the manuscript to be published, are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, and accept responsibility for submitting the article for publication.

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Competing interests All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. AW, PC, NYK and BAC declare support from grants from Mercatus Center, George Mason University, and from UC Office of the President, during the conduct of the study. All authors declare no other competing interests, no relationships with any organisations that might have a financial interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the University of California San Francisco's Institutional Review Board (IRB), the San Francisco VA Research and Development (R&D) committee and the Public Health Institute's IRB (US VA IRB project number: 10-03609). This study uses existing data available from the US Department of Veterans Affairs Corporate Data Warehouse and does not require informed consent but does require IRB approval.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data requests for access to the de-identified (anonymised) data must be submitted to AWW (the chief investigator) for evaluation of the request. Requests will be reviewed by the chief investigator and the VA Informatics and Computing Infrastructure director and staff. Approval of requests to the de-identified (anonymised) data requires execution of a data use agreement.

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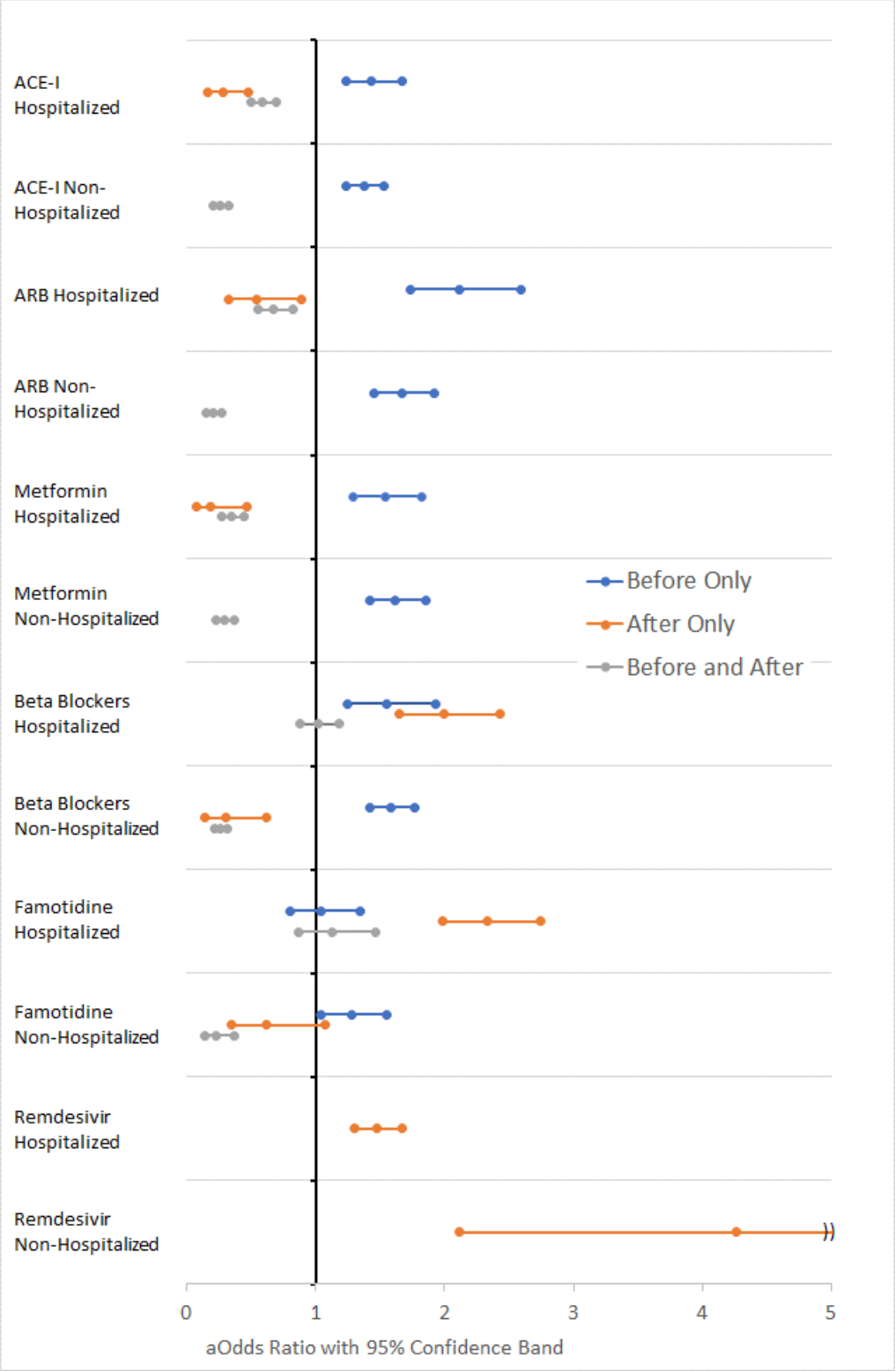

The upper 95% confidence limit for Remdesivir (95% CI 2.1 – 8.6) is truncated to enhance visualization of associations for other medications with much narrower confidence bands.