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BMJ Open 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.

INTRODUCTION

COVID-19 caused by SARS-CoV-2 has created a worldwide pandemic. As of 23 December 2020, over 76 million people worldwide

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 preexisting 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.

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

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Correspondence to Dr Arthur W Wallace; art.wallace@va.gov approved medications may identify therapies that can improve outcomes.

At present, there are few specific treatments widely available for COVID-19.34 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 reninangiotensin–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

	Medication	use by timing of	COVID-19 p	Medication use by timing of COVID-19 positive test result	t				
Medication/outcome*	Not used		Taken be	Taken before only†	Taken a	Taken after only‡	Taken be	Taken before and after§	1
(A) ACE-Is and ARBs in hospitalised VA patients with COVID-19 followed for 60 days	ents with COVID-19 fol	lowed for 60 day	s						
ACE-I	Z	Mean (SD)	z	Mean (SD)	z	Mean (SD)	z	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/m²)† 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
	Z	(%)	z	(%)	z	(%)	z	(%)	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	თ	103	ω	26	7	167	б	0.3509
Overweight	425	7	129	6	34	10	187	10	0.0005
Smoker at diagnosis	573	12	159	12	19	6	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 diseaset†	2182	37	660	48	72	21	808	42	<0.0001
Pre-index emphysema ††	160	ი	46	c	2	-	50	З	0.0377
Death	1284	22	411	30	34	10	283	15	<0.0001
ARB	z	Mean (SD)	z	Mean (SD)	z	Mean (SD)	z	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/m²)† 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
	z	(%)	z	(%)	z	(%)	z	(%)	P value**
Male gender	7216	93	530	97	198	91	986	95	0.0003

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				and by thinking of OTID to positive test test	:				
Medication/outcome*	Not used		Taken before only†	ore onlyt	Taken	Taken after only‡	Taken be	Taken before and after§	
Black	2664	35	233	43	34	34	408	39	<0.0001
Hispanic	685	б	32	6	19	0	85	8	0.1087
Overweight	584	\$##	51	6	13	9	127	12	<0.0001
Smoker at diagnosis	832	13	63	12	26	17	85	6	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	o	69	13	18	ω	151	15	<0.0001
Pre-index acute respiratory failure††	529	7	89	16	0	4	92	6	<0.0001
Pre-index asthma††	434	6	52	10	14	9	91	6	<0.0001
Pre-index chronic lung disease††	2861	37	295	54	68	31	498	48	<0.0001
Pre-index emphysema ††	193	3	28	5	ი	Ŧ	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	VA patients with	COVID-19 followe	d for 60 days						
Metformin	z	Mean (SD)	z	Mean (SD)	z	Mean (SD)	z	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/m²)† 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
	z	(%)	z	(%)	z	(%)	z	(%)	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	0	103	6	0.3546
Overweight	467	7	136	11	23	15	149	12	<0.0001
Smoker at diagnosis	756	13	125	11	6	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
Dro. indov. CV/D++	0010	10	707	en	47	31	620	52	<0.0001

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thmath 144 6 79 6 14 conic lung diseaseth 268 39 525 44 40 physema th 1536 22 366 30 7 physema th 1536 22 366 30 7 N Mean (SD) N Mean (SD) N 7 $A174$ 29.6 (7.2) 683 70.3 (13.0) 1012 $A174$ 29.6 (7.2) 683 70.3 (13.0) 1012 $A147$ 29.6 (7.2) 683 70.3 (13.0) 1012 $A147$ 29.6 (7.2) 683 7.2 (2.9) 1041 $A149$ 70 70 1012 20 $A149$ 70 83 27 20 21 $A149$ 35 27 94 94 $A100$ 7 11 49 7 61 $A100$ 35 27 27 28 27 $A100$ 3	Immath 414 6 79 6 onic lung diseaseth 268 39 525 44 physema th 1536 29 2 44 physema th 1536 29 30 2 physema th 1536 29 36 30 noic lung diseaseth 863 29 5 30 noit lung diseaseth 843 643 166 883 703 313.00 at diagnosis 4174 29.6 (72) 883 703 313.00 at diagnosis 4174 29.6 (72) 883 72 703 704 70 70 <		ω	111	6	9	4	74	9	0.0128
coric lung diseaset 268 39 52.5 44 40 physema tt 1536 22 366 30 7 n N Mean (SD) N Mean (SD) N at diagnosis 4247 643 (16.6) 683 70.3 (13.0) 1041 at diagnosis 4174 29.6 (7.2) 683 27.9 (7.0) 1012 at diagnosis 4174 29.6 (7.2) 683 27.9 (7.0) 1012 at diagnosis 4174 29.6 (7.2) 683 27.9 (7.0) 1012 at diagnosis 4177 1479 29.6 (7.2) 683 42.6 81 agnosis 1479 35 270 39 351 67 dignosis 156 46 340 56 88 616 f 62 127 88 57 87 87 f 62 56 58 86 86 86 <td>contic lung diseaseth 268 39 525 44 physema th 1536 2 2 2 physema th 1536 2 36 30 notic lung diseaseth 1536 2 36 30 notic lung diseaseth \mathbf{N} Mean (SD) N Mean (SD) notic lung diseaseth 477 64.3 (16.6) 683 70.3 (13.0) at diagnosis 477 20 (2.3) 683 4.2 (2.9) at diagnosis 477 20 (2.3) 683 4.2 (2.9) 470 866 91 645 94 477 1479 20 (2.3) 683 4.2 (2.9) 477 1479 20 (7.2) 683 4.2 (2.9) 477 1479 20 (7.2) 683 4.2 (2.9) 499 7 20 36 50 490 35 270 36 50 62 diabetesth 1499</td> <td></td> <td>9</td> <td>79</td> <td>9</td> <td>14</td> <td>თ</td> <td>84</td> <td>7</td> <td>0.1896</td>	contic lung diseaseth 268 39 525 44 physema th 1536 2 2 2 physema th 1536 2 36 30 notic lung diseaseth 1536 2 36 30 notic lung diseaseth \mathbf{N} Mean (SD) N Mean (SD) notic lung diseaseth 477 64.3 (16.6) 683 70.3 (13.0) at diagnosis 477 20 (2.3) 683 4.2 (2.9) at diagnosis 477 20 (2.3) 683 4.2 (2.9) 470 866 91 645 94 477 1479 20 (2.3) 683 4.2 (2.9) 477 1479 20 (7.2) 683 4.2 (2.9) 477 1479 20 (7.2) 683 4.2 (2.9) 499 7 20 36 50 490 35 270 36 50 62 diabetesth 1499		9	79	9	14	თ	84	7	0.1896
physema t1 205 3 29 2 1 1536 22 366 30 7 N Mean (SD) N Mean (SD) N Mean (SD) N 4247 $64.3 (16.6)$ 683 $70.3 (13.0)$ 1041 477 477 $29.6 (7.2)$ 683 $4.2 (2.9)$ 1041 477 $20 (2.3)$ 683 $4.2 (2.9)$ 1041 866 91 645 94 984 477 117 $29 (7.2)$ 393 357 367 393 866 91 645 94 984 984 477 117 29 7 61 986 875 82 82 52 88 87 886 986 98 7 61 7 81000515 810 122 821 821 821	physema th 205 3 29 2 1536 22 366 30 N Mean (SD) N Mean (SD) 30 4247 64.3 (16.6) 683 70.3 (13.0) 4174 29.6 (7.2) 683 27.9 (7.0) $at diagnosis$ 4174 29.6 (7.2) 683 42.7 (7.0) $at diagnosis$ 4174 29.6 (7.2) 683 42.6 (7.0) 477 17 20.6 (7.2) 683 42.6 (7.0) 477 1479 26.7 89 27.9 (7.0) 477 117 49 7 62 diabetest 147 117 89 7 62 diabetest 129 89 7 79 170 292 340 52 72 170 292 58 72 72 170 17 292 58 72			525	44	40	27	469	39	0.0001
1536 22 366 30 7 N Mean (SD) N Mean (SD) N Mean (SD) N at diagnosis 4247 643 (16.6) 683 70.3 (13.0) 1041 at diagnosis 4174 296 (72) 683 70.3 (13.0) 1041 4247 2.0 (2.3) 683 27.9 (7.0) 1012 102 4247 2.0 (2.3) 683 4.2 (2.9) 1041 866 91 61 984 984 984 147 11 49 7 61 984 9109 357 270 397 367 367 147 11 49 7 61 984 984 9109 920 357 367 367 367 367 91009 920 920 920 920 920 920 920 920	1536 22 366 30 N Mean (SD) N Mean (SD) N Mean (SD) 4247 64.3 (16.6) 683 70.3 (13.0) at diagnosis 4174 29.6 (7.2) 683 70.3 (13.0) at diagnosis 4174 29.6 (7.2) 683 7.9 (7.0) 4247 20.6 (7.2) 683 4.2 (2.9) M $(\%)$ N $(\%)$ N 4247 20.6 (7.2) 683 4.2 (2.9) 477 177 20.7 39 4.2 (2.9) 477 11479 357 807 397 477 117 297 370 397 397 610 1256 126 396 727 397 610 129 327 361 52 72 610 129 326 52 72 72 610 129 <		ო	29	2	-	F	23	N	0.0668
N Mean (SD) N Mean (SD) N 4247 64.3 (16.6) 683 70.3 (13.0) 1041 at diagnosis 4174 29.6 (72) 683 70.3 (13.0) 1041 at diagnosis 427 2.0 (2.3) 683 4.2 (2.9) 1041 N $(\%)$ N $(\%)$ N $(\%)$ N N $(\%)$ N $(\%)$ N $(\%)$ N A 7 2.0 (2.3) 683 4.2 (2.9) 1041 N $(\%)$ N $(\%)$ N $(\%)$ N A 7 617 355 27 361 361 A 147 117 28 361 361 361 A 1000 355 361 361 361 361 A 1000 352 361 361 361 361 361 <tr< td=""><td>N Mean (SD) N Mean (SD) 4247 64.3 (16.6) 68.3 70.3 (13.0) at diagnosis 4174 29.6 (7.2) 683 71.9 (7.0) at diagnosis 4174 29.6 (7.2) 683 4.2 (2.9) 417 $20(2.3)$ 683 4.2 (2.9) 886 91 645 94 8866 91 645 82 27.9 (7.0) 39 477 1479 356 270 39 4.2 (2.9) 477 1479 357 270 39 4.2 (2.9) 477 117 28 370 52 52 900 17 370 52 52 910 170 380 52 52 810 820 360 52 52 910 120 320 320 52 810 810 810</td><td>153</td><td></td><td>366</td><td>30</td><td>7</td><td>5</td><td>103</td><td>Q</td><td><0.0001</td></tr<>	N Mean (SD) N Mean (SD) 4247 64.3 (16.6) 68.3 70.3 (13.0) at diagnosis 4174 29.6 (7.2) 683 71.9 (7.0) at diagnosis 4174 29.6 (7.2) 683 4.2 (2.9) 417 $20(2.3)$ 683 4.2 (2.9) 886 91 645 94 8866 91 645 82 27.9 (7.0) 39 477 1479 356 270 39 4.2 (2.9) 477 1479 357 270 39 4.2 (2.9) 477 117 28 370 52 52 900 17 370 52 52 910 170 380 52 52 810 820 360 52 52 910 120 320 320 52 810 810 810	153		366	30	7	5	103	Q	<0.0001
4247 64.3 (16.6) 683 70.3 (13.0) 1041 $(g/m^2)^4$ at diagnosis 4174 29.6 (7.2) 683 27.9 (7.0) 1012 $(g/m^2)^4$ at diagnosis 4174 29.6 (7.2) 683 4.2 (2.9) 1041 $(gender)$ N $(\%)$ N $(\%)$ N $(\%)$ N $(gender)$ 3866 91 645 94 94 94 $(gender)$ 3866 91 61 94 94 94 $(gender)$ 3866 91 117 495 7 61 $(gender)$ 337 88 355 55 87 87 $(gender)$ 337 87 347 942 87 87 87 $(gender)$ 355 55 56 58 87 942 $(gender)$ 356 356 366 367 367 367 3	4247 64.3 (16.6) 683 70.3 (3.0) $(kg/m^2)t$ at diagnosis 4174 29.6 (7.2) 683 27.9 (7.0) $(kg/m^2)t$ at diagnosis 477 2.0 (2.3) 683 4.2 (2.9) $(kg/m^2)t$ $(kg/m$		Mean (SD		Mean (SD)	z	Mean (SD)	z	Mean (SD)	P value
s 4174 $296 (7.2)$ 683 $27.9 (7.0)$ 1012 4247 $2.0 (2.3)$ 683 $4.2 (2.9)$ 1041 N $(\%)$ N $(\%)$ N $(\%)$ N 866 91 645 94 984 984 1479 35 270 39 561 984 477 11 49 7 61 984 337 8 355 570 391 351 337 8 121 49 7 61 864 126 12 86 86 86 1556 122 86 323 361 237 817 814 1211 28 492 72 360 86 814 121 281 88 88 66 814 121 322 124 166 117 232 321 241 166 817 <	is 4174 29.6 (7.2) 683 27.9 (7.0) 4247 2.0 (2.3) 683 4.2 (2.9) N (%) N (%) 4.2 (2.9) N (%) N (%) 14.2 (2.9) 3866 91 645 94 1479 355 270 39 1479 11 49 7 337 8 35 5 477 11 49 7 337 8 35 5 47 11 49 7 156 46 340 52 537 84 35 58 541 149 35 58 537 56 598 88 541 10 302 44 537 56 598 88 547 10 302 44 548 6 598 88 549 6 395 58 549 6 395 58 549 6 395 58 549 6 333 33 549 549 533 53 549	424			70.3 (13.0)	1041	70.9 (12.7)	3561	71.6 (10.8)	<0.0001
4247 $2.0(2.3)$ 683 $4.2(2.9)$ 1041 2.1 N $(%)$ N $(%)$ N $(%)$ N $(%)$ 3866 91 645 94 984 94 94 94 94 3866 91 645 94 984 94 94 94 94 1479 11 49 7 61 61 6 94 94 477 11 49 7 61	$\begin{array}{llllllllllllllllllllllllllllllllllll$			683	27.9 (7.0)	1012	29.6 (7.5)	3559	30 (7.2)	<0.0001
N (%) N (%) N N 3866 91 645 94 98 98 3866 91 645 94 98 98 1479 35 270 39 351 98 477 11 49 7 61 98 337 8 35 5 87 351 426 12 80 12 88 87 1556 46 340 52 367 367 1511 28 361 53 350 367 1211 28 361 53 350 367 1211 28 361 53 350 350 1211 28 598 88 608 350 11 302 41 28 61 350 11 61 305 58 361 350 11 28 <t< td=""><td>N (%) N (%) 3866 91 645 94 3866 91 645 94 1479 35 270 39 477 11 49 7 477 11 49 7 337 8 35 5 426 12 80 12 1556 46 340 52 1556 46 340 53 1556 46 340 53 1556 46 340 53 1511 28 361 53 1211 28 361 53 1211 28 56 72 1211 28 59 72 11 10 302 44 11 10 302 44 11 65 361 58 11 53 55 58 11</td><td>424</td><td></td><td>683</td><td>4.2 (2.9)</td><td>1041</td><td>2.1 (2.2)</td><td>3561</td><td>4.3 (2.9)</td><td><0.0001</td></t<>	N (%) N (%) 3866 91 645 94 3866 91 645 94 1479 35 270 39 477 11 49 7 477 11 49 7 337 8 35 5 426 12 80 12 1556 46 340 52 1556 46 340 53 1556 46 340 53 1556 46 340 53 1511 28 361 53 1211 28 361 53 1211 28 56 72 1211 28 59 72 11 10 302 44 11 10 302 44 11 65 361 58 11 53 55 58 11	424		683	4.2 (2.9)	1041	2.1 (2.2)	3561	4.3 (2.9)	<0.0001
3866 91 645 94 984 1479 35 270 39 351 477 11 49 7 61 337 8 35 5 87 337 8 35 5 87 337 8 35 5 81 337 8 35 5 87 337 8 35 5 87 156 46 340 52 367 1556 46 340 52 367 151 28 361 53 361 151 28 361 53 367 151 28 361 53 367 151 28 361 53 361 151 28 361 53 350 16 302 44 10 166 17 302 44 166 166 16 395 58 58 541 17 222 33 33 178 17 23 34 17 17	3866 91 645 94 1479 35 270 39 1477 11 49 7 337 8 35 5 337 8 35 5 337 8 35 5 337 8 35 5 337 8 35 5 337 8 340 52 1556 46 340 52 1511 28 492 72 1211 28 492 72 2379 56 598 88 2379 56 598 88 16 302 44 10 17 302 44 18 4 194 19 55 58 11 535 58 11 535 58 11 535 58 11 535 58 11 535 58 11 535 58 12 533 33 13 533 53 14 17 53 17 52 53	Z	(%)	z	(%)	z	(%)	z	(%)	P value**
1479 35 270 39 351 477 11 49 7 61 337 8 35 5 8 61 337 8 35 5 8 61 337 8 35 5 5 87 426 12 80 12 80 12 86 1556 46 340 52 367 367 1211 28 361 53 421 367 1211 28 361 53 53 53 1211 28 361 53 53 53 1211 28 361 53 53 53 147 10 28 49 56 56 56 15 44 10 305 58 56 54 16 16 395 58 58 54 17 222 33 33 56 56 17 57 53 56 <t< td=""><td>1479 35 270 39 477 11 49 7 337 8 35 5 337 8 35 5 337 8 35 5 337 8 35 5 426 12 80 12 1556 46 340 52 155 46 340 52 1211 28 361 53 2379 56 598 88 447 10 302 44 16 302 44 17 335 58 17 223 33 33</td><td></td><td></td><td>645</td><td>94</td><td>984</td><td>94</td><td>3435</td><td>96</td><td><0.0001</td></t<>	1479 35 270 39 477 11 49 7 337 8 35 5 337 8 35 5 337 8 35 5 337 8 35 5 426 12 80 12 1556 46 340 52 155 46 340 52 1211 28 361 53 2379 56 598 88 447 10 302 44 16 302 44 17 335 58 17 223 33 33			645	94	984	94	3435	96	<0.0001
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	147		270	39	351	34	1280	36	0.0590
37 8 35 5 87 426 12 80 12 88 1556 46 340 52 367 151 1499 35 361 53 367 1211 28 492 72 350 1211 28 492 72 350 1211 28 192 72 350 1211 28 194 28 608 1211 28 194 28 608 137 10 302 44 166 147 10 302 58 66 15 395 58 58 541 16 395 58 541 56 17 222 33 33 96 378 9 74 11 55	337 8 35 5 426 12 80 12 1556 46 340 52 151 1499 35 361 53 1211 28 492 72 2379 56 598 88 2379 56 598 88 17 10 302 44 187 4 194 28 1 672 16 395 58 1 672 16 395 58 1 67 16 395 58 1 67 16 395 58 1 249 6 233 33 1 724 17 222 33	477	11	49	7	61	9	234	7	<0.0001
426 12 80 12 88 1556 46 340 52 367 155 46 340 52 367 121 28 361 53 421 1211 28 492 72 350 1211 28 56 598 88 608 1211 28 56 598 88 608 1211 28 10 302 44 166 137 10 302 44 166 66 14 17 233 335 58 241 15 249 6 233 33 33 36 17 222 33 33 33 36 36 17 222 33 33 37 37 36 178 9 17 22 33 37 37 36	426 12 80 12 1556 46 340 52 1556 46 340 52 121 28 361 53 1211 28 492 72 2379 56 598 88 447 10 302 44 187 4 10 302 44 16 395 58 58 17 274 17 222 53	337	8	35	5	87	8	316	0	0.0108
	1556 46 340 52 st1 1499 35 361 53 1211 28 492 72 1211 28 492 72 1211 28 56 598 88 2379 56 598 88 147 10 302 44 187 4 194 28 14 672 16 395 58 17 223 33 33		12	80	12	88	12	412	12	0.9895
stt 1499 35 361 53 421 1211 28 492 72 350 1211 28 698 608 2379 56 598 88 608 447 10 302 44 166 187 4 194 28 66 19 57 16 395 58 66 11 672 16 395 58 241 19 233 33 33 96 10 74 17 222 33 178 378 9 74 11 522 53 16	stt 1499 35 361 53 1211 28 492 72 1211 28 598 88 2379 56 598 88 247 10 302 44 187 4 194 28 19 572 16 395 58 10 247 10 305 58 11 672 16 395 58 12 249 6 233 33 724 17 222 33 33			340	52	367	50	1859	55	<0.0001
1211 28 492 72 350 2379 56 598 88 608 247 10 302 44 166 187 4 194 28 668 197 16 395 58 66 19 67 16 395 58 241 19 74 17 222 33 96 10 74 17 222 33 178 10 74 11 274 11 65	1211 28 492 72 2379 56 598 88 247 10 302 44 187 4 194 28 14 672 16 395 58 15 249 6 233 33 724 17 222 33 33			361	53	421	40	2222	62	<0.0001
2379 56 598 88 608 447 10 302 44 166 187 4 194 28 66 17 672 16 395 58 66 17 249 6 233 33 96 17 222 33 178 96 378 9 74 11 65	2379 56 598 88 447 10 302 44 187 4 194 28 187 4 194 28 19 572 16 395 58 10 249 6 233 33 10 724 17 222 33			492	72	350	34	2750	77	<0.0001
447 10 302 44 166 187 4 194 28 66 14 672 16 395 58 241 15 249 6 233 33 96 154 17 222 33 178 378 9 74 11 65	447 10 302 44 187 4 194 28 17 672 16 395 58 17 223 33 33			598	88	608	58	3266	92	<0.0001
187 4 194 28 66 11 672 16 395 58 241 12 249 6 233 33 96 124 17 222 33 178 378 9 74 11 65	187 4 194 28 ++ 672 16 395 58 - 249 6 233 33 724 17 222 33		10	302	44	166	16	1905	54	<0.0001
1 672 16 395 58 241 249 6 233 33 96 724 17 222 33 178 378 9 74 11 65	1 672 16 395 58 249 6 233 33 724 17 222 33		4	194	28	66	6	1207	34	<0.0001
. 249 6 233 33 96 724 17 222 33 178 378 9 74 11 65	249 6 233 33 724 17 222 33		16	395	58	241	23	2381	67	<0.0001
724 17 222 33 178 378 9 74 11 65	724 17 222 33		9	233	33	96	6	1406	39	<0.0001
378 9 74 11 65			17	222	33	178	17	1243	35	<0.0001
	Pre-index bronchitis†† 378 9 74 11 65		0	74	11	65	9	447	13	<0.0001
Pre-index acute respiratory failure†† 146 3 81 12 43 4	146 3 81 12		ю	81	12	43	4	449	13	<0.0001

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	Medication		ל הוח-ומל	use by uniting or covid-13 positive test result	2				
Medication/outcome*	Not used		Taken be	Taken before only†		Taken after only‡	Taken b	Taken before and after§	1
Pre-index asthma††	257	9	55	8	48	5	231	9	0.0265
Pre-index chronic lung disease††	1302	31	341	50	287	28	1792	50	<0.0001
Pre-index emphysema ††	84	Ŋ	30	4	22	CI	122	З	<0.0001
Death	695	16	202	30	316	30	799	22	<0.0001
(C) Famotidine and remdesivir in hospitalised VA patients with CO	VA patients with CO	VID-19 followed for 60 days	for 60 days						
Famotidine	z	Mean (SD)	z	Mean (SD)	z	Mean (SD)	z	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
	z	(%)	z	(%)	z	(%)	z	(%)	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	ω	44	10	136	12	36	6	0.0001
Overweight	608	Ø	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	9	40	6	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	ი	21	5	26	CI	15	4	0.0420
Death	1436	19	66	22	379	34	98	23	<0.0001
Remdesivir‡‡	z	Mean (SD)	z	Mean (SD)	z	Mean (SD)	z	Mean (SD)	P value¶
Age	6800	38.1 (14.8)			2732	68.3 (13.5)			0.6342
BMI (ka/m ²)† at diagnosis	6710	29.1 (7.1)			2718	31.1 (7.5)			<0.0001

Medication de tree	Table 1 Continued									
Notated Identify		Medication	use by timing o	f COVID-19 pos	sitive test res	ult				
600 3.2 (2.9) 2.7 (2.5) 2.7 (2.5) nder (9) N (9) N (9) N (9) order 243 93 2 2 (2.5) N (9) N (9) order 2619 93 2 <th2< th=""> 2 2 <th2< th=""></th2<></th2<>	Medication/outcome*	Not used		Taken befo	re only†	Taken a	fter only‡	Taken b	oefore and after§	I
N (a) N (b) N (b) N (b) ender 5349 33 33 34 33 34 (b) (b) <t< th=""><th>CCI</th><th>6800</th><th>3.2 (2.9)</th><th></th><th></th><th>2732</th><th>2.7 (2.5)</th><th></th><th></th><th><0.0001</th></t<>	CCI	6800	3.2 (2.9)			2732	2.7 (2.5)			<0.0001
ender E349 83 2581 84 94 ic 2619 38 761 28 761 28 ic 512 8 761 26 11 26 1 idit 480 7 265 11 265 1 265 1 idit 480 7 264 285 1293 51 26 26 in oker 3506 52 1289 51 26 <td< td=""><td></td><td>z</td><td>(%)</td><td>z</td><td>(%)</td><td>z</td><td>(%)</td><td>z</td><td>(%)</td><td>P value**</td></td<>		z	(%)	z	(%)	z	(%)	z	(%)	P value**
2619 38 761 28 int 512 8 309 11 int 480 7 295 11 int 480 7 295 11 int 823 49 204 #18 int diagnosis 862 14 204 #18 int vipe 2 dialeterit 3119 46 1293 51 ex type 2 dialeterit 3119 46 1384 51 ex type 2 dialeterit 319 46 1384 51 ex type 2 dialeterit 319 46 334 51 ex thirti 4318 71 203 74 51 ex CHFT 1268 19 203 74 56 55 ex CHFT 1268 19 203 74 56 56 55 ex CHFT 1268 19 56 35 56 14 56 ex controlit 16 7	Male gender	6349	93			2581	94			0.0449
ic 512 8 309 11 eight 7 205 1 205 11 rat diagnosis 802 14 205 205 14 rat diagnosis 802 14 204 148 rat diagnosis 802 14 204 148 oker 203 64 1289 55 oker 319 46 1384 51 oker 310 3206 52 1384 51 oker 131 43 71 2033 74 oker 141 128 1283 74 26 oker 141 128 1283 74 26 oke CHIT 128 1283 1283 1283 14 oker 1283 1283 1283 1283 14 oker 1384 1384 1384 1384 1384 oker 1365 136 <	Black	2619	38			761	28			<0.0001
eight 1 295 1 rat diagnosis 802 1 204 #8 rat diagnosis 802 1 204 #16 noker 283 49 204 #16 noker 283 49 204 #16 noker 319 46 128 51 ex VDH 3506 52 1384 51 ex VDH 3506 52 1384 51 ex CAHDH 3506 52 1283 74 ex CAHDH 148 71 2033 74 ex CAHDH 1268 13 74 26 ex CAHDH 1268 14 263 74 ex CAHDH 1268 14 263 14 ex CAHDH 1268 126 26 26 ex chatlautett 1505 22 266 35 ex contrist 150 27 26 26	Hispanic	512	8			309	11			<0.0001
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ex CHD†t 2066 30 754 28 ex CHF†t 1268 19 386 14 ex CHF†t 1268 19 386 14 ex CHF†t 2733 40 956 35 ex heart disease†t 2733 40 956 35 ex heart disease†t 1505 22 469 17 ex heart disease†t 1678 25 26 25 ex bronchtist†t 167 26 290 11 ex bronchtist†t 167 10 290 11 ex actit respiratory failure†t 18 8 260 17 ex actit respiratory failure†t 136 6 7 7 ex actit respiratory failure†t 263 39 40 7 ex emphysema †t 176 2 20 1963 40	Pre-index HTN††	4818	71			2033	74			0.0005
iex CHFt 1268 19 386 14 iex heart diseasett 2733 40 956 35 iex heart diseasett 1505 22 956 35 iex heart failue†t 1505 22 469 17 iex coPDtt 1678 25 26 73 iex CoPDtt 1678 26 290 11 iex corter respiratory failue†t 518 8 290 11 iex cute respiratory failue†t 395 6 7 7 iex acture respiratory failue†t 283 39 25 7 iex acture ruspiratory failue†t 263 39 7 7 iex chronic lung disease†t 175 2 83 40 iex chronic lung disease†t 175 2 83 40 iex chronic lung disease†t 175 2 83 40	Pre-index CAHD††	2066	30			754	28			0.0071
tex heart disease t 2733 40 956 35 lex heart failure t150522 469 17 lex heart failure t167825 689 25 lex COPDtt 674 10 290 11 lex bronchitis t 518 8 201 7 lex acute respiratory failure t 395 6 201 7 lex acute respiratory failure t 290 11 7 lex acute respiratory failure t 292 201 7 lex acute respiratory failure t 263 39 106 lex acute respiratory failure t 175 2 83 40 lex chronic lung disease t 175 2 83 40 lex emphysema t 175 20 83 40 lex emphysema t 175 20 83 40 lex emphysema t 175 20 83 40 lex emphysema t 1362 20 83 40	Pre-index CHF††	1268	19			386	14			<0.0001
tex heart failure†t15052246917lex COP116782568925lex COP16741068925lex bronchits†t6741029011lex acute respiratory failure†t51882017lex acute respiratory failure†t39567lex acture respiratory failure†t263939108340lex chronic lung disease†t17528340lex onphysema t†17520835050lex onphysema t†1362206024	Pre-index heart disease††	2733	40			956	35			<0.0001
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lex bronchitist 674 10 290 11 lex acute respiratory failure 1 518 8 201 7 lex acute respiratory failure 1 395 6 201 7 lex actimatif 293 39 196 7 lex chronic lung disease 11 2639 39 1083 40 lex emphysema 11 175 2 83 4 lex emphysema 1162 20 20 650 24	Pre-index COPD††	1678	25			689	25			0.5789
lex acute respiratory failure†51882017lex acute respiratory failure† 395 6 196 7lex chronic lung disease† 2639 39 1083 40 lex emphysema †† 175 2 83 ‡lex emphysema †† 175 20 20 650 24	Pre-index bronchitis††	674	10			290	11			0.3032
lex asthmat† 395 6 196 7 lex chronic lung disease†† 2639 39 1083 40 lex emphysema †† 175 2 83 ‡ 1362 20 20 650 24	Pre-index acute respiratory failure††	518	80			201	7			0.6633
lex chronic lung disease†† 2639 39 1083 40 lex emphysema †† 175 2 83 ‡ 1362 20 650 24	Pre-index asthma††	395	6			196	7			0.0124
lex emphysema †† 175 2 2 83 ‡ 1362 20 650 24	Pre-index chronic lung disease††	2639	39			1083	40			0.4513
1362 20 650 24	Pre-index emphysema ††	175	0			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.

IP 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.

t+Pre-index conditions are coded if ever present in 2 years preceding positive COVID-19 test result.

t#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.

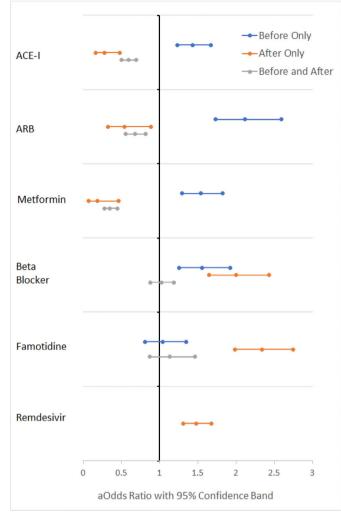


Figure 1 Associations of mortality with patterns of medication use among hospitalised VA patients with COVID-19 followed for 60 days, estimated from logistic regression models adjusted for adjusted for age, race, ethnicity, sex, overweight, smoking status and pre-existing morbidity. ACE-I, ACE inhibitor; 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 $\times \log(-\log(survival time))$ 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).

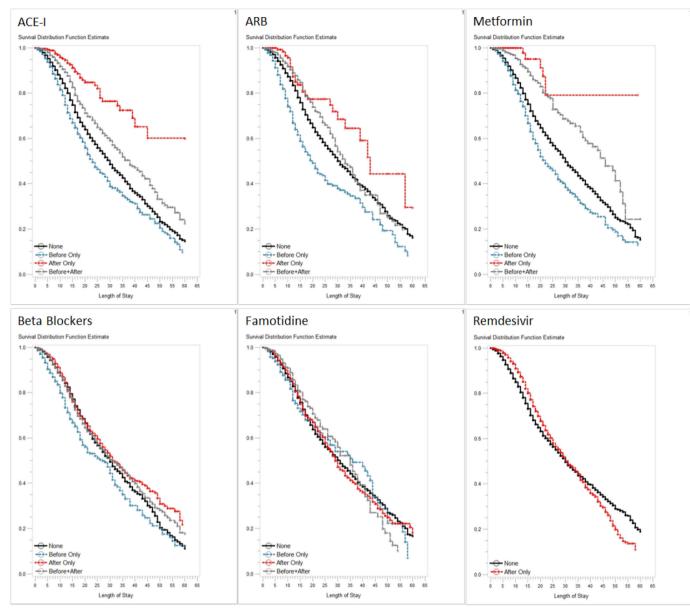


Figure 2 Survival curves by patterns of medication use among hospitalised VA patients with COVID-19 followed for 60 days. ACE-I, ACE inhibitor; ARB, angiotensin receptor blocker; VA, Veterans Affairs.

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 2Associations of mortality with patterns ofmedication use among hospitalised VA patients withCOVID-19 followed for 60 days according to mechanicalventilation status

ventilation status				
	Receit (n=13	ved ventilation* 15)		t receive tion* (n=6847)
		95%		95%
	OR†	Confidence limits	OR†	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.

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
 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

		ntinued beta er* (n=651)		nuous beta er* (n=3361)
		95%		95%
	OR†	Confidence limits	OR†	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.

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

score weighted prop	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.

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-Arg⁹-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 at' 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

⁺P_{(ACE-I: before and afterxlog (-log(survival)))}=0.0451. +P_{(ARB: before onlyxlog (-log(survival)))}=0.0267.

SP (ARB: before and after×log (-log(survival))) <0.0001.

aHRs, adjusted HRs; CAHD, coronary atherosclerotic heart disease;

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 antiviral⁴ 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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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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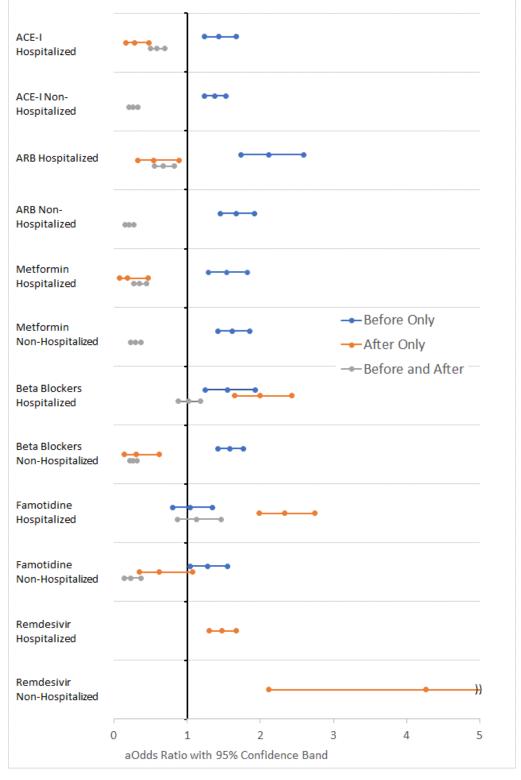
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The upper 95% confidence limit for Remdesivir (95% Cl 2.1 - 8.6) is truncated to enhance visualization of associations for other medications with much narrower confidence bands.