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 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.

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. 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. 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. Despite potent in vitro antiviral effects, clinical studies of hydroxychloroquine in COVID-19 have been disappointing. Similarly, the antiviral drug remdesivir has received Emergency Use Authorization from the US FDA but has shown only limited clinical efficacy. 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. 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. 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 95,322 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), 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-I 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/outcome* | Not used | Taken before only† | Taken after only‡ | Taken before and after§ |
|---------------------|----------|---------------------|-------------------|-------------------------|
| **ACE-I**           | **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/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 (8.0)              | 351     | 1.9 (2.5)     | 1920         | 3.4 (2.5)     | <0.0001      |

| **N (%)** | **N (%)** | **N (%)** | **N (%)** | **P value*** |
|-----------|-----------|-----------|-----------|--------------|
| Male gender | 5423 | 92       | 1320      | 97           | 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†† | 2818 | 44       | 924       | 68           | 125  | 36         | 1136         | 59           | <0.0001      |
| Pre-index HTN†† | 3574 | 61       | 1277      | 94           | 193  | 55         | 1807         | 94           | <0.0001      |
| Pre-index CAHDT†† | 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 COPDT†† | 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)** | **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 (8.0)     | 218   | 2.3 (2.5)     | 1039          | 3.9 (2.7)     | <0.0001      |

| **N (%)** | **N (%)** | **N (%)** | **P value*** |
|-----------|-----------|-----------|--------------|
| Male gender | 7216 | 93       | 530        | 97           | 198  | 91         | 986          | 95           | 0.0003       |
Table 1 Continued

| Medication/outcome* | Not used | Taken before only† | Taken after only‡ | Taken before and after§ |
|---------------------|----------|--------------------|-------------------|------------------------|
| Black               | 2664     | 35                 | 233               | 43                     |
| Hispanic            | 685      | 9                  | 32                | 19                     |
| Overweight          | 584      | ††8                | 51                | 9                      |
| Smoker at diagnosis | 832      | 13                 | 63                | 12                     |
| Past smoker         | 3259     | 50                 | 264               | 51                     |
| Pre-index type 2 diabetes†† | 3317 | 43                 | 364               | 67                     |
| Pre-index CVD††      | 3639     | 47                 | 400               | 73                     |
| Pre-index HTN††      | 5197     | 67                 | 521               | 96                     |
| Pre-index CAHD††     | 2057     | 27                 | 274               | 50                     |
| Pre-index CHF††      | 1128     | 15                 | 209               | 38                     |
| Pre-index heart disease†† | 2718 | 35                 | 339               | 62                     |
| Pre-index heart failure†† | 1364 | 18                 | 234               | 43                     |
| Pre-index COPD††     | 1799     | 23                 | 206               | 38                     |
| Pre-index bronchitis†† | 726   | 9                  | 69                | 13                     |
| Pre-index acute respiratory failure†† | 529   | 7                  | 89                | 16                     |
| Pre-index asthma††   | 434      | 6                  | 52                | 10                     |
| Pre-index chronic lung disease†† | 2861 | 37                 | 295               | 54                     |
| Pre-index emphysema †† | 193   | 3                  | 28                | 5                      |
| Death               | 1607     | 21                 | 212               | 39                     |
|                     |          |                    |                   |                        |
| **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/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   |
| 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* | Not used | Taken before only† | Taken after only‡ | Taken before and after§ | P value |
|---------------------|----------|--------------------|-------------------|--------------------------|---------|
| Pre-index HTN††     | 4641     | 67                 | 1075              | 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 |
| Death                | 1536     | 22                 | 366               | 30                       | 7       | 5    | 103 | 9  | <0.0001 |

** Beta blockers **

| N (%)                              | 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  | 0.8985 |
| 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 use by timing of COVID-19 positive test result

| Medication/outcome* | 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/m²)† 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   |
| 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††    | 3623 (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/m²)† at diagnosis | 6710 (29.1 (7.1)) | 2718 (31.1 (7.5)) | <0.0001       |
Table 1 Continued

| Medication/outcome*                  | Not used | Taken before only† | Taken after only‡ | Taken before and after§ | P value** |
|--------------------------------------|----------|--------------------|-------------------|--------------------------|-----------|
| CCI                                  | 6800     | 3.2 (2.9)          | 2732              | 2.7 (2.5)                | <0.0001   |
| 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 asthema††                  | 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 χ² 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-I, 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.
variables using the $\chi^2$ test. ORs for risk of death were estimated from logistic regression and HRs from Cox proportional hazards models adjusted for: age, race, ethnicity, sex, overweight, smoking status and pre-existing morbidity; ACE-I, ACE inhibitor; ARB, angiotensin receptor blocker; VA, Veterans Affairs.

**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).
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
These medications is critical.

Wallace AW, et al. BMJ Open 2021;11:e050051. doi:10.1136/bmjopen-2021-050051

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) |
|----------------|-------------------------------|--------------------------------------|
|                | 95% OR† Confidence limits      | 95% 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.

Supplementary analysis examining associations controlled for multiple medication use showed similar findings for ACE-I, 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. 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. Despite their structural homology, ACE1 and ACE2 appear to play counterbalancing roles on vascular function and
inflammatory cytokines, including interleukin 6 (IL-6), interferon (IFN) γ, tumour necrosis factor α, CCL2, IL-12 and IL-5. Unlike ACE1, ACE2 exhibits promiscuous proteolytic activity against additional specific inflammatory mediators des-Arg¹-bradykinin, neurotensin, dynorphin A(1–13) and the inflammatory adipokine apelin-13. After viral entry, SARS-CoV-2 triggers ACE2 shedding from infected cells through induction of the ADAM17 protease during SARS-CoV-2 replication. 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. 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. Moreover, ACE2 in the heart is required for normal cardiac activity, as ACE2 deficiency in mice leads to severe left ventricular dysfunction.

**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-IIs 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. Potential concern about ACE-I and/or ARB use on COVID-19 severity have been reported in early studies. Evidence recently reported from the Randomized Elimination and Prolongation of ACE Inhibitors and ARBs in Coronavirus 2019 Trial (REPLACE COVID) and the Angiotensin Receptor Blockers and Angiotensin-converting Enzyme Inhibitors and Adverse Outcomes in Patients with COVID-19 (BRACE-CORONOA) randomised clinical trials and from a ‘living’ systematic review by Mackey et al 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.

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

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**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

| Medication | Before | After | Before and after | ARB | Before | After | Before and after | Metformin | Before | After | Before and after |
|------------|--------|-------|-----------------|-----|--------|-------|-----------------|-----------|--------|-------|-----------------|
| ACE-I      |        |       |                 |     |        |       |                 |           |        |       |                 |
| Before only| 1.39   | 1.24  | 1.57            |     |        |       |                 |           |        |       |                 |
| After only | 0.24   | 0.14  | 0.39            |     |        |       |                 |           |        |       |                 |
| ≤40 days   | 0.73   | 0.63  | 0.84            |     |        |       |                 |           |        |       |                 |
| >40 days   | 0.79   | 0.50  | 1.24            |     |        |       |                 |           |        |       |                 |
| ARB        |        |       |                 |     |        |       |                 |           |        |       |                 |
| Before only| 1.97   | 1.67  | 2.32            |     |        |       |                 |           |        |       |                 |
| >25 days   | 1.17   | 0.73  | 1.88            |     |        |       |                 |           |        |       |                 |
| After only | 0.53   | 0.33  | 0.84            |     |        |       |                 |           |        |       |                 |
| ≤20 days   | 0.65   | 0.52  | 0.81            |     |        |       |                 |           |        |       |                 |
| >20 days   | 1.42   | 1.09  | 1.83            |     |        |       |                 |           |        |       |                 |
| Metformin  |        |       |                 |     |        |       |                 |           |        |       |                 |
| Before only| 1.53   | 1.32  | 1.77            |     |        |       |                 |           |        |       |                 |
| >25 days   | 1.88   | 1.43  | 2.47            |     |        |       |                 |           |        |       |                 |
| After only | 0.20   | 0.07  | 0.54            |     |        |       |                 |           |        |       |                 |

*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, bronchiolitis, 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 <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(ACE-I: before and after×log(−log(survival)))=0.0451.

‡P(ARB: before and after×log(−log(survival)))=0.0267.

¶P(metformin: before only×log(−log(survival)))=0.0001.

| Medication | Before | After | Before and after | ARB | Before | After | Before and after | Metformin | Before | After | Before and after |
|------------|--------|-------|-----------------|-----|--------|-------|-----------------|-----------|--------|-------|-----------------|
| ACE-I      |        |       |                 |     |        |       |                 |           |        |       |                 |
| Before only| 1.39   | 1.24  | 1.57            |     |        |       |                 |           |        |       |                 |
| After only | 0.24   | 0.14  | 0.39            |     |        |       |                 |           |        |       |                 |
| ≤40 days   | 0.73   | 0.63  | 0.84            |     |        |       |                 |           |        |       |                 |
| >40 days   | 0.79   | 0.50  | 1.24            |     |        |       |                 |           |        |       |                 |
| ARB        |        |       |                 |     |        |       |                 |           |        |       |                 |
| Before only| 1.97   | 1.67  | 2.32            |     |        |       |                 |           |        |       |                 |
| >25 days   | 1.17   | 0.73  | 1.88            |     |        |       |                 |           |        |       |                 |
| After only | 0.53   | 0.33  | 0.84            |     |        |       |                 |           |        |       |                 |
| ≤20 days   | 0.65   | 0.52  | 0.81            |     |        |       |                 |           |        |       |                 |
| >20 days   | 1.42   | 1.09  | 1.83            |     |        |       |                 |           |        |       |                 |
| Metformin  |        |       |                 |     |        |       |                 |           |        |       |                 |
| Before only| 1.53   | 1.32  | 1.77            |     |        |       |                 |           |        |       |                 |
| >25 days   | 1.88   | 1.43  | 2.47            |     |        |       |                 |           |        |       |                 |
| After only | 0.20   | 0.07  | 0.54            |     |        |       |                 |           |        |       |                 |
| Before and after | 0.28 | 0.21 | 0.37          |     |        |       |                 |           |        |       |                 |
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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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, favipiravir, lopinavir, ritonavir, oseltamivir, methylprednisolone, bevacizumab and traditional Chinese medicines.\textsuperscript{33} Despite the testing of multiple antiviral\textsuperscript{4} and/or anti-inflammatory drugs,\textsuperscript{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-5) 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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