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LETTER TO THE EDITOR

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Interaction effects between angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and steroid or antiviral therapies in COVID-19: A population-based study

To the Editor,

We read the recent article published in your journal on the predictors of mortality in patients with coronavirus 2019 (COVID-19) infection with great interest.[1] In that study, treatment with antibiotics, antifungals, antivirals, steroids, blood transfusion, and intubation was associated with increased mortality. Indeed, whether steroids have beneficial effects on mortality in COVID-19 remains controversial.[2] There may also be interactions between steroids and the renin-angiotensin-aldosterone system as well as differential effects between angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in COVID-19 outcomes.[3] The benefit of ACEIs/ARBs has also been controversial[4–6] and the association with worse outcomes may partly be explained by the presence of comorbidities.[7,8] Therefore, using a local population-based administrative health record system, we examined the interaction effects between the use of ACEIs or ARBs with steroids or antiviral therapies on severe disease outcome in COVID-19 patients.

This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster. The patients were identified from the Clinical Data Analysis and Reporting System, a territory-wide database that centralizes patient information from 43 local hospitals and their associated ambulatory and outpatient facilities to establish comprehensive medical data, including clinical characteristics, disease diagnosis, laboratory results, and drug treatment details. The system has been previously used by both our team and other teams in Hong Kong, including COVID-19 research.[9,10] The list of ICD-9 codes for comorbidities and intubation procedures is detailed in Tables S1 and S2.

A total of 1281 patients tested positive for COVID-19, and were prescribed treatment for the infection with antiviral or steroid drugs between January 1st, 2020 and November 20th, 2020 in Hong Kong, China, were included. The primary outcome was a composite of the need for intubation or all-cause mortality. 1:2 propensity score matching between ACEI users and non-users, and ARB users and non-users were performed.

On follow-up until December 7th, 2020, a total of 73 patients (5.7%) met the primary outcome of need for intensive care unit admission or intubation, or death in the unmatched cohort. The baseline clinical characteristics of patients in the unmatched cohort are shown in Table 1. Those for the cohort stratified by ACEI or ARB use before and after propensity score matching for baseline demographics, past medical comorbidities and medication history are shown in Tables S3 and S4, respectively. The results of the univariate regression analysis on the matched cohorts are shown in Table S5. Increasing age, higher Charlson comorbidity score, and the use of medications such as steroids, diuretics for heart failure, antidiabetic drugs, proton pump inhibitors, anticoagulants, low albumin, and the presence of acidosis were significantly associated with higher odds of meeting the primary outcome in both cohorts. Although ACEI and ARB use was significantly associated with higher odds of meeting the primary outcome, the application of propensity score matching analysis revealed a greater comorbidity burden to be the likely explanation. Thus, before matching, the percentage of patients meeting the composite outcome was 19.78% for ACEI users and 4.62% for non-users ($p < .0001$). The gap between these percentages was smaller after matching, to the extent that they were no longer statistically significantly different from each other (19.78% vs. 14.28%, $p = .4175$). Similarly, for ARB users and non-users, these percentages were 10.57% and 5.26% before matching ($p = .0635$), and the gap was reduced after matching to 10.57% and 16.82% ($p = .2678$).

Interaction effects between ACEIs, ARBs, and individual drugs in these classes with antiviral therapies or steroids were assessed in the unmatched cohort (Table 2). For ACEI, there were significant interactions with steroids (odds ratio [OR]: 8.64, 95% confidence interval [CI], 4.55–16.42; $p < .001$), ribavirin and interferon β-1b combination (OR, 5.06; 95% CI, 1.98–12.96; $p < .001$) and lopinavir/ritonavir and interferon β-1b combination (OR, 4.67; 95% CI, 2.07–10.57; $p < .0001$) for meeting the primary outcome. For ARB, only an interaction with remdesivir was found (OR, 2.78; 95% CI, 1.53–47.08; $p < .05$). On the ACEI/control matched cohort, interactions between ACEI and steroids acted to reduce their individual effects on the primary outcome (OR for ACEI: 1.48 [0.76,2.87]; $p = .2463$; OR for steroids: 8.29 [3.15,21.8], $p < .0001$; OR for ACEI/steroids: 2.87; 95% CI, 1.42–5.82; $p < .01$; Table S6). For the ARB/control matched cohort, there was no significant interaction with remdesivir (OR, 2.98; 95% CI, 0.53–16.75; $p > .05$; Table S7).

However, some limitations of our study should be noted. Firstly, while all reverse-transcription polymerase chain reaction tests conducted in the public system were fully captured, those that were conducted privately were not. Secondly, the identification of comorbidities and outcomes relied on International classification of

TABLE 1 Baseline clinical characteristics of COVID-19 patients treated with antiviral agents or steroids

Characteristics	All (*N* = 1281) median (IQR); Max; *N* or count (%)	Composite outcome (*N* = 73) median (IQR); Max; *N* or count (%)	No composite outcome (*N* = 1208) median (IQR); Max; *N* or count (%)	*p* value
Suboutcomes				
Mortality	38 (2.96%)	38 (52.05%)	0 (0.00%)	<.0001***
Intubation	47 (3.66%)	47 (64.38%)	0 (0.00%)	<.0001***
Male gender	649 (50.66%)	41 (56.16%)	608 (50.33%)	.6581
Baseline age, years	52.34 (35.18–64.62); 99.71; *n* = 1281	70.34 (62.3–81.13); 98.66; *n* = 73	51.1 (33.9–63.11); 99.71; *n* = 1208	<.0001***
<60	816 (63.70%)	11 (15.06%)	805 (66.63%)	<.0001***
[60,64]	129 (10.07%)	10 (13.69%)	119 (9.85%)	.4544
[65,69]	84 (6.55%)	9 (12.32%)	75 (6.20%)	.1016
[70,75]	84 (6.55%)	11 (15.06%)	73 (6.04%)	.0125*
>75	121 (9.44%)	27 (36.98%)	94 (7.78%)	<.0001***
Charlson score	1.0 (0.0–2.0); 35.0; *n* = 1281	3.0 (2.0–4.0); 12.0; *n* = 73	1.0 (0.0–2.0); 35.0; *n* = 1208	<.0001***
Diabetes mellitus	48 (3.74%)	11 (15.06%)	37 (3.06%)	<.0001***
Systemic embolism	4 (0.31%)	0 (0.00%)	4 (0.33%)	.5551
Hypertension	262 (20.45%)	40 (54.79%)	222 (18.37%)	<.0001***
Heart failure	7 (0.54%)	0 (0.00%)	7 (0.57%)	.8656
Atrial fibrillation	23 (1.79%)	3 (4.10%)	20 (1.65%)	.2978
Chronic renal failure	3 (0.23%)	0 (0.00%)	3 (0.24%)	.4109
Liver diseases	6 (0.46%)	1 (1.36%)	5 (0.41%)	.7853
Ventricular tachycardia/ fibrillation	9 (0.70%)	3 (4.10%)	6 (0.49%)	.0051**
Dementia and alzheimer	5 (0.39%)	0 (0.00%)	5 (0.41%)	.6755
AMI	15 (1.17%)	3 (4.10%)	12 (0.99%)	.0733
COPD	12 (0.93%)	0 (0.00%)	12 (0.99%)	.8235
IHD	50 (3.90%)	7 (9.58%)	43 (3.55%)	.0340*
PVD	7 (0.54%)	2 (2.73%)	5 (0.41%)	.0771
Stroke/TIA	30 (2.34%)	7 (9.58%)	23 (1.90%)	.0003***
Gastrointestinal bleeding	22 (1.71%)	4 (5.47%)	18 (1.49%)	.0448*
Cancer	35 (2.73%)	8 (10.95%)	27 (2.23%)	.0001***
Obesity	6 (0.46%)	1 (1.36%)	5 (0.41%)	.7853
ACEI	91 (7.10%)	18 (24.65%)	73 (6.04%)	<.0001***
ARB	104 (8.11%)	11 (15.06%)	93 (7.69%)	.0733
Captopril	2 (0.15%)	1 (1.36%)	1 (0.08%)	.243
Enalapril	11 (0.85%)	3 (4.10%)	8 (0.66%)	.0171*
Lisinopril	61 (4.76%)	11 (15.06%)	50 (4.13%)	.0003***
Ramipril	4 (0.31%)	0 (0.00%)	4 (0.33%)	.5551
Perindopril	18 (1.40%)	3 (4.10%)	15 (1.24%)	.1434
Candesartan	1 (0.07%)	0 (0.00%)	1 (0.08%)	.0558

TABLE 1 (Continued)

Characteristics	All (*N* = 1281) median (IQR); Max; *N* or count (%)	Composite outcome (*N* = 73) median (IQR); Max; *N* or count (%)	No composite outcome (*N* = 1208) median (IQR); Max; *N* or count (%)	*p* value
Entresto	1 (0.07%)	1 (1.36%)	0 (0.00%)	.0578
Irbesartan	1 (0.07%)	0 (0.00%)	1 (0.08%)	.0558
Losartan	99 (7.72%)	9 (12.32%)	90 (7.45%)	.2481
Telmisartan	2 (0.15%)	0 (0.00%)	2 (0.16%)	.2381
Steroid	565 (44.10%)	62 (84.93%)	503 (41.63%)	<.0001***
Remdesivir	51 (3.98%)	9 (12.32%)	42 (3.47%)	.0015**
Lopinavir/ritonavir	65 (5.07%)	2 (2.73%)	63 (5.21%)	.5341
Interferon β-1B	70 (5.46%)	10 (13.69%)	60 (4.96%)	.0079**
Lopinavir/ritonavir and ribavarin	417 (32.55%)	15 (20.54%)	402 (33.27%)	.1201
Ribavirin and interferon β-1B	460 (35.90%)	22 (30.13%)	438 (36.25%)	.5337
Lopinavir/ritonavir and interferon β-1B	582 (45.43%)	38 (52.05%)	544 (45.03%)	.551
Lopinavir/ritonavir and ribavarin and interferon β-1B	236 (18.42%)	10 (13.69%)	226 (18.70%)	.4524
Calcium channel blockers	277 (21.62%)	43 (58.90%)	234 (19.37%)	<.0001***
β blockers	140 (10.92%)	22 (30.13%)	118 (9.76%)	<.0001***
Diuretics for hypertension	51 (3.98%)	6 (8.21%)	45 (3.72%)	.1346
Diuretics for heart failure	81 (6.32%)	41 (56.16%)	40 (3.31%)	<.0001***
Nitrates	40 (3.12%)	5 (6.84%)	35 (2.89%)	.1453
Antihypertensive drugs	66 (5.15%)	10 (13.69%)	56 (4.63%)	.0043**
Antidiabetic drugs	205 (16.00%)	47 (64.38%)	158 (13.07%)	<.0001***
Statins and fibrates	247 (19.28%)	34 (46.57%)	213 (17.63%)	<.0001***
Lipid-lowering drugs	239 (18.65%)	32 (43.83%)	207 (17.13%)	<.0001***
Sodium-glucose cotransporter 2 inhibitors	21 (1.63%)	4 (5.47%)	17 (1.40%)	.0352*
Dipeptidyl peptidase-4 inhibitors	38 (2.96%)	5 (6.84%)	33 (2.73%)	.1159
Proton pump inhibitors	280 (21.85%)	59 (80.82%)	221 (18.29%)	<.0001***
Famotidine	258 (20.14%)	26 (35.61%)	232 (19.20%)	.0133*
Anticoagulants	154 (12.02%)	53 (72.60%)	101 (8.36%)	<.0001***
Antiplatelets	118 (9.21%)	18 (24.65%)	100 (8.27%)	.0001***
Mean corpuscular volume, fL	87.7 (84.0–90.79); 104.5; *n* = 565	89.3 (85.5–92.2); 99.2; *n* = 44	87.6 (84.0–90.7);104.5; *n* = 521	.1005
Basophil, $\times 10^9$/L	0.01 (0.0–0.02); 0.2; *n* = 885	0.0 (0.0–0.02); 0.13; *n* = 48	0.01 (0.0–0.02); 0.2; *n* = 837	.1063
Eosinophil, $\times 10^9$/L	0.01 (0.0–0.07); 1.91; *n* = 913	0.0 (0.0–0.02); 0.17; *n* = 51	0.01 (0.0–0.08);1.91; *n* = 862	.0011**
Lymphocyte, $\times 10^9$/L	1.23 (0.89–1.66); 6.1; *n* = 913	1.0 (0.68–1.5); 3.44; *n* = 51	1.25 (0.9–1.67); 6.1; *n* = 862	.0059**
Metamyelocyte, $\times 10^9$/L	0.23 (0.18–0.46); 0.7; *n* = 3	0.7 (0.7-0.7); 0.7; *n* = 1	0.18 (0.18–0.18); 0.23; *n* = 2	.5403

(Continues)

TABLE 1 (Continued)

Characteristics	All (*N* = 1281) median (IQR); Max; *N* or count (%)	Composite outcome (*N* = 73) median (IQR); Max; *N* or count (%)	No composite outcome (*N* = 1208) median (IQR); Max; *N* or count (%)	*p* value
Monocyte, $\times 10^9$/L	0.49 (0.36–0.62); 3.15; *n* = 913	0.49 (0.36–0.62);1.2; *n* = 51	0.48 (0.36–0.62); 3.15; *n* = 862	.8536
Neutrophil, $\times 10^9$/L	3.2 (2.4–4.37); 23.16; *n* = 913	4.76 (3.79–9.25);18.63; *n* = 51	3.14 (2.39–4.22); 23.16; *n* = 862	<.0001***
White cell count, $\times 10^9$/L	5.2 (4.18–6.6); 25.58; *n* = 922	6.65 (5.3–11.38); 21.19; *n* = 51	5.1 (4.14–6.46); 25.58; *n* = 871	<.0001***
Mean cell hemoglobin, pg	30.2 (28.75–31.6); 37.0; *n* = 922	31.3 (29.3–32.85); 36.2; *n* = 51	30.2 (28.7-31.5); 37.0; *n* = 871	.0425*
Myelocyte, $\times 10^9$/L	0.35 (0.15–0.42); 1.29; *n* = 15	0.44 (0.36–0.64);1.29; *n* = 7	0.15 (0.1–0.29); 0.41; *n* = 8	.0128*
Platelet, $\times 10^9$/L	205.0 (169.0–251.0); 778.0; *n* = 921	179.0 (142.5–220.5); 637.0; *n* = 51	205.55 (170.0–253.0); 778.0; *n* = 870	.0029**
Red blood count, x10^12/L	4.63 (4.31–5.05); 7.18; *n* = 922	4.42 (3.82–4.74); 6.79; *n* = 51	4.64 (4.34–5.06); 7.18; *n* = 871	.0004***
Hematocrit, L/L	0.4 (0.38–0.43); 0.498; *n* = 229	0.4 (0.35–0.42); 0.424; *n* = 8	0.4 (0.38–0.43); 0.498; *n* = 221	.3255
K/potassium, mmol/L	3.81 (3.6–4.11); 6.8; *n* = 831	3.94 (3.66–4.22); 6.8; *n* = 46	3.8 (3.6–4.11); 5.59; *n* = 785	.1614
Urate, mmol/L	0.29 (0.23–0.43); 0.58; *n* = 30	0.26 (0.14–0.31); 0.32; *n* = 4	0.31 (0.24–0.44); 0.58; *n* = 26	.2589
Albumin, g/L	41.0 (37.0–44.0); 118.2; *n* = 836	34.0 (27.85–38.0); 44.9; *n* = 46	41.0 (37.5–44.25); 118.2; *n* = 790	<.0001***
Na/sodium, mmol/L	138.62 (136.41–140.0); 146.0; *n* = 832	137.0 (133.0–139.0); 144.1; *n* = 46	138.91 (136.7-140.0); 146.0; *n* = 786	.0016**
Urea, mmol/L	4.0 (3.2–4.92); 59.3; *n* = 832	6.2 (4.65–7.82); 59.3; *n* = 46	3.99 (3.2–4.8); 15.77; *n* = 786	<.0001***
Protein, g/L	74.3 (70.7-78.0); 92.7; *n* = 709	70.7 (66.5–75.0); 87.0; *n* = 36	74.6 (71.0–78.02); 92.7; *n* = 673	.001**
Creatinine, umol/L	72.0 (60.0–87.0); 1248.0; *n* = 834	82.5 (70.55–113.5); 1248.0; *n* = 46	71.8 (59.4–85.05); 321.0; *n* = 788	.0002***
Alkaline phosphatase, U/L	65.0 (54.0–77.0); 350.0; *n* = 833	66.0 (55.0–99.0); 166.0; *n* = 45	65.0 (54.0–77.0); 350.0; *n* = 788	.1875
Aspartate transaminase, U/L	29.0 (22.0–46.0); 202.0; *n* = 317	42.0 (24.65–63.5); 201.0; *n* = 23	29.0 (22.0–42.0); 202.0; *n* = 294	.028*
Alanine transaminase, U/L	24.0 (16.0–38.0); 173.0; *n* = 697	28.0 (16.8–38.0); 150.0; *n* = 39	24.0 (16.0–37.2); 173.0; *n* = 658	.7424
Bilirubin, umol/L	7.4 (5.2–10.4); 60.4; *n* = 833	10.4 (6.9–14.0); 30.3; *n* = 45	7.2 (5.2–10.15); 60.4; *n* = 788	.0005***
Triglyceride, mmol/L	1.53 (1.04–2.11); 9.35; *n* = 128	1.85 (1.27-2.14); 3.77; *n* = 18	1.5 (1.04–2.09); 9.35; *n* = 110	.2624
Low-density lipoprotein, mmol/L	2.39 (1.9–2.95); 6.8719; *n* = 117	1.62 (1.36–2.11); 3.3778; *n* = 17	2.54 (2.04–3.07); 6.8719; *n* = 100	.0001***
High-density lipoprotein, mmol/L	1.1 (0.94–1.29); 1.87; *n* = 120	1.0 (0.59–1.13); 1.86; *n* = 17	1.12 (0.97-1.29); 1.87; *n* = 103	.0685
Cholesterol, mmol/L	4.26 (3.68–5.09); 7.319; *n* = 121	3.41 (2.68–4.7); 5.1; *n* = 17	4.3 (3.79–5.16); 7.319; *n* = 104	.0029**
Clearance, ml/min	188.6749 (14.72%)	188.6749 (258.45%)	0.0 (0.00%)	<.0001***

TABLE 1 (Continued)

Characteristics	All (*N* = 1281) median (IQR); Max; *N* or count (%)	Composite outcome (*N* = 73) median (IQR); Max; *N* or count (%)	No composite outcome (*N* = 1208) median (IQR); Max; *N* or count (%)	*p* value
HbA1c, g/dl	13.7 (12.7-14.7); 94.1; *n* = 927	13.6 (11.4–14.9); 60.8; *n* = 53	13.7 (12.8–14.7); 94.1; *n* = 874	0.1949
Glucose, mmol/L	5.8 (5.14–7.0); 25.17; *n* = 594	7.1 (5.98–9.24); 17.69; *n* = 42	5.73 (5.1–6.85); 25.17; *n* = 552	<.0001***
D-dimer, ng/ml	363.6 (190.0–680.62); 4340.0; *n* = 214	848.5 (474.11–1052.15); 2596.65; *n* = 18	349.84 (190.0–597.98); 4340.0; *n* = 196	0.0062**
High sensitive troponin-I, ng/L	3.45 (2.16–6.78); 373.6; *n* = 505	10.73 (5.93–29.9); 108.87; *n* = 29	3.3 (2.08–6.12); 373.6; *n* = 476	<.0001***
Lactate dehydrogenase, U/L	201.0 (166.3–251.75); 813.0; *n* = 620	250.5 (211.5–345.0); 716.0; *n* = 40	198.0 (164.5–247.5); 813.0; *n* = 580	<.0001***
APTT, s	30.6 (27.7–34.6); 120.0; *n* = 526	32.9 (29.25–36.9); 120.0; *n* = 46	30.4 (27.5–34.25); 54.5; *n* = 480	.003**
Prothrombin time/INR, s	11.9 (11.4–12.5); 43.4; *n* = 373	12.5 (11.7–13.3); 27.0; *n* = 36	11.9 (11.4–12.5); 43.4; *n* = 337	.0067**
C-reactive protein, mg/dl	0.52 (0.23–1.9); 33.99; *n* = 780	6.57 (1.83–9.29); 32.529; *n* = 50	0.46 (0.22–1.5); 33.99; *n* = 730	<.0001***
Calcium, mmol/L	1.16 (1.14–1.17); 1.19; *n* = 10	1.16 (1.14–1.17); 1.19; *n* = 9	1.18 (1.18–1.18); 1.18; *n* = 1	.4822
HCO_3/bicarbonate, mg/dL	24.1 (20.7–26.2); 32.5; *n* = 101	21.2 (18.5–24.3); 29.3; *n* = 31	24.75 (22.65–26.8); 32.5; *n* = 70	<.0001***
Base excess, mmol/L	−0.4 (−2.9 to 1.6); 6.8; *n* = 129	−2.4 (−4.7 to 0.6); 3.9; *n* = 43	0.7 (−1.7 to 2.1); 6.8; *n* = 86	<.0001***
Blood pCO_2, kPa	4.8 (4.15–5.76); 10.15; *n* = 130	4.6 (4.01–5.14); 7.94; *n* = 43	5.05 (4.28–5.86); 10.15; *n* = 87	.059
Blood pH	7.43 (7.39–7.46); 7.6; *n* = 129	7.42 (7.34–7.46); 7.55; *n* = 43	7.44 (7.39–7.47); 7.6; *n* = 86	.1238

Note: The comparisons were made between patients meeting primary outcome versus those that did not.

Abbreviations: ACEI, angiotensinogen converting enzyme inhibitor; AMI, acute myocardial infarction; APTT, activated partial thromboplastin time; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; PVD, Peripheral vascular disease; TIA, transient ischemic attack.

*SMD ≥ 0.2.

**$p \leq .01$.

***$p \leq .001$.

diseases (ICD) coding. Although this capture is complete for outcomes such as mortality, those for certain comorbidities are under-coded, an example of which is obesity. This is because medical conditions that require treatment in outpatient or inpatient settings are more likely to be coded. Therefore, we were unable to identify a significant relationship between obesity and severe outcomes. This issue has been addressed elsewhere. A noteworthy point is that the renin-angiotensin-aldosterone system may interact with the Kinin–Kallikrein system and coagulation cascade.[11] Therefore, at the very least, interactions aside, prevention of thromboembolic phenomena may improve outcomes in COVID-19 patients. More broadly, the maintenance of a healthy lifestyle can provide beneficial immune-modulatory effects and should be promoted at the public health level.[12]

Taken together, our population-based study found significant interaction effects between ACEI and steroids, which acted to reduce the risk of the primary outcome, but no significant interactions between ARB with an antiviral agent or steroids in the propensity-score matched cohorts. Therefore, ACEI use was protective of the severe disease outcome in COVID-19 patients receiving steroid therapy.

AUTHOR CONTRIBUTIONS

Jiandong Zhou, Gary Tse: *data analysis, data interpretation, statistical analysis, manuscript drafting, critical revision of the manuscript*. Sharen Lee, Keith Sai Kit Leung, Abraham Ka Chung Wai: *data acquisition and interpretation, critical revision of the manuscript*. Tong Liu, Zhidong Cao, Daniel Dajun Zeng, Ian Chi Kei Wong, Bernard Man Yung Cheung: *project planning, data acquisition, data interpretation, critical revision of*

TABLE 2 Significant drug interaction effects for severe COVID-19 treatments before propensity score matching

	Steroid	Remdesivir	Lopinavir/ ritonavir	Interferon β-1B	Lopinavir/ritonavir and ribavarin	Ribavirin and interferon β-1B	Lopinavir/ritonavir and interferon β-1B	Lopinavir/ritonavir and ribavarin and interferon β-1B
ACEI	8.64 [4.55, 16.42]***	2.78 [0.33, 23.42]	2.38 [0.29, 19.63]	4.23 [0.88, 20.27]	2.78 [0.33, 23.42]	5.06 [1.98, 12.96]**	4.67 [2.07, 10.57]***	-
ARB	3.72 [1.74, 7.95]**	8.48 [1.53, 47.08]*	2.38 [0.29, 19.63]	-	1.38 [0.18, 10.79]	1.07 [0.25, 4.56]	3.18 [1.44, 7.03]**	2.08 [0.26, 16.88]
Captopril	130.65 [0, Inf]*	-	-	-	-	1207.5 [0, Inf]**	-	-
Enalapril	12.9 [2.83, 58.76]**	-	1307.65 [0, Inf]*	-	-	4.18 [0.46, 37.89]	5.58 [0.57, 54.3]	-
Lisinopril	7.51 [3.46, 16.32]**	4.18 [0.46, 37.89]	-	4.83 [0.99, 23.69]	3.34 [0.39, 28.98]	3.66 [1.03, 13.02]**	4.37 [1.59, 11.99]**	-
Ramipril	-	-	-	-	-	-	-	-
Perindopril	3.37 [0.73, 15.69]	-	-	-	-	8.37 [0.75, 93.45]	3.07 [0.67, 14.09]	-
Candesartan	-	-	-	-	-	-	-	-
Entresto	1307.65 [0, Inf]*	-	-	-	-	1207.6 [0, Inf]*	-	-
Irbesartan	-	-	-	-	-	-	-	-
Losartan	2.87 [1.24, 6.63]*	8.48 [1.53, 47.08]	2.78 [0.33, 23.42]	-	1.51 [0.19, 11.87]	0.56 [0.08, 4.2]	2.81 [1.22, 6.47]**	2.38 [0.29, 19.63]
Telmisartan	-	-	-	-	-	-	-	-

Abbreviations: ACEI, angiotensinogen converting enzyme inhibitor; AMI, acute myocardial infarction; APTT, activated partial thromboplastin time; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; PVD, Peripheral vascular disease; TIA, transient ischemic attack.

*$p \leq .05$.

**$p \leq .01$.

***$p \leq .001$.

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CONFLICTS OF INTERESTS

The authors declare that there are no conflict of interests.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.