Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2007621

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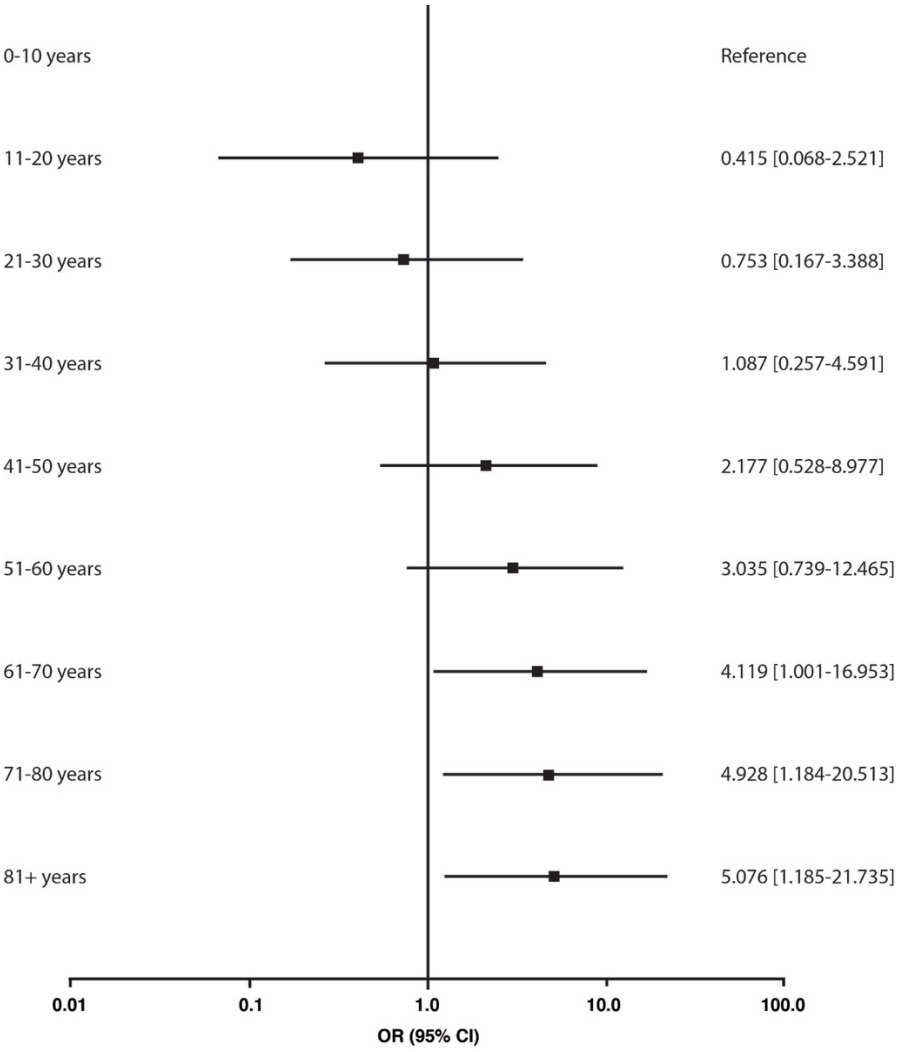
Figure S1. Association Between Age and Mortality



Age is depicted in deciles; OR (95% CI) refers to odds ratios with the corresponding 95% confidence intervals. The 95% confidence intervals have not been adjusted for multiple testing and should not be used to infer definitive effects.

SUPPLEMENTARY TABLES

Table S1. Study sample by continent, country, and number of hospitals

Continent	Country	Number of Hospitals	Number of Patients
North America	United States	121	1,499
North America	Canada	4	37
Europe	Spain	7	1,793
Europe	Italy	8	2,602
Europe	Germany	5	201
Europe	France	5	107
Europe	United Kingdom	7	706
Europe	Turkey	3	346
Asia	China	7	1,507
Asia	South Korea	1	88
Asia	Japan	1	24

Table S2. Summary Data by Continent

	North America	Europe	Asia
N	1,536	5,755	1,619
Age	49.6 +/- 16.7	49.0 +/- 16.7	49.2 +/- 16.3
Female	609 (39.6)	2,322 (40.3)	640 (39.5)
CAD	209 (13.6)	629 (10.9)	172 (10.6)
CHF	45 (2.9)	116 (2.0)	28 (1.7)
Arrhythmia	57 (3.7)	188 (3.3)	59 (3.6)
DM	218 (14.2)	826 (14.4)	228 (14.1)
HTN	419 (27.3)	1,495 (26.0)	432 (26.7)
Hyperlipidemia	501 (32.6)	1,733 (30.1)	481 (29.7)
COPD	51 (3.3)	140 (2.4)	34 (2.1)
Current Smoker	86 (5.6)	309 (5.4)	96 (5.9)
Former Smoker	257 (16.7)	954 (16.6)	282 (17.4)
Immunocompromised Status	48 (3.1)	162 (2.8)	39 (2.4)
ACEI	143 (9.3)	494 (8.6)	133 (8.2)
ARB	97 (6.3)	356 (6.2)	103 (6.4)
Beta Blocker	97 (6.3)	329 (5.7)	99 (6.1)
Antiplatelet	48 (3.1)	190 (3.3)	57 (3.5)
Statin	163 (10.6)	539 (9.4)	158 (9.8)
Insulin	62 (4.0)	186 (3.2)	54 (3.3)
Other hypoglycemics	146 (9.5)	551 (9.6)	154 (9.5)
Mortality	88 (5.7)	351 (6.1)	76 (4.7)

Table S3. Summary Data for High Income Countries (HIC) and Low-Middle Income (LMIC) Countries

Variable	HIC	LMIC
Age (Years)	49.2 +/- 16.7	48.9 +/- 16.3
Female	40.3%	39.1%
CAD	11.5%	10.4%
CHF	2.2%	1.7%
Arrhythmia	3.4%	3.5%
DM	14.5%	13.7%
HTN	26.2%	27.0%
Hyperlipidemia	30.7%	29.3%
COPD	2.6%	2.2%
Current	5.3%	6.1%
Former	16.7%	16.9%
Immunocompromised	2.8%	2.8%
ACEI	8.6%	9.0%
ARB	6.2%	6.3%
Beta Blocker	5.8%	6.4%
Antiplatelet	3.2%	3.7%
Statin	9.7%	9.6%
Insulin	3.4%	3.2%
Other hypoglycemics	9.6%	9.3%
Mortality	6.3%	4.8%

HIC and LMIC were defined based on WHO classifications (https://www.who.int/healthinfo/global_burden_disease/definition_regions/en/)

Table S4. Multivariable Logistic Regression Analysis by Continent

a) Multivariable logistic regression analysis for in-hospital mortality: North America

Variable	Odds Ratio	95% CI (Low)	95% CI (High)
Age	1.026	0.966	1.089
Age^2	1.000	0.999	1.000
Female	0.761	0.507	1.141
CAD	2.477	1.465	4.188
CHF	3.117	1.432	6.784
Arrhythmia	2.887	1.419	5.870
COPD	2.203	1.015	4.780
Current smoker	1.657	0.833	3.299
ACE inhibitor	0.231	0.072	0.743
Statin	0.261	0.110	0.618

b) Multivariable logistic regression analysis for in-hospital mortality: Europe

Variable	Odds Ratio	95% CI (Low)	95% CI (High)
Age	1.094	1.047	1.142
Age^2	0.999	0.999	1.000
Female	0.775	0.612	0.982
CAD	2.573	1.835	3.608
CHF	1.897	1.044	3.446
Arrhythmia	1.307	0.743	2.299
COPD	3.373	2.048	5.555
Current smoker	1.728	1.142	2.614
ACE inhibitor	0.335	0.182	0.618
Statin	0.372	0.230	0.601

c) Multivariable logistic regression analysis for in-hospital mortality: Asia

Variable	Odds Ratio	95% CI (Low)	95% CI (High)
Age	1.124	1.019	1.239
Age^2	0.999	0.998	1.000
Female	0.765	0.475	1.232
CAD	2.722	1.387	5.341
CHF	1.085	0.242	4.859
Arrhythmia	3.121	1.322	7.371
COPD	7.241	2.512	20.869
Current smoker	3.961	2.078	7.55
ACE inhibitor	0.099	0.013	0.736
Statin	0.169	0.039	0.739

The 95% confidence intervals have not been adjusted for multiple testing and should not be used to infer definitive effects.

Table S5. Multivariable Logistic Regression Analysis for In-Hospital Mortality: Low-Middle Income Countries

Variable	Odds Ratio	95% CI (Low)	95% CI (High)
Age	1.188	1.051	1.343
Age^2	0.998	0.997	1.000
Female	1.021	0.615	1.695
CAD	4.691	2.528	8.705
CHF	2.665	0.891	7.966
Arrhythmia	3.805	1.653	8.760
COPD	3.381	1.226	9.321
Current smoker	2.969	1.465	6.018
ACE inhibitor	0.135	0.018	0.992
Statin	0.145	0.040	0.517

The 95% confidence intervals have not been adjusted for multiple testing and should not be used to infer definitive effects.

Table S6. Age- and Sex-Adjusted Multivariable Logistic Regression Analysis

a) Age-adjusted multivariable regression model for in-hospital mortality

Variable	Odds Ratio	95% CI (Low)	95% CI (High)
Age	1.069	1.034	1.105
Age^2	1.000	0.999	1.000
Female	0.793	0.656	0.959
CAD	2.474	1.899	3.223
CHF	2.235	1.455	3.433
Arrhythmia	1.968	1.343	2.884
COPD	3.193	2.138	4.768
Current smoker	1.723	1.240	2.396
ACE inhibitor	0.267	0.157	0.456
Statin	0.299	0.197	0.454

b) Multivariable regression model for in-hospital mortality: females

Variable	Odds Ratio	95% CI (Low)	95% CI (High)
Age	1.044	0.989	1.102
Age^2	1.000	0.999	1.000
Female	N/A	N/A	N/A
CAD	3.849	2.505	5.913
CHF	3.103	1.626	5.920
Arrhythmia	2.520	1.396	4.550
COPD	4.967	2.618	9.425
Current smoker	1.934	1.103	3.392
ACE inhibitor	0.306	0.125	0.746
Statin	0.320	0.167	0.616

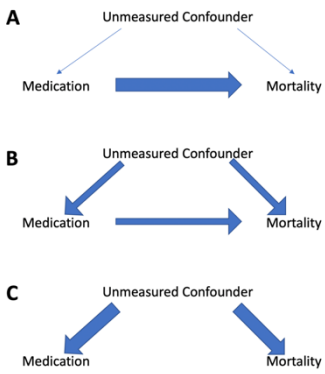
c) Multivariable regression model for in-hospital mortality: males

Variable	Odds Ratio	95% CI (Low)	95% CI (High)
Age	1.090	1.044	1.138
Age^2	0.999	0.999	1.000
Male	N/A	N/A	N/A
CAD	1.897	1.347	2.672
CHF	1.657	0.903	3.041
Arrhythmia	1.488	0.882	2.512
COPD	2.630	1.572	4.403
Current smoker	1.653	1.100	2.484
ACE inhibitor	0.247	0.126	0.483
Statin	0.280	0.161	0.486

The 95% confidence intervals have not been adjusted for multiple testing and should not be used to infer definitive effects.

Table S7. Tipping Point Analysis for Unmeasured Confounders

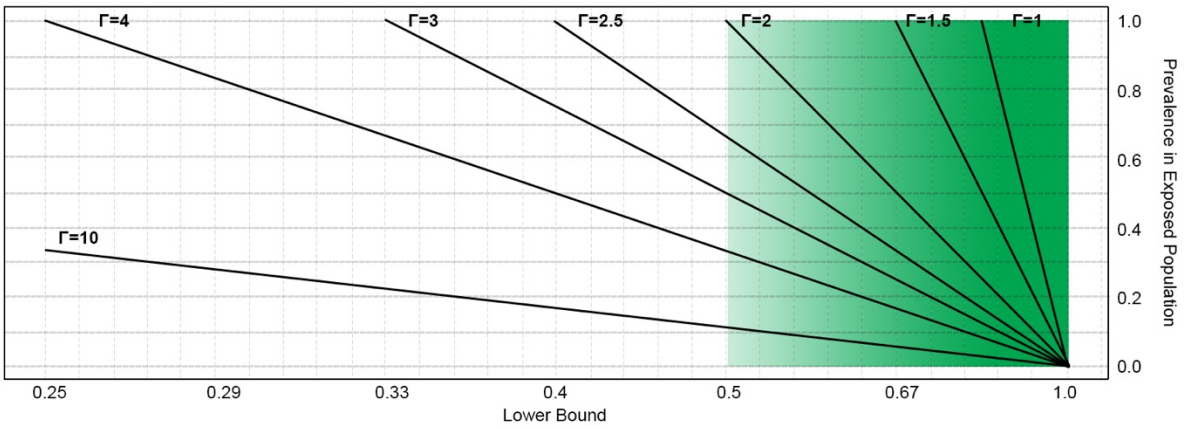
A tipping point analysis was completed to assess the effects of an unmeasured confounder on the findings of significance with ACE inhibitors or statins. An unmeasured confounder of size G was created using the lower bound of the 95% confidence interval for ACE inhibitors (0.54 – the value closest to 1) and statins (0.52). For all practical purposes, the lower bound for ACE inhibitors and statins are similar at 0.54 and 0.52, respectively, and can be treated the same for the purposes of this tipping point analysis. The threshold prevalence of the unmeasured confounder was determined for each medication as follows:



$$P(LB, \Gamma) = \frac{LB - 1}{\Gamma - 1}$$

(Where 1 < LB ≤ G)

The figure below shows the sensitivity threshold for unmeasured confounders of various effect sizes as a function of the lower bound on the 95% confidence interval. Area of safety is shaded in green.



The primary analysis demonstrated that ACE inhibitors were associated with survival in COVID-19 patients; OR (95% CI): 0.33 (0.20, 0.54). The primary analysis also demonstrated that statins were associated with survival in COVID-19 patients; OR (95% CI): 0.35 (0.24, 0.52).

A hypothetical unobserved binary confounder with a prevalence of 10% in the exposed population would need to have an odds ratio of 10 to tip this analysis to non-significance at the 5% level for both ACE inhibitors and statins. Stated differently, 73 patients with ACE inhibitors would have had to survive for reasons other than the use of this medication to tip the odds ratio to non-significance – and that this would have to be due to an extremely strong effector (OR 10).

An unobserved confounder with a prevalence of 50% in the exposed population would need to have an odds ratio of 3 to tip this analysis. The presence of confounders of this effect size or prevalence are unlikely in the present study. For a comparison with the observed confounders in the study, COPD (which has an OR of 3) would need to have a prevalence of 50% in the population to lead to confounding in the analysis had it not been adjusted for in the multiple regression analysis.

Table S8. Subgroup Analyses (Hypertension and Hyperlipidemia)

We sought to determine whether the effect of ACE inhibitors and statins noted in the overall study was also seen when confined to a limited subset of patients who might have an indication for these agents. In order to accomplish this for ACE inhibitors we examined the subset of patients in the cohort with hypertension divided into those treated with ACE inhibitors versus not. Such an analysis helps to determine the effects in patients that presumably are "more similar." Furthermore, such an analysis may help to deal with an unresolvable problem of missing data (due to lack of coding).

We performed a similar analysis for statins and used the subset with a diagnosis of hyperlipidemia. Thus, we developed the following subgroup analyses:

A. We evaluated the association between ACE inhibitors and mortality in patients with hypertension
B. We evaluated the association between statins and mortality in patients with hyperlipidemia

Logistic regression analyses were performed with adjustment for age and sex. The following tables describe the findings.

A. Subgroup analysis evaluating the association between ACE inhibitors and mortality in patients with hypertension.

Variable	Odds Ratio	95% CI (Low)	95% CI (High)
Age (years)	1.023	1.011	1.034
Female sex	0.690	0.472	1.010
ACE inhibitor	0.266	0.156	0.453

B. Subgroup analysis evaluating the association between statins and mortality in patients with hyperlipidemia.

Variable	Odds Ratio	95% CI (Low)	95% CI (High)
Age (years)	1.022	1.011	1.034
Female sex	0.899	0.657	1.230
Statins	0.508	0.349	0.740

This subgroup analysis is consistent with the findings in the overall study.