BRIEF REPORT

Managing endothelial dysfunction in COVID-19 with statins, beta blockers, nicorandil, and oral supplements: A pilot, double-blind, placebo-controlled, randomized clinical trial

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Abstract

Coronavirus disease 2019 (COVID-19) is associated with endothelial dysfunction. Pharmacologically targeting the different mechanisms of endothelial dysfunction may improve clinical outcomes and lead to reduced morbidity and mortality. In this pilot, double-blind, placebo-controlled, randomized clinical trial, we assigned patients who were admitted to the hospital with mild, moderate, or severe COVID-19 infection to receive, on top of optimal medical therapy, either an endothelial protocol consisting of (Nicorandil, L-arginine, folate, Nebivolol, and atorvastatin) or placebo for up to 14 days. The primary outcome was time to recovery, measured by an eight category ordinal scale and defined by the time to being discharged from the hospital or hospitalized for infection-control or other nonmedical reasons. Secondary outcomes included the composite outcome of intensive care unit (ICU) admission or the need for mechanical ventilation, all-cause mortality, and the occurrence of side effects. Of 42 randomized patients, 37 were included in the primary analysis. The mean age of the patients was 57 years; the mean body mass index of study participants was 29.14. History of hypertension was present in 27% of the patients, obesity in 45%, and diabetes mellitus in 21.6%. The median (interquartile range) time to recovery was not significantly different between the endothelial protocol group (6 [4–12] days) and the placebo group (6 [5–8] days; p value = 0.854). Furthermore, there were no statistically significant differences in the need for mechanical ventilation or ICU admission, all-cause mortality, or the occurrence of side effects between the endothelial protocol group and the placebo group. Among patients hospitalized with mild, moderate,

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or severe COVID-19 infection, targeting endothelial dysfunction by administering Nicorandil, L-arginine, Folate, Nebivolol, and Atorvastatin on top of optimal medical therapy did not decrease time to recovery. Based on this study's findings, targeting endothelial dysfunction did not result in a clinically significant improvement in outcome and, as such, larger trials targeting this pathway are not recommended.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
Coronavirus disease 2019 (COVID-19) infection initially emerged as a respiratory infection. However, endothelial dysfunction plays a major role in the COVID-19 induced morbidity and mortality. To the best of our knowledge, this is the first pilot, double-blind, placebo-controlled, randomized clinical trial to assess the efficacy and safety of managing endothelial dysfunction in patients with COVID-19.

WHAT QUESTION DID THIS STUDY ADDRESS?
This study aims to assess the efficacy and safety of pharmacologically targeting the different mechanisms of endothelial dysfunction in COVID-19 infection.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
Targeting endothelial dysfunction in COVID-19 infection by administering atorvastatin, L-arginine, folic acid, Nebivolol, and Nicorandil did not significantly improve clinical outcomes. However, it was associated with a good safety profile.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
Due to the lack of clinically meaningful effect of treating endothelial dysfunction demonstrated in this study, we do not recommend targeting this pathway in the treatment of COVID-19 infection.

INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to be a global challenge worldwide. Although considered at its emergence as a respiratory infection, recent studies demonstrated tropism toward endothelial cells.[1] Endothelial dysfunction may be a common pathophysiological process underlying the resulting morbidity and mortality.[2]

Treating endothelial dysfunction is a promising approach to improve outcomes in patients with COVID-19.[3] In the resting state, the endothelium regulates blood flow and vascular tone in addition to providing vasodilatory, anticoagulant, anti-inflammatory, and antioxidant properties.[4] So far, several medications that act directly on the endothelium demonstrated an improved clinical outcome in patients with COVID-19. Dexamethasone and anticoagulants, when used in the treatment of patients with COVID-19, were found to improve endothelial injury and dysfunction.[5,6] Clinically, this was translated into a statistically significant decrease in mortality.[7,8] However, the pathophysiology of endothelial dysfunction is

multifactorial and, as such, cannot be optimally targeted and fully treated with a single agent. This is evidenced by the fact that even with the use of those medications, mortality and morbidity remained high.[4] Thus, targeting the different mechanisms of endothelial dysfunction concurrently might result in an improved clinical outcome and halt the progression of the disease.

Several medications with endothelial healing properties and excellent safety profiles used for the treatment of other conditions might play a role in the treatment of COVID-19. Nicorandil is a vasodilator drug with antioxidant and anti-inflammatory properties.[9] Nebivolol, a cardioselective beta-blocker has also shown vasodilating properties, alongside antioxidative, anti-atherosclerotic activities, and antiviral properties.[3] L-arginine and folic acid, which enhances the synthesis and stabilization of BH4, have also an established role in NO-mediated vasodilation.[10] Atorvastatin, which is cardioprotective, may also improve endothelial function by increasing the production of NO, and subsequent vasodilatory effect, along with its established anti-inflammatory and antioxidant properties.[3]

Hence, we designed this double-blind placebo-controlled randomized pilot clinical trial to investigate the

efficacy and safety of simultaneously treating the multiple pathways of endothelial dysfunction in hospitalized patients with COVID-19 with a five-drug protocol that consists of Nicorandil, L-arginine, folate, Nebivolol, and atorvastatin in an attempt to improve clinical outcome and demonstrate the safety of such a treatment.

METHODS

Design

This study is a single-center, pilot, double-blind, placebo-controlled, randomized clinical trial (ClinicalTrials.gov Identifier: NCT04631536) at the Lebanese American University Medical Center – Rizk Hospital (LAUMC-RH). The trial protocol was approved by the institutional review board (IRB) at the Lebanese American University, approval number LAUMCRH.GG2.4/Jan/2021 and was supervised by an independent board responsible for monitoring data safety. Consent was taken from the patient or the patient's legal guardian in conformity with the IRB rules and regulations.

Participants

Enrollment for MEDIC-LAUMC began on January 21, 2021, and ended on August 21, 2021, at the LAUMC-RH. Recruited patients were randomly assigned to receive either the endothelial treatment protocol or a placebo.

Inclusion criteria

Patients who were at least 18 years or more, hospitalized with polymerase chain reaction-confirmed COVID-19 with mild, moderate, or severe disease as defined by the US Food and Drug Administration, 2020 were eligible for inclusion (Table S1).[11] Moreover, recruitment had to be done within 48 h of admission to the hospital.

Exclusion criteria

Exclusion criteria for recruitment included patients with any of the following: patients with critical COVID-19 (Table S1). In addition, other exclusion criteria included inability to tolerate oral medications, patients already taking beta-blockers, Nicorandil, PDE5 inhibitors, or Riociguat, patients with shock defined by systolic blood pressure less than 90 mmHg for more than 30 min not responding to i.v. fluids with evidence of end-organ damage,

severe bradycardia (<50 beats per minute [bpm]) or heart block greater than first-degree (except in patients with a functioning artificial pacemaker), decompensated heart failure and sick sinus syndrome (unless a permanent pacemaker is in place), severe hepatic impairment (Child-Pugh class C) or active liver disease with unexplained persistent elevations of serum transaminases, pregnant or breastfeeding patients, hypersensitivity to any of the medications in the trial, patients who took the protocol for less than 48 h, myocarditis, acute pulmonary edema, and hypovolemia, and patients enrolled in a different randomized study and/or COVID-19 interventional study.

Randomization procedures and study interventions

The hospitalized patients enrolled in the trial received the medications or placebo daily up to 14 days or until hospital discharge or death, whichever event occurred first. At the hospital, the study participants were assessed daily from day 1 until day 28. Patients discharged before 28 days were assessed by telephone once weekly. All adverse events or hypersensitivity reactions were recorded.

Assignment of patients was done in a 1:1 ratio between the endothelial protocol arm or the placebo arm. A staff member who had no role in the study managed randomization and created the randomization list via a computer-generated code with block sizes of eight and sent directly to the central hospital pharmacy where the kits were prepared by pharmacy personnel not included in the trial.

In the endothelial protocol group, patients received a five-drug regimen. Atorvastatin 40 mg per os once daily was given to patients who were statin naïve. However, patients already taking a statin as part of their home treatment had the same statin resumed because it was unethical to remove such therapy with the possibility of having a placebo given instead after preliminary reports showed a clinical benefit might be associated with the use of statins in patients with COVID-19.[12] In addition, folic acid and L-arginine were given per os as 5 mg once daily and 1 g three times daily, respectively. Nicorandil was given at a dose of 10 mg twice daily. Nebivolol was given at doses of 2.5 mg or 5 mg p.o. once daily. The dose was chosen based on the patients' heart rate upon trial enrollment where patients with heart rates greater than 70 bpm received the 5 mg dose. In the placebo group, patients received a matching five-drug placebo regimen that contained an identical number of pills administered similarly at the same schedule as the endothelial treatment arm. In the case where the patient continued the statin taken at home, one less placebo pill was administered. The medications were prepared and labeled

by the central pharmacy staff who did not participate in the study. Patients and investigators were blinded to randomization throughout the study period up until the final analysis.

Outcomes

The primary outcome was the time to recovery, defined as the first day, during the 28 days after enrollment, on which a patient met the criteria for category 1, 2, or 3 on the eight-category ordinal scale. The categories are as follows: 1, not hospitalized and no limitations of activities; 2, not hospitalized, with limitation of activities, home oxygen requirement, or both; 3, hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control or other nonmedical reasons); 4, hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (related to COVID-19 or other medical conditions); 5, hospitalized, requiring any supplemental oxygen; 6, hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices; 7, hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation; and 8, death.

The secondary outcomes were: the need for invasive mechanical ventilation or intensive care unit (ICU) admission, all-cause mortality, and occurrence of side effects.

Statistical analysis

Calculations were done using the G*Power software. The time to clinical improvement, which is the primary outcome, was assumed to be ~10 days, alpha was fixed at 5% and beta at 20%; subsequently, the sample size was calculated. At least 17 patients in each group and minimum total sample size for both arms = 34 were expected to make a difference of 4 days in time to clinical improvement, with a power of 80%. Therefore, the study was stopped early when those numbers were achieved.[13]

Data was entered on an Excel spreadsheet (Microsoft, Redmond, WA) and analyzed using SPSS version 25.0. A descriptive analysis presented the data, using means and SD for normal continuous variables, median and interquartile range for non-normal variables, whereas frequency and percentages were used for multinomial and dichotomous variables. For the bivariate analysis, we used the chi-square test to compare percentages, and the COX regression to compare time to requiring mechanical ventilation or ICU admission. In all cases, a p value < 0.05 was considered significant.

RESULTS

Patients

One hundred seventy-seven patients were assessed for eligibility, and 42 were eligible and randomized to either the endothelial protocol or the placebo group. The rest were not eligible for inclusion due to the following reasons: 50 patients did not fulfill the inclusion or exclusion criteria, 30 patients refused to participate, and 15 patients were missed by recruiters because they were in the hospital for more than 48 h when assessed for eligibility. Moreover, 24 already had critical disease, one was pregnant, and 20 had their treating physicians refusing participation in the trial. Of the 42 randomized patients, four withdrew their consent and one died after less than 48 h of randomization and thus were excluded.

A total of 37 were included in the final analysis and underwent randomization (17 to the endothelial protocol group and 20 to the placebo group). They were included in the primary intention-to-treat analysis, received the corresponding study protocol, and were followed up for a total of 28 days.

The baseline characteristics of the patients are presented in Table 1. No significant differences in vital signs, laboratory results, or baseline medications were observed between groups at baseline ($p > 0.05$ for all). The mean age of the study participants was 57 years. There was a higher percentage of male patients in this study (81.1%). The mean body mass index of study participants was 29.14. History of hypertension was present in 27% of the patients, obesity in 45%, and diabetes mellitus in 21.6%. The average number of days since symptom onset was 7.6 days.

Primary outcome

The median (interquartile range) time to recovery was not significantly different between the endothelial protocol group (6 [4–12] days) and the placebo group (6 [5–8] days; p value = 0.854; Table 2).

Secondary outcomes

There were no statistically significant differences in the need for mechanical ventilation or ICU admission between the endothelial protocol group and the placebo group (17.6% vs. 10%; odds ratio [OR] = 1.93, 95% confidence interval [CI], 0.28–13.16, p = 0.644). Furthermore, during the 28-day follow-up, no mortality cases were recorded in either arm. However, after the 28 days follow-up duration, one patient from each arm eventually died (Table 2).

TABLE 1 Patient characteristics

Characteristics	All N = 37	Placebo N = 20	Drug N = 17
Mean age – year	56.62	56.1	57.2
Male sex, n (%)	30 (81.8)	17 (85)	13 (76.5)
Female sex, n (%)	7 (18.9)	3 (15)	4 (23.5)
BMI	29.14	29.12	29.9
Days since symptom onset	7.6	6.78	8.56
SpO2 on arrival %	91.6	91.2	92.1
Co-existing conditions, n/total n (%)			
Hypertension	10 (27)	7 (35)	3 (17.6)
Diabetes mellitus	8 (21.6)	6 (30)	2 (11.8)
Coronary artery disease	2 (5.4)	2 (10)	0 (0)
Congestive heart failure	0 (0)	0 (0)	0 (0)
Asthma	4 (10.8)	2 (10)	2 (11.8)
Chronic obstructive pulmonary disease	0 (0)	0 (0)	0 (0)
Cancer	1 (2.7)	0 (0)	1 (5.9)
Chronic kidney disease	1 (2.7)	1 (5)	0 (0)
Thrombo-embolic disease	0 (0)	0 (0)	0 (0)
Current tobacco use	10 (27)	5 (25)	5 (29.4)
Previous tobacco use	2 (5.4)	0 (0)	2 (11.8)
Alcohol use	4 (10.8)	2 (10)	2 (11.8)
Previous medications used, n (%)			
ACEI or ARB	6 (16.2)	4 (20)	2 (11.8)
Anticoagulation	14 (37.8)	8 (40)	6 (35.3)
Antiplatelets	14 (37.8)	10 (50)	4 (23.5)
Corticosteroids	18 (48.6)	12 (60)	6 (35.3)
Immunosuppressants	1 (2.7)	0 (0)	1 (5.9)
Colchicine	3 (8.1)	2 (10)	1 (5.9)
Ivermectin	8 (21.6)	2 (10)	6 (35.3)
Inpatient treatments during trial, n (%)			
Supplemental oxygen	31 (83.8)	17 (85)	14 (82.4)
Glucocorticoids	34 (91.9)	19 (95)	15 (88.2)
Remdesivir	22 (59.5)	12 (60)	10 (58.8)
Favipiravir	5 (13.5)	3 (15)	2 (11.8)
Tocilizumab	3 (8.1)	3 (15)	0 (0)
Tofacitinib	15 (40.5)	7 (35)	8 (47.1)
Colchicine	5 (13.5)	2 (10)	3 (17.6)
Anticoagulation	37 (100)	20 (100)	17 (100)
Antiplatelets	15 (40.5)	12 (60)	3 (17.6)

Abbreviation: BMI, body mass index.

Safety outcomes

All patients were followed up for a period of 28 days. The use of the endothelial protocol was not associated with an increased risk of the overall incidence of side effects when compared to placebo (OR = 1.213, 95% CI 0.211–6.985, $p = 0.828$). There was a total of six adverse events in the endothelial protocol and three in the placebo group experienced by six different patients. There were no severe adverse events (Table 2).

TABLE 2 Primary and secondary outcomes

	Endothelial protocol	Placebo	p value
Primary outcome			
Time to recovery, days-median (IQR)	6 [4–12]	6 [5–8]	0.854
Secondary outcomes			
Need for mechanical ventilation or ICU admission, n (%)	3 (17.6)	2 (10)	0.644
All-cause mortality, n (%)	0 (0)	0 (0)	–
Adverse events, n (%)	3 (17.6)	3 (15)	0.828

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

The most common side effect was bradycardia, defined as having a heart rate less than 50 bpm, which was responsible for four out of the six reported side effects (3 in the endothelial protocol mainly when the dose of 5 mg of nebivolol was used and 1 in the placebo arm). The remaining events were one case of nausea and vomiting which was in the placebo group and one case of hypotension in the endothelial protocol group where Nebivolol 5 mg was stopped and restarted at a dose of 2.5 mg the next day with no further problems recorded.

DISCUSSION

To the best of our knowledge, this is the first pilot, double-blind, placebo-controlled, randomized clinical trial to assess the efficacy and safety of managing endothelial dysfunction in patients with COVID-19. Our study shows that, in patients treated with optimal medical therapy for COVID-19 infection, targeting endothelial dysfunction medically did not result in a statistically significant clinical benefit or reach a statistically significant difference in the primary end points and the secondary outcomes among hospitalized patients with non-critical COVID-19 infection. However, the endothelial protocol demonstrated an excellent safety profile.

COVID-19, in the end, in its acute form or as long COVID syndrome, directly affects the endothelium.[4,14,15] Thus, and as recommended by the European Society of Cardiology (ESC), we therapeutically targeted the different mechanisms of endothelial dysfunction. Therefore, in addition to optimal medical therapy against COVID-19 infection, we used a five-drug endothelial protocol with proven efficacy against endothelial dysfunction and an excellent safety profile. This protocol consisted of Nicorandil, L-arginine, folic acid, Nebivolol, and atorvastatin.

Several studies showed a positive outcome when endothelial dysfunction was targeted in patients with COVID-19. Khider et al.[6] conducted a prospective cohort and reported that patients with COVID-19 treated with anticoagulation prior to admission demonstrated a statistically significant decrease in the circulating endothelial cells, a marker of endothelial injury and dysfunction when compared to those who were untreated ($p = 0.02$). Furthermore, Targeting the endothelial activation by monoclonal antibodies narsoplimab and adrecizumab were associated with improved outcomes in patients with COVID-19.[16,17] The clinical benefits noted with the use of tocilizumab and dexamethasone were attributed to the immunomodulation at the level of the endothelium.[18,19] Byttebier et al.[20] demonstrated in a retrospective study that the concurrent treatment with statins, aspirin, and ACE/ARBs, which have protective effects on the endothelium, resulted in a three-fold reduction in the odds of hospital mortality. In our study, treatment with the endothelial dysfunction protocol resulted in no benefit probably due to the small sample size and the fact that the meantime after presentation was around 7.5 days. By then, the acute phase had already passed and the endothelial damage incurred probably became irreversible with permanent target organ damage. Furthermore, the vast majority of patients received a treatment with anticoagulation and steroids. As mentioned previously, those medications have a proven efficacy in treating endothelial dysfunction in COVID-19 and as such might have blunted the therapeutic response to our protocol keeping in mind the small sample size. In addition, approximately half of the patients received antibiotics which can alter the microbiome by that impacting the inflammatory response.

Even though treating endothelial dysfunction did not demonstrate a better clinical outcome, it showed an excellent safety profile with no increase in the occurrence of major and minor side effects.

The strengths of this study include the randomized, double-blind, placebo-controlled, experimental design; it was done in a day-to-day healthcare setting. Furthermore, an extensive safety analysis as well as extensive adverse event reporting were done.

This pilot study has several limitations that warrant careful interpretation of the results. The relatively low sample size in this trial could have had inadequate power to exclude small, but clinically meaningful findings, because it was designed to explore a potential signal for the use of endothelial protocol in COVID-19, not to provide definitive evidence on the subject. This pilot was restricted to subjects with non-severe disease. The patients had several co-existing diseases and were subjected to a diverse medication regimen. Consequently, larger scale studies are thus necessary to demonstrate efficacy and confirm safety of the suggested protocol.

CONCLUSION

Among hospitalized patients with COVID-19, the use of an endothelial protocol consisting of Atorvastatin, L-arginine, folic acid, Nebivolol, and nicorandil to treat endothelial dysfunction did not significantly improve clinical outcomes. However, an excellent safety profile was found. Due to the lack of a large difference between the treatment groups and the absence of a clinically meaningful effect of treating endothelial dysfunction, we do not recommend further targeting this pathway in the treatment of COVID-19 infection.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

DATA AVAILABILITY STATEMENT

All data relevant to the study are included in the article and are available on reasonable request from the last author G.G.

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REFERENCES

1. Bernard I, Limonta D, Mahal LK, Hobman TC. Endothelium infection and dysregulation by SARS-CoV-2: Evidence and caveats in COVID-19. *Viruses*. 2020;13(1):29. doi:10.3390/v13010029

2. Maruhashi T, Higashi Y. Pathophysiological association of endothelial dysfunction with fatal outcome in COVID-19. *Int J Mol Sci*. 2021;22(10):5131. doi:10.3390/ijms22105131

3. Evans PC, Rainger GE, Mason JC, et al. Endothelial dysfunction in COVID-19: a position paper of the ESC Working Group for Atherosclerosis and Vascular Biology, and the ESC Council of Basic Cardiovascular Science. *Cardiovasc Res*. 2020;116(14):2177-2184. doi:10.1093/cvr/cvaa230

4. Matli K, Farah R, Maalouf M, Chamoun N, Costanian C, Ghanem G. Role of combining anticoagulant and antiplatelet agents in COVID-19 treatment: a rapid review. *Open Heart*. 2021a;8(1):e001628. doi:10.1136/openhrt-2021-001628

5. Kim WY, Kweon OJ, Cha MJ, Baek MS, Choi SH. Dexamethasone may improve severe COVID-19 via ameliorating endothelial injury and inflammation: A preliminary pilot study. *PLoS One*. 2021;16(7):e0254167. doi:10.1371/journal.pone.0254167

6. Khider L, Gendron N, Goudot G, et al. Curative anticoagulation prevents endothelial lesion in COVID-19 patients. *J Thromb Haemost*. 2020;18(9):2391-2399. doi:10.1111/jth.14968

7. Matli K, Chamoun N, Fares A, et al. Combined anticoagulant and antiplatelet therapy is associated with an improved outcome in hospitalised patients with COVID-19: a propensity matched cohort study. *Open Heart*. 2021b;8(2):e001785. doi:10.1136/openhrt-2021-001785

8. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med* 2021;384(8):693–704. doi:10.1056/NEJMoa2021436

9. Ashour H, Elsayed MH, Elmorsy S, Harb IA. Hypothesis: The potential therapeutic role of nicorandil in COVID-19. *Clin Exp Pharmacol Physiol*. 2020;47(11):1791-1797. doi:10.1111/1440-1681.13395

10. Daiber A, Steven S, Weber A, et al. Targeting vascular (endothelial) dysfunction. *Br J Pharmacol*. 2017;174(12):1591-1619. doi:10.1111/bph.13517

11. US Food and Drug Administration, Center for Drug Evaluation and Research (CDER). COVID-19: developing drugs and biological products for treatment or prevention; 2020. Available at: fda.gov

12. Gupta A, Madhavan MV, Poterucha TJ, et al. Association between antecedent statin use and decreased mortality in hospitalized patients with COVID-19. *Nat Commun*. 2021;12(1):1325. doi:10.1038/s41467-021-21553-1

13. Rahmani H, Davoudi-Monfared E, Nourian A, et al. Interferon β-1b in treatment of severe COVID-19: A randomized clinical trial. *Int Immunopharmacol*. 2020;88:106903. doi:10.1016/j.intimp.2020.106903

14. Charfeddine S, Ibn Hadj Amor H, Jdidi J, et al. Long COVID 19 syndrome: is it related to microcirculation and endothelial dysfunction? Insights from TUN-EndCOV study. *Front Cardiovasc Med*. 2021;8:745758. doi:10.3389/fcvm.2021.745758

15. Libby P, Lüscher T. COVID-19 is, in the end, an endothelial disease. *Eur Heart J*. 2020;41(32):3038-3044. doi:10.1093/eurheartj/ehaa623

16. Rambaldi A, Gritti G, Micò MC, et al. Endothelial injury and thrombotic microangiopathy in COVID-19: Treatment with the lectin-pathway inhibitor narsoplimab. *Immunobiology*. 2020;225(6):152001. doi:10.1016/j.imbio.2020.152001

17. Karakas M, Jarczak D, Becker M, et al. Targeting endothelial dysfunction in eight extreme-critically ill patients with COVID-19 using the anti-adrenomedullin antibody

adrecizumab (HAM8101). *Biomol Ther.* 2020;10(8):1171. doi:10.3390/biom10081171

18. Ikonomidis I, Pavlidis G, Katsimbri P, et al. Tocilizumab improves oxidative stress and endothelial glycocalyx: a mechanism that may explain the effects of biological treatment on COVID-19. *Food Chem Toxicol.* 2020;145:111694. doi:10.1016/j.fct.2020.111694

19. Keskinidou C, Vassiliou AG, Zacharis A, et al. Endothelial, immunothrombotic, and inflammatory biomarkers in the risk of mortality in critically ill COVID-19 patients: the role of dexamethasone. *Diagnostics.* 2021;11(7):1249. doi:10.3390/diagnostics11071249

20. Byttebier G, Belmans L, Alexander M, et al. Hospital mortality in COVID-19 patients in Belgium treated with statins, ACE inhibitors and/or ARBs. *Hum Vaccin Immunother.* 2021;17(9):2841-2850. doi:10.1080/21645515.2021.1920271

SUPPORTING INFORMATION

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