Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

and Regeneron; and serves on the Board of Directors of the Canadian Allergy Society of Allergy and Clinical Immunology. D. Lang is on the Editorial Board for *Allergy and Asthma Proceedings*; is Topic Editor for DynaMed; is Associate Editor for *J Asthma*; and is Delegate to NQF representing the American Academy of Allergy, Asthma, and Immunology (AAAAI). J. Lieberman has received research support (money to institution) from DBV, Aimmune, and Regeneron; is on the Advisory Boards for DBV, Genentech, and Covis; and is a Consultant for Kaleo. D. Fleischer received institutional research funding from DBV Technologies; institutional research funding from Aimmune Therapeutics; has served as a consultant and received personal fees from DBV Technologies, Aimmune Therapeutics, Kaleo Pharmaceutical, INSYS Therapeutics, Abbott, Allergenis, Acquestive, and Nestle; is a non-paid member of the scientific advisory council for the National Peanut Board and a non-paid member of clinical advisory boards for Food Allergy Research & Education and Food Allergy and Anaphylaxis Connectivity Team. D. B. K. Golden has received financial support from Aquestive, Sandoz, ALK-Abello, Genentech, Stallergenes-Greer, and UpToDate. D. Wallace has received financial support from Mylan, Kaleo, Optinose, ALK, Bryan, and Sanofi. J. Portnoy has received financial support from Thermofisher, Kaleo, Teva, Novartis, Hycor, and Boehringer-Ingelheim. G. Mosnaim received research grant support from AstraZeneca and GlaxoSmithKline; currently receives research grant support from Propeller Health; owned stock in Electrocore; and served as a consultant and/or member of a scientific advisory board for GlaxoSmithKline, Sanofi-Regeneron, Teva, Novartis, Astra Zeneca, Boehringer Ingelheim, and Propeller Health. M. Greenhawt is supported by grant #5K08HS024599-02 from the Agency for Healthcare Research and Quality; is an expert panel and coordinating committee member of the NIAID-sponsored Guidelines for Peanut Allergy Prevention; has served as a consultant for the Canadian Transportation Agency, Thermo Fisher, Intrommune, and Aimmune Therapeutics; is a member of physician/medical advisory boards for Aimmune Therapeutics, DBV Technologies, Sanofi/Genzyme, Genentech, Nutricia, Kaleo Pharmaceutical, Nestle, Acquestive, Allergy Therapeutics, Allergenis, Aravax, and Monsanto; is a member of the scientific advisory council for the National Peanut Board; has received honorarium for lectures from Thermo Fisher, Aimmune Therapeutics, DBV Technologies, Before Brands, multiple state allergy societies, the American College of Allergy Asthma and Immunology, the European Academy of Allergy and Clinical Immunology; is Associate Editor for the *Annals of Allergy, Asthma, and Immunology*; and is a member of the Joint Taskforce on Allergy Practice Parameters.

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Debate on drugs that may aggravate COVID-19

To the Editor:

The Journal of Allergy and Clinical Immunology: *In Practice* published a contingency planning article by Shaker et al[1] to guide the allergists/immunologists through the coronavirus disease 2019 (COVID-19) pandemic. They provided suggestions for a logical approach to quickly adjust our services to mitigate risk to both medical staff and patients during the pandemic, while social distancing is being encouraged. In this context, there is an ongoing worldwide debate regarding the use of angiotensin-converting enzyme (ACE) inhibitors and ibuprofen in patients with COVID-19. The concern is that these drugs could worsen the prognosis of patients with the infection.[2]

The 2 coronaviruses of the "severe acute respiratory syndrome," China, 2002/2003, and of the "Middle East respiratory syndrome," Middle Eastern countries, 2012, use angiotensin-converting enzyme 2 (ACE2) and dipeptidyl peptidase 4, respectively, as their receptors to infect human cells.[3] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the coronavirus involved in COVID-19, also depends on ACE2 for cell entry.[4]

Drugs that inhibit ACE paradoxically upregulate ACE2 expression on the cell surface and could theoretically facilitate coronavirus infection and progression.[5] There is no definitive evidence that this effect is clinically relevant, but some retrospective observational studies suggest an association between the use of these drugs and a worse outcome of COVID-19.[6] A cause-effect association cannot be confirmed, and ACE inhibitors could be confounding factors that indicate comorbidities, such as cardiopathy, hypertension, and diabetes, besides advancing age, which are well-recognized risk factors for worse outcome of COVID-19. Myocardial injury, indicated by increased serum levels of troponin T, and cardiovascular disease had a significant association with fatal outcomes of COVID-19.[6] Moreover, withdrawal of ACE inhibitors could aggravate an underlying disease and make patients more unstable to overcome a coronavirus infection.

Coincidentally or not, the receptors of coronavirus, ACE2 and dipeptidyl peptidase 4, are enzymes that break down bradykinin in addition to their main functions. After SARS-CoV-2 binding to ACE2, the viral complex undergo endocytosis and surface ACE2 is downregulated (Figure 1). ACE also degrades bradykinin and drugs that inhibit this enzyme lead to an increase in tissue bradykinin and may even trigger cough and angioedema in hypersensitive individuals. We speculate whether the excess of bradykinin in patients taking ACE inhibitors could complicate coronavirus infection, because of its effects of vasodilation, increase in vascular permeability, and cough reflex exacerbation.[7] However, no study has been done investigating this hypothesis and current data do not justify the discontinuation of ACE inhibitors in patients at risk or with COVID-19.

Some experts' opinions and unpublished French cases suggested an association between the use of ibuprofen and a worse outcome of COVID-19,[8] but there are no studies supporting this hypothesis. A recent publication stated that ibuprofen also increases ACE2 expression, but the authors did not provide the reference that supports this statement.[2] Ibuprofen use could be a marker of disease severity and not necessarily the cause of a worse prognosis. Patients more toxemic and symptomatic, having fever, asthenia, and myalgia, are more prone to use nonsteroidal

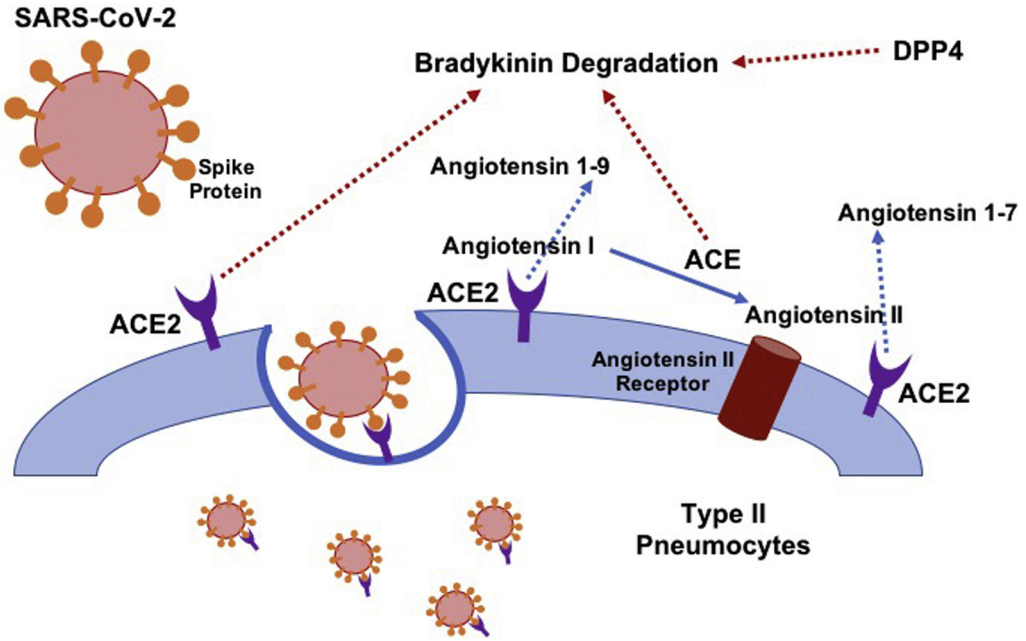

FIGURE 1. Interaction between the renin-angiotensin-aldosterone system and the bradykinin system. During SARS-CoV-2 infection, there is down-regulation of ACE2 at type II pneumocytes surface, decreasing bradykinin degradation. ACE also degrades bradykinin, and drugs that inhibit this enzyme increase bradykinin levels. Red dashed line (ACE, ACE2, and DPP4 degrade bradykinin); blue dashed line (ACE2 degrades angiotensin I to angiotensin 1-9 and angiotensin II to angiotensin 1-7); blue solid line (conversion of angiotensin I to angiotensin II). *DPP4*, Dipeptidyl peptidase 4.

anti-inflammatory drugs (NSAIDs). If ibuprofen is indeed associated with worse COVID-19 outcomes, whether or not a possible association would relate to the specific agent ibuprofen or the larger group of NSAIDs would require further investigation. The European Medicines Agency concluded that there is currently no scientific evidence establishing a link between ibuprofen or NSAIDs and worsening of COVID-19.[8]

Knowledge of SARS-CoV-2 infection increases daily and further studies are needed to better understand the influence, if any, of ACE inhibitors and NSAIDs in COVID-19 severity. At present, there is no evidence to generate even a weak recommendation to discontinue these medications during the pandemic. Patients' care must be personalized, and ACE inhibitors and/or NSAIDs may be used if indicated, after weighing the benefits and risks.

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Evidence-based considerations for exercise-induced dyspnea

To the Editor:

In an extensive review, Hull et al[1] have described exercise-induced laryngeal obstruction (EILO) as including various causes of upper airway obstruction, particularly during exercise. However, there are distinct entities with specific treatments within EILO. An evaluation that identifies the specific abnormality provides more clinical relevance than lumping the various disorders into the EILO terminology. Vocal cord dysfunction (VCD), an entity within the EILO conglomerate, itself has 2 distinct phenotypes, exercise-induced VCD and spontaneous VCD.[2] Exercise-inced VCD has been reported to be prevented by pretreatment with an