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.

THE AMERICAN JOURNAL of MEDICINE®

The Reply

We thank Drs Chiang and Gupta for their thoughtful comments on our paper[1] relating to thromboxane A_2 activation and thrombosis in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; coronavirus disease 2019 [COVID-19]) infection. We share the same concerns that there may be an overwhelming activation of this pathway that could overcome the inhibitory effects of aspirin on cyclooxygenase-1 and induce the converse process of "aspirin resistance."[2] Recently Chow et al[3] reported that 23.7% of hospitalized patients received antecedent aspirin and after adjustment, aspirin use was associated with decreased risk of mechanical ventilation (adjusted hazard ratio [HR] 0.56, 95% confidence interval [CI] 0.37-0.85, $P = .007$), admission to the intensive care unit (adjusted HR 0.57, 95% CI 0.38-0.85, $P = .005$), and in-hospital mortality (adjusted HR 0.53, 95% CI 0.31-0.90, $P = .02$). There were no differences in major bleeding ($P = .69$) or overt thrombosis ($P = .82$) between aspirin users and nonaspirin users. The National Institutes of Health Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV-4) Program ($N = 7000$) started September 7, 2020, is testing placebo, aspirin 81 mg, apixaban 2.5 mg twice daily, or apixaban 5 mg orally twice daily.[4] It would be ideal if current patients could be enrolled, and if not feasible, we advise aspirin 325 mg every day, and in higher-risk patients, apixaban 5 mg orally twice daily or enoxaparin 40 mg subcutaneously twice daily. Given the fatal nature of progressive COVID-19, we are uncomfortable with therapeutic nihilism outside of monitored placebo-controlled randomized trials. We look forward to the late results of ACTIV-4 and the development of novel agents such as ramatroban, which could address the inflammatory component of pathologic platelet-rich thrombosis in COVID-19.[5,6]

Peter A. McCullough, MD, MPH
Baylor Heart and Vascular Institute, Baylor University Medical Center, Dallas, Tex

https://doi.org/10.1016/j.amjmed.2020.11.028

References

1. McCullough PA, Kelly RJ, Ruocco G, et al. Pathophysiological basis and rationale for early outpatient treatment of SARS-CoV-2 (COVID-19) infection. *Am J Med.* 2021;134(1):16–22. https://doi.org/10.1016/j.amjmed.2020.07.003.
2. Vasudevan A, Bottiglieri T, Tecson KM, et al. Residual thromboxane activity and oxidative stress: influence on mortality in patients with stable coronary artery disease. *Coron Artery Dis* 2017;28(4):287–93. https://doi.org/10.1097/MCA.0000000000000461.
3. Chow JH, Khanna AK, Kethireddy S, et al. Aspirin use is associated with decreased mechanical ventilation, ICU admission, and in-hospital mortality in hospitalized patients with COVID-19 [e-pub ahead of print]. *Anesth Analg*. Accessed January 27, 2021. doi: 10.1213/ANE.0000000000005292.
4. COVID-19 positive Outpatient Thrombosis Prevention in Adults Aged 40-80. Available at: https://clinicaltrials.gov/ct2/show/NCT04498273?term=ACTIV-4&draw=2&rank=2. Accessed January 27, 2021.
5. Gupta A, Kalantar-Zadeh K, Reddy ST. Ramatroban as a novel immunotherapy for COVID-19. *J Mol Genet Med* 2020;14(3). https://doi.org/10.37421/jmgm.2020.14.457 [10.37421/jmgm.2020.14.457.
6. Zhang J, Tecson KM, McCullough PA. Endothelial dysfunction contributes to COVID-19-associated vascular inflammation and coagulopathy. *Rev Cardiovasc Med* 2020;21(3):315–9. https://doi.org/10.31083/j.rcm.2020.03.126.

Funding: None.
Conflict of Interest: None.
Authorship: The author is solely responsible for the content of this manuscript.

Requests for reprints should be addressed to Peter A. McCullough, MD, MPH, Baylor Heart and Vascular Institute, 621 N. Hall St, H030, Dallas, TX, 75226.
E-mail address: peteramccullough@gmail.com