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.

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Editorial

Further evidence for the use of aspirin in COVID-19

The coronavirus disease (COVID)-19 is associated with cytokine storm attendant with very high levels of inflammation biomarkers, hypercoagulability marked by elevated levels of d-dimer, and fibrinogen, modest consumption of coagulation factors, and mild abnormalities in platelet count, platelet activation and prothrombin time [1]. Therefore, patients with COVID-19 are at risk for multiorgan thrombotic and thromboembolic events that can rapidly lead to critical lung illness and death. Patients with COVID-19 have benefited from concomitant treatment with antiinflammatory, antiviral, and anticoagulant agents. Currently available therapies that are directly targeting the virus may exhibit limited effectiveness over time due to continuous mutations into new variant forms [2].

Observational studies have demonstrated the potential efficacy of adjunctive therapy of low-dose aspirin (81–100 mg per day) in patients with COVID-19. In an earlier small observational cohort study of adult patients with COVID-19 by Chow et al., aspirin use (n = 98) at least seven days before hospitalization or within 24 h of hospitalization compared to no aspirin use (n = 314) was significantly associated with lower intensive care unit (ICU) admission, risk of mechanical ventilation, and in-hospital mortality. There were no differences in overt thrombosis or major bleeding between groups [3]. In another recent observational study, among 730 patients on antiplatelet therapy, 645 patients were treated with either oral or intravenous aspirin during hospitalization. Compared to 6986 patients on no antiplatelet therapy, patients on antiplatelet therapy had lower in-hospital mortality and a shorter duration of mechanical ventilation. The mortality benefit was also observed in ICU patients and patients with a history of cancer. There was no increased risk of bleeding with antiplatelet therapy. These studies lend support for the use of aspirin in patients with COVID-19 [4]. However, in a multinational, randomized trial, hospitalized COVID-19 patients who were treated with 150 mg aspirin (n = 7351) as compared to usual care (n = 7541) had a similar rate of death at 28 days (17% in each group, rate ratio = 0·96; 95% CI = 0·89–1·04; 41 p = 0·35) with no reduction in the risk of progression to the composite endpoint of invasive mechanical ventilation or death. These study results have not yet been published in a peer-reviewed journal. This latter study was associated with many important caveats but suggests that uniform use of aspirin in patients with COVID-19 should be implemented with caution [5].

In this issue of International Journal of Cardiology, Sissini et al. report the results of a multicenter, retrospective study of 253 patients who were treated with daily aspirin, mostly with a 100 mg dose, for at least 7 days before hospital admission and continued during the hospitalization with the same dose were compared to 731 patients not on aspirin. Patients on aspirin were older and had more comorbidities and higher prevalence of coronary artery disease [6]. There were no differences in most of the prehospitalization infection-related symptoms, quick sepsis-related organ failure assessment, the degree of respiratory impairment as indicated by arterial blood gas analysis at admission, and hospital duration. Finally, aspirin-treated patients had lower estimated glomerular filtration rate (p = 0.001), whereas liver function tests and d-dimer levels were similar between groups. Slightly more than half of the patients were treated with low-molecular weight heparin (LMWH) and therapeutic dose LWWH use was less frequent in patients treated with aspirin compared to patients not treated with aspirin (44% vs. 57%, p = 0.015) [6]. In the thirty-day Kaplan Meir analysis, aspirin-treated patients compared to non- aspirin-treated patients had higher survival free from the primary endpoint of composite of in-hospital death and/or need for respiratory support upgrade (75% vs. 63%; HR = 0.79, log-rank p = 0.013) and need for respiratory upgrade (49% vs. 33%; HR = 0.64, log-rank p = 0.008), but there was no significant difference in in-hospital death (52% vs. 53%, p = 0.65). In a multivariate analysis, aspirin use was associated with a lower probability of reaching the primary endpoint (HR = 0.69, 95CI, 0.52–0.94: p = 0.012) and need for less respiratory support upgrade ((HR 0.53, 95% CI = 0.33–0.84; p = 0.007). Despite the inherent limitations of a retrospective analysis, these results further support the previous studies demonstrating the clinical utility of prior and in-hospital use of aspirin in patients with COVID-19 [6].

There are some caveats for using aspirin in patients with COVID-19. In the presence of hypercoagulability, cytokine storm, and endothelial dysfunction, low-dose aspirin therapy may have limited efficacy. Based on the assessment of urinary 11-dehydrothromboxane B_2, a marker of whole-body cyclooxygenase inhibition, we have shown that 81 mg per day aspirin may be inefficient to produce a pharmacodynamic effect strong enough to translate to better clinical outcomes [7]. However, low-dose aspirin on the background of anticoagulants might add some therapeutic benefit. In-hospital higher dose (325 mg) aspirin therapy may be associated with greater antithrombotic and antiinflammatory effects. However, the potential increase in bleeding risk when added to therapeutic anticoagulation that is widely used in patients with COVID-

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; COVID 19, coronavirus disease; ICU, intensive care unit; LMWH, lowmolecular weight heparin; LASAG, L-lysine acetylsalicylate+glycine.

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19 is a concern. Finally, aspirin effects may be enhanced by aerosol delivery to the damaged lung in COVID-19. Potent antiviral effects have been reported at millimolar levels of salicylate with D, L-lysine acetylsalicylate+glycine (LASAG), that can be achieved locally by aerosol delivery. In *in vitro* studies using low (HCoV-229E) and highly (Middle East respiratory syndrome coronavirus) pathogenic beta coronavirus strains, LASAG at millimolar concentrations has been shown to inhibit virus-induced nuclear factor (NF)-κB activity and decreased viral protein formation, ribonucleic acid synthesis, and the formation of replication transcription complexes [8]. Furthermore, LASAG at 5 mmol/L concentration has been shown to inhibit IκB kinase–mediated NF-κB activation and virus production in human epithelial cells infected with influenza A. In patients afflicted with influenza virus, administration of nebulized LASAG showed faster alleviation of symptoms [9]. These effects support further investigation of this delivery strategy during the critical initial course of the disease. COVID-19 is a worldwide pandemic and most of the current treatment options may not be readily available in underserved communities and in remote areas of the world whereas aspirin is inexpensive and widely available. The proposed antiviral, antiinflammatory and antithrombotic properties of aspirin support further research into its efficacy as an adjunctive agent in COVID-19.

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