A discussion on the possible therapeutical use of acetylsalicylic acid on COVID-19

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Acetylsalicylic acid (ASA) has been traditionally used on many blood coagulations diseases for its pharmacological properties in reducing some pathophysiologic events that lead to thromboembolism. Recently many Authors have been discussing the possible use of ASA on supporting patients that present blood complications by the SARS-Cov-2 infection for its anti-thrombotic effects. Whether it may be harmful or beneficial to patients remains to be concluded.

The coronavirus disease 2019 (COVID-19) is an infection caused by a novel coronavirus, and it was officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease was recognized by World Health Organization (WHO) as a pandemic, and by June 22nd, 2021, there have been 178.360.849 confirmed cases of COVID-19, including 3.869.384 deaths all over the world. Even though we already have available vaccines, the rhythm and speed that they are being acquired and applied abroad still does not provide us the necessary tranquility to return to something that would be close to normal life. For this reason, measures of social distance, restriction of circulation, use of masks and hygiene, continue to be our main allies to protect from the pandemic.

Since we still don't have a non-prophylactic, antiviral pharmacological treatment against the SARS-COV-2 to cure or to prevent the disease, so far we are treating the consequences of the infection, especially in relation to the immune response. Although information from clinical trials is continuously generated, nevertheless to date there is a lack of a completely effective drug to treat COVID-19. The steroidal anti-inflammatory dexamethasone was the first approved drug for the consequences of cytokine storm of the inflammatory phase of the disease. Some monoclonal antibodies (MAB's) such as casirivimab, im-

devimab, bamlanivimab, etesevimab, tocizilumab, for instance, have been already authorized by some healthy agencies as well. In both cases they are considerable valuable tolls to reduce the period of the intubation of patients. Besides, the antiviral remdesevir has been approved for emergency use in several countries. Although the results obtained in clinical trials were not conclusive for primary outcomes, we believe that having treatment options that can reduce the time of UCI hospitalizations is of capital importance to diminish the pressure on health systems.

It is already well recognized that Inflammatory cytokines can stimulate the activation of blood coagulation in many ways, and then can promote the occurrence of venous thromboembolism (VTE) (Poll and Levi, 2012). A plenty of consequences for the SARS-CoV-2 infection have been reported; considering the blood circulation, a high incidence of coagulation related dysfunction in intensive care unit (ICU) patients - but also in non-ICU patients - have been reported. Actually COVID-19 is clearly associated with a higher risk for thrombosis (Bilaloglu et al., 2021) .The increased risk for blood clots in patients hospitalized with COVID-19 has been a major issue throughout the pandemic.

In fact, since the beginning of the pandemic studies from China reported increased D-dimers (0.5 mg/L or higher) in patients, as well as other signs of coagulation activation (Zhou et al., 2020). In COVID-19 patients elevated D-dimer level is a sign of excessive coagulation activation and hyperfibrinolysis. For example, Wang et al. (2020) have described that patients who died of COVID-19 had higher D-dimers on admission compared with those who survived, whereas D-dimer levels increased further during hospital stay in patients who died, but not in survivors.

To further explore the correlation of severe pneumonia by SARS-CoV-2 and VTE, Cui et al. (2020) have investigated the incidence of VTE in ICU patients with severe novel coronavirus pneumonia (NCP) and the differences between VTE patients and non-VTE patients. In their study they have enrolled 81 patients with severe NCP and many biochemical parameters and image analysis were performed. Authors have concluded for a high incidence of VTE in patients with severe NCP and also confirmed the application of the elevation D-dimer in VTE prediction. Indeed, a high cumulative incidence of thrombotic complications in critically ill patients with COVID-19 admitted to the ICU's was also reported by Klok et al. (2020) in three Dutch hospitals. Authors have performed diagnostic tests in case of clinically suspected thrombotic complications. The crude cumulative incidence of the multiple outcomes was 57% (95%CI 47–67%; Figure 1), and authors have shown that patients diagnosed with thrombotic complications were at higher risk of all-cause death. Authors confirmed the very high cumulative incidence of thrombotic complications in critically ill patients with COVID-19 pneumonia. They also emphasize to strictly apply pharmacological thrombosis prophylaxis in all COVID-19 patients admitted to the ICU. In another investigation, Middeldorp et al. (2020) have done a comparison between ICU and ward patients using standard descriptive statistics. They observed that symptomatic VTE was detected in 21 (28%) ICU patients and 4 (3.3%) ward patients. Authors have also detected that the risk of VTE in ICU's patients was not lower during the period when the standard dose of nadroparin prophylaxis was doubled (58%) vs in the first follow-up period (41%). They also described that some risk factors associated with VTE besides de ICU were a higher white blood cell count, higher neutrophil-to-lymphocyte ratio and a higher D-dimer level.

Therefore, the researches have been pointing out that systemic anticoagulation reduces mortality in mechanically ventilated COVID-19 patients. In all the above studies, low molecular-weight heparins prophylaxis was regularly employed as therapeutical approach. This is of no surprise since those molecules are strongly recommended in the treatment and prophylaxis of thrombotic events such as VTE.

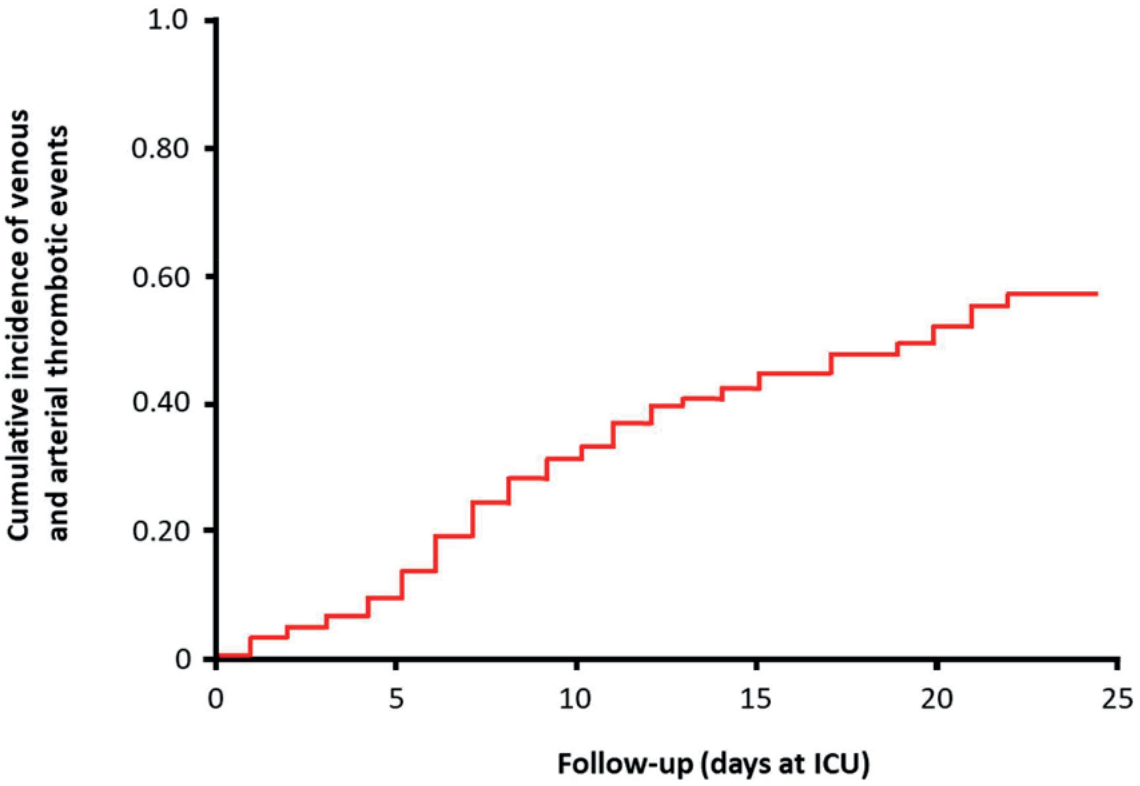

Figure 1. Cumulative incidence of venous and arterial thrombotic complications during the course of intensive care unit admission of patients with proven COVID-19 pneumonia (Extracted from F.A. Klok et al. Thrombosis Research).

However, two recent published articles have discussed the possibility of including low dose acetylsalicylic acid (ASA; Aspirin) as a pharmacological tool for the blood consequences of severe COVID-19. Jonathan H. Chow et al (2021) performed a retrospective, observational cohort study of adult patients admitted with COVID-19 to multiple hospitals in the United States between March 2020 and July 2020. The primary outcome was the need for mechanical ventilation. Secondary outcomes were ICU admission and in-hospital mortality. In their study, three hundred fourteen patients (76.3%) did not receive aspirin, while 98 patients (23.7%; dose ratio 81-85 mg) received aspirin within 24 hours of admission or 7 days before admission. Patients receiving other therapeutics such as azithromycin, convalescent plasma, dexamethasone, therapeutic heparin, hydroxychloroquine, remdesivir, and tocilizumab, did not differ in each group. They have found that aspirin use was independently associated with decreased risk of mechanical ventilation (adjusted HR, 0.56, 95% confidence interval [CI], 0.37-0.85, P = 0.007), ICU admission (adjusted HR, 0.57, 95% CI, 0.38-0.85, P = 0.005), and in-hospital mortality (adjusted HR, 0.53, 95% CI, 0.31-0.90, P = 0.02; Figure 2). There were no differences in major bleeding (P = 0.69) or overt thrombosis (P = 0.82) between aspirin users and non-aspirin users. They concluded that aspirin use may be associated with improved outcomes in hospitalized COVID-19 patients.

In the research of Cacciapuoti & Cacciapuoti (2021) authors hypothesized that low doses of ASA are useful for weaken the thrombotic complications induced by COVID-19 based on the inflammatory effects of virus infection in the cells of pulmonary alveoli.

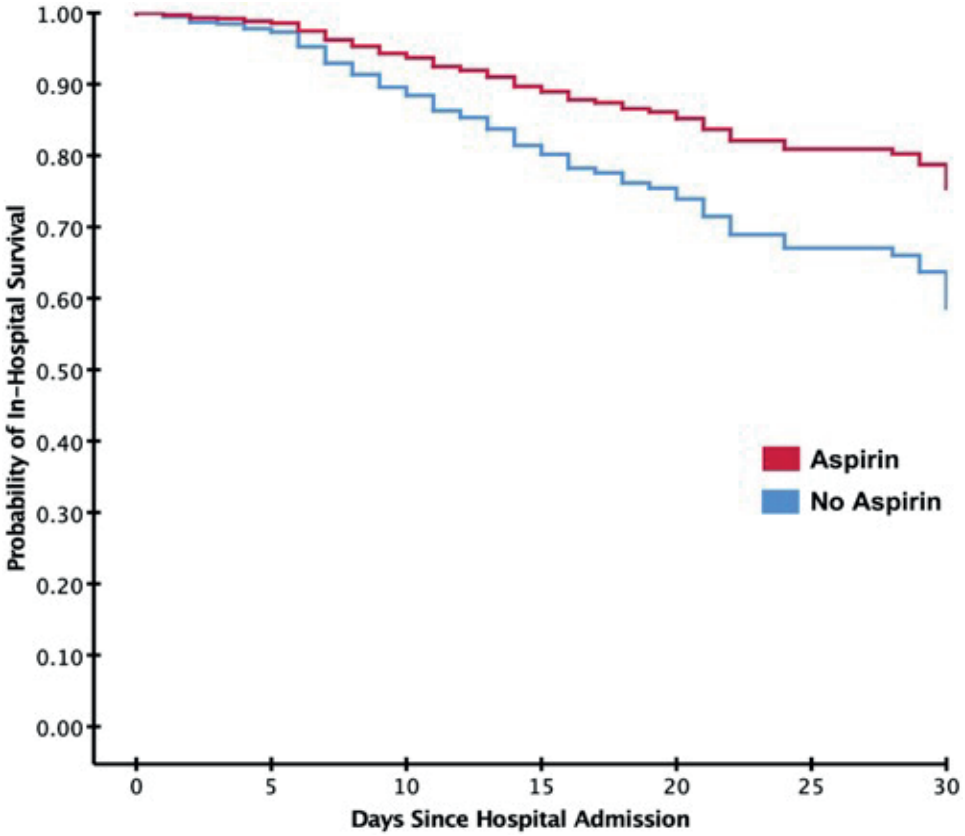

Figure 2. Survival function for in-hospital mortality. Patients are stratified by aspirin use. Patients discharged within the study period are right-censored. Aspirin use was associated with a decreased hazard for in-hospital mortality (adjusted HR = 0.53, 95% CI, 0.31-0.90, P = 0.02). CI indicates confidence interval; HR, hazard ratio. (Extracted from Jonathan H. Chow, Ashish K. Khanna, Shravan Kethireddy et al.).

Thus, thrombocytopenia, elevated fibrin degradation products, prothrombin time (PT), and activated partial thromboplastin time (aPTT) prolongation, venous thromboembolism and disseminated intravascular coagulation (DIC) that have been reported in COVID-19 patients might have Aspirin in the treatment protocol. ASA is broadly recognized as prostaglandin (PG) and thromboxane synthesis inhibits by irreversible inactivation of both cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2; Gierse et al., 1996). Other mechanisms of ASA-induced effects include modulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, down-regulation of inducible nitric oxide synthase (iNOS), oxidative phosphorylation uncoupling, and increased permeability in mitochondria (Vane and Botting, 1998).

However, although all the described effects for ASA in coagulation system, no consensus on the use on blood circulation pathologies there exits. Actually, the risk of hemorrhage with the use of Aspirin was always present as an uncertainty within its therapeutic employment since it may increase the risk of bleeding. For instance, The European Society of Cardiology Guideline (2016) has withdrawn the recommendation of the use of Aspirin for primary prevention, that is, for patients without previous cardiovascular or cerebrovascular episodes. So, as one easily can see, many concerns still persist in relation to ASA use in coagulation disturbs (Santos, 2019). May the casted doubts have prompted Bianconi et al (2020) to ask about the usefulness of acetylsalicylic acid adult patients with COVID-19. Authors have discussed the theme at the light of the multiple pharmacological

properties of ASA, which could exert potential benefits and provide a rationale for its use as supportive therapy in COVID-19 patients.

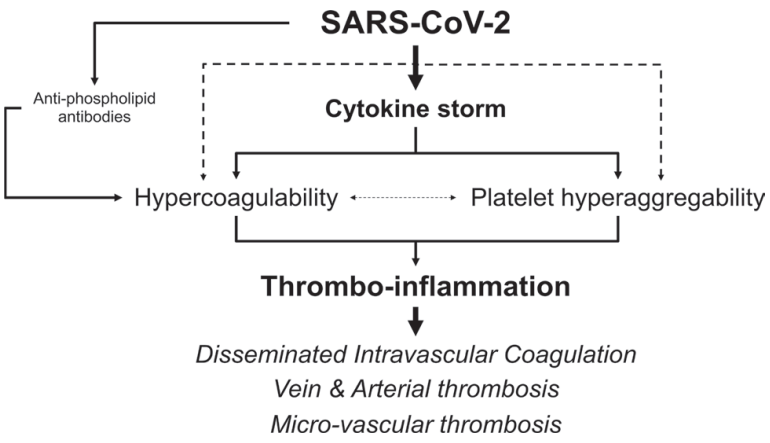

Figure 3. Proposed mechanisms for the increased thrombotic risk related to SARS-CoV-2 infection. SARS-CoV-2 Severe Acute Respiratory Syndrome-Coronavirus-2. Extracted from Bianconi et al (2020).

For all the researches quoted in here, it should be considered that we really should wait for the results from the clinical trials that are been conducted on the possible use of ASA on COVID-19 to better understand whether it could be a benefit or a damage to patients with the terrible disease, actually a challenge pandemic.

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