probably also the dosing regimen. If early intervention is possible, prophylactic doses of heparin may be adequate. Prophylactic doses of heparin rarely cause increased bleeding even when mild to moderate renal impairment or thrombocytopenia (>25 × 10^9/L) complicate the clinical scenarios in which the non-anticoagulant properties may be desirable. On the other hand, if the inflammatory process has progressed, much higher—even therapeutic—doses of heparin may be required, which clearly has an increased bleeding risk in these complex patients. Needless to say, one of the reasons for the increased bleeding in critically ill patients is the marked endothelial dysfunction and leakage, which would obviously be compounded by therapeutic heparin administration.[7]

How may the non-anticoagulant properties of heparins be relevant to the COVID-19 patient? If we examine the patient journey, symptoms from the SARS CoV-2 usually start in the pre-hospital setting. Persistent fever for 48 to 72 hours and/or extreme fatigue could be considered as signs of continued inflammation in COVID-19.[8] If these symptoms are associated with a decrease in oxygen saturation; it may be prudent to commence prophylactic doses of heparin to benefit from its anti-inflammatory properties. In the current pandemic, many of these patients may not attend hospitals until they are much more symptomatic, when the continued inflammation would progress and have a significant impact on their prognosis. Once the patient reaches the hospital, current trials look at intensifying heparin doses even in the absence of thrombosis but we need to worry about higher bleeding risks with this approach with possibly little anti-inflammatory benefit. It may be better to continue prophylactic doses of heparin and consider additional anti-inflammatory agents to maximize therapeutic benefits with minimal drug-related complications.

There have been suggestions for considering the more practical, direct oral anticoagulants (DOACs) instead of parenteral heparins in the pre-hospital COVID-19 setting. Although a more convenient and reasonable approach, we need evidence for their non-anticoagulant properties, which is currently lacking but an interesting research prospect. Similarly, questions arise about post-discharge thromboprophylaxis of COVID-19 patients who did not develop a thrombotic complication—are they protected from future complications (including thrombosis) with the use of low-dose DOACs or prophylactic dose low molecular weight heparins? Hopefully, the several ongoing studies will provide us effective answers soon.

CONFLICT OF INTEREST

None.

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Ibuprofen and thromboembolism in SARS-COV2

Recent and developing literature has begun reporting on the incidence of thromboembolic events associated with COVID-19. Klok et al analyzed 184 SARS-CoV2–positive intensive care unit (ICU) patients in two Dutch University Hospitals, reporting an incidence of thrombotic complications to be 31%, with pulmonary embolism (PE) comprising 81% of these complications.[1] Moreover, Cui et al reports on a population of 81 ICU patients at the Union Hospital, Wuhan, an incidence of 25% in venous thromboembolism (VTE), also possibly related to worse prognosis.[2] Wang et al collected data from 1026 COVID-19–positive patients in 31 provincial administrative regions in China and found 40% of the patients as high risk for VTE according

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to the Padua Prediction Score, with 11% being predicted to go on to develop VTE.[3] Other reports and studies have also discussed the role of acute PE in COVID-19. Recent studies have also reported and advised on the use of prophylactic low molecular weight heparin (LMWH) in COVID-19 patients, to prevent the severe outcomes associated with thromboembolic complications.

Elevation of inflammatory markers including D-dimer, C-reactive protein, ferritin, and interleukin-6 levels contributing to a procoagulant profile has been reported in the current SARS-COV2 pandemic.[4] Although the exact causes of such an extreme procoagulant profile and an increased risk of thromboembolic events has not been completely established, potential risk factors have been outlined. Indeed, the increased risk of both venous and arterial thromboembolism in COVID-19 exists and is linked to the excessive inflammation, endothelial pathomechanisms in acute lung injury, severe infection, endothelial dysfunction, platelet activation, immobilization, respiratory failure, mechanical ventilation, and central venous catheter use.[3,5] Whether the increased risk of a thromboembolic event is linked directly to the action of SARS-CoV2 or to the secondary effects of the cytokine storm induced during the severe infection in COVID-19 has not been established yet.

Ibuprofen has been a nonsteroidal anti-inflammatory drug (NSAID) of much contention when various authorities in France, the UK, and the World Health Organization advised against its use based on case reports that have not yet been discovered upon extensive research. By being one of the most widely used NSAIDs worldwide, the implications on the use of ibuprofen and any correlation with adverse reactions in COVID-19 should be taken into serious consideration. Even though previous research in the field of thromboembolism and NSAIDs is limited and less commonly reported, there are case reports, case control, meta-analyses, and systematic reviews illustrating a possible correlation between the use of ibuprofen and the increased risk of thromboembolism development, including deep vein thrombosis (DVT) and PE.

The association between the use of ibuprofen and the development of vascular events was first notably brought into discussion by the meta-analysis conducted by Kearney et al illustrating an increased risk of serious vascular events with high doses of ibuprofen and diclofenac.[6] Five years after this research was published, a case-control study in the Netherlands by Biere-Rafi et al showed a three-fold increase in risk for PE associated with the use of ibuprofen.[7] This study included more than 20 000 Dutch participants and showed the risk of PE was greatest within the first 30 days of use, and lower in chronic users, possibly due to a compensatory effect.[7] A population-based case-control study that was similar to Biere-Rafi et al was conducted in Northern Denmark. Schmidt et al conducted research on a larger scale showing a two-fold or more increase in the risk of VTE for long-term use in all non-aspirin NSAIDs.[7,8]

To add support to the evidence a meta-analysis conducted in the UK combined data from six studies, with 21 401 VTE events, to show that NSAID users have a 1.8-fold increase in risk compared with users who do not use NSAIDs, citing the increased risk of vascular events associated with ibuprofen.[9] This paper was published in 2015 and was the first systematic review and meta-analysis published on the topic, hence the data used was limited and conflicting. They believe further research and epidemiological data is needed in the area. Nevertheless, their results are statistically significant and they warn physicians to prescribe with caution.[9] A more recent UK-based case-control study, in 2016, compared 24 079 current, recent, and remote NSAID users for knee osteoarthritis and their risk of VTE.[10] Remote users (the control group) were classed as those with a prescription >365 days and recent users as those with <60 days. The results showed an increased risk of VTE for current users of ibuprofen and other NSAIDs compared with remote users in all categories—sex, age, and calendar period. The results also showed an increased effect of ibuprofen and other NSAIDs on subjects <70 years of age.[10]

No conclusion of causation between the effects of ibuprofen and thromboembolic event has been made and several limitations in the following area of research exist, including conflicting evidence on the role of ibuprofen on a vascular level. Whether ibuprofen is able to interact with SARS-COV2 through any mechanism is also not clear. Nevertheless, careful consideration should be made on avoiding high dosage of ibuprofen in subjects at particular risk of thromboembolic events. Furthermore, factors including decreased mobility and the limited exercise rates resulting from nationwide lockdowns pose frail patients at increased risk of developing thromboembolic events. Therefore, considerations should be made on two fronts of action. First, patient advice should be considered regarding possible side effects and avoidance of high dosage of ibuprofen. Second, a need for a large-scale study assessing any possible correlation between NSAIDs and the worsening or increased risk of thromboembolic event in COVID-19 should be considered.

CONFLICTS OF INTEREST

The authors declare that they have no financial or other interest in the product or distributor of the product or the nature of any relationship between himself or herself and the manufacturer or distributor of the product.

AUTHOR CONTRIBUTIONS

All authors contributed in the collection of data and manuscript development. All authors read and approved the final manuscript.

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Reply to "Ibuprofen and thromboembolism in SARS-COV2"

We appreciate the opportunity to respond to the comments by Drs. Rad et al. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in many countries for the relief of symptoms of pain, inflammation, and fever, which reduce the conversion of arachidonic acid to prostaglandins, prostacyclin (PGI_2), and thromboxane (Tx) A_2 by inhibiting cyclooxygenase (COX). At present, it is recognized that there are two related but different types of COX activity, COX-1 and COX-2. COX-1 is continuously expressed in most tissues, and platelets containing COX-1 are the main source of TXA2,[1] which affects vascular smooth muscle contraction and platelet aggregation.[2] COX-2 is mainly expressed in the inflammatory response and is the main source of PGI_2.[3] According to the different selectivity for COX inhibition, NSAIDs are divided into nonselective and COX-2 selective. Ibuprofen is a type of nonselective NSAIDs.

As the authors said, several studies have confirmed that NSAIDs (including ibuprofen) are significantly associated with the occurrence of venous thromboembolism, especially in selective COX-2 inhibitors, and are related to the dose and duration of administration, but the mechanism is not clear. The primary hypothesis is that NSAIDs may create an imbalance between PGI_2 and TXA_2, resulting in a relative increase in TXA_2, leaving the body in a hypercoagulable state.[4] Moreover, the reduction of prostaglandin leads to the decrease of thrombomodulin, which increases the incidence of thrombosis.[5]

During COVID-19 treatment, the use of NSAIDs was very common. In addition to increasing the risk of thrombosis, NSAIDs (including ibuprofen) may also reduce host defense capability during infection.[6] On the one hand, NSAIDs may mask the early symptoms of the disease, leading to delays in diagnosis and treatment; on the other hand, NSAIDs can inhibit the immune response of the body through a variety of ways, leading to disease progression.[7] Even though some studies have shown that NSAIDs may be beneficial to patients with viral infection, it is still necessary to use them with great caution.

In the clinical diagnosis and treatment of novel coronavirus patients, more attention should be paid to the use and management of NSAIDs. Clinicians need to determine whether patients have a history of gastrointestinal ulcers and cardiovascular events, and avoid overdose or long-term medication. Now, more research is really needed to determine the effects of NSAIDs on the incidence of venous thromboembolism and viral infection in novel coronavirus patients.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

All the authors participated in the coordination and drafting of the text. All the authors read and approved the final manuscript.

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