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

Anticoagulation in COVID-19: not strong for too long?

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Several randomised controlled trials are currently underway to evaluate the value of increasing the dose of prophylactic anticoagulation in critically ill COVID-19 patients, either at an intermediate or therapeutic dose, in order to decrease thrombotic complications, organ failure and possibly reduce mortality in these patients.

INSPIRATION investigators recently published the results of the first large-scale randomised controlled trial evaluating the benefit of intermediate dose prophylactic anticoagulation in critically ill COVID-19 patients [1]. Their results showed that intermediate-dose prophylactic anticoagulation did not significantly reduce their composite endpoints (30-day mortality, need for extracorporeal membrane oxygenation (ECMO), thrombotic events) and therefore do not support the routine use of an increased dose of anticoagulation in unselected critically ill COVID-19 patients.

However, there are several critical points that need to be highlighted in this trial as they could limit the potential impact of these results on our daily clinical practice.

First, composite end points must be taken with caution because they combine different elements that are not necessarily all related to the same end goal. The inclusion of the need for ECMO in the primary endpoint of this study is questionable, because the link between anticoagulation and the need for ECMO is not clearly established. A similar comment can be made about the multiplatform randomised trial (ATTAC, REMAP-CAP, and ACTIV-4) on therapeutic anticoagulation. The choice of 21-day organ support free days as the primary end point is questionable because organ failure in COVID-19 is multifactorial and the direct effect of anticoagulation on this end point may be diluted, which could lead to a false conclusion of futility.

Only about 20% of the included patients underwent invasive ventilation, and the length of stay in the ICU was short, with a median of 6 [2–11] days, which is very different from the data observed in other ICU cohorts [2]. In addition, the mortality rate was strikingly high (42% of the study population), raising the question of a possible mismatch between needs and availability of ICU resources.

The rate of thrombotic events in the standard-dose prophylactic anticoagulation group was very low, at 3.5%, which differed greatly from previously published studies on critically ill patients [3–5] (*e.g.*, 27.9% (95% CI 22.1–34.1) in the recent meta-analysis by Jimenez et al. [6]), one may wonder if all thrombotic events in the INSPIRATION trial were diagnosed. This low rate of thrombotic events could have led to an underestimation of the benefit of intermediate-dose prophylactic anticoagulation.

The final concern regarding the results of the INSPIRATION trial results is the relatively high rate of bleeding in the intermediate dose group (6.2% of bleeding events) where patients were exposed to the assigned treatment for 20 [7–30] days. Several studies have reported a significant risk of bleeding in patients with COVID-19, particularly in the most severe patients and in those on enhanced-dose anticoagulation [6–9]. The longitudinal evaluation of haemostatic biomarkers showed that the procoagulant status of COVID-19 patients seems to be particularly marked during the first few days of hospitalisation and then gradually decreases to normal levels [10]. This raises the question of the temporal relationship between thrombosis and the bleeding risk, and whether these risks are concomitant or staggered in time.

We performed a literature review of all studies on the thrombotic and bleeding risk associated with COVID-19. On the 5th of March 2021, we searched MEDLINE and looked for studies on COVID-19 written in English that reported a median (or mean) duration and interquartile range – IQR - (or standard deviation - SD) between hospital or ICU admission and thrombotic or bleeding events. Case series with the time between admission and the event available were also included.

Twenty-two studies were identified, 13 of which specifically focusing on critically ill patients [3,7–9,11–28]. Thirteen studies reported only the time from admission to thrombotic events [3,11–16,18–21,24], four studies reported only the time from admission to bleeding events [8,25–27] and five studies reported both [7,9,22,23,28]. One study analysed two different waves of patients [15]. All but two studies reported this delay as the median and interquartile range. Fig. 1 shows distribution of the median (or mean) and the IQR (or SD) of time from admission to event in each study. Pooled medians were estimated using a quantile estimation method. The results of the meta-analysis showed that thrombotic events occurred 7.0 [5.9–8.2] days after admission (713 events) while bleeding events occurred 11.4 [8.6–14.1] days after admission (163 events).

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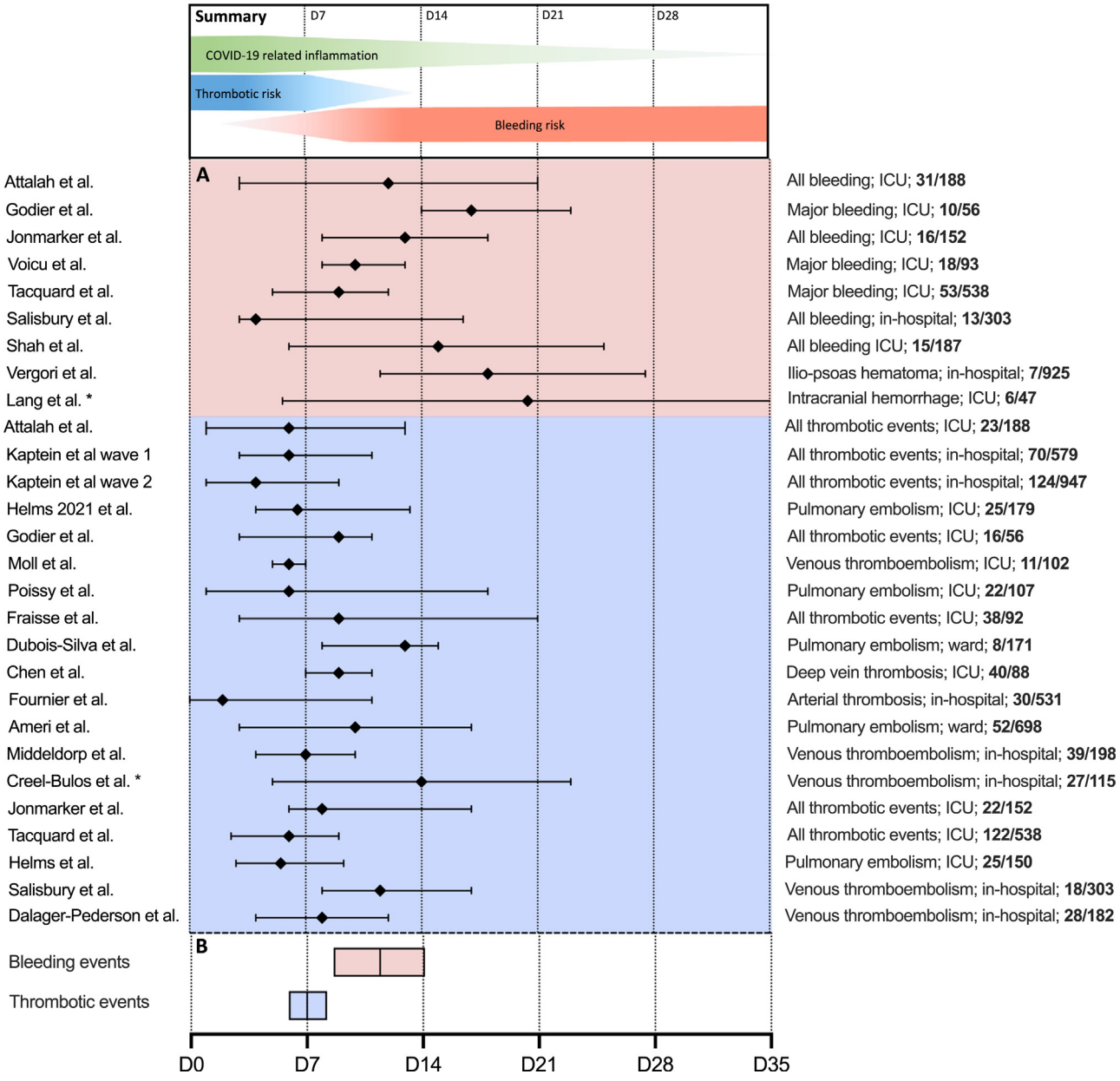

Fig. 1. (A) Distribution of medians and interquartile ranges for duration between admission (hospital/ICU) and events (thrombosis in blue, bleeding in red) based on selected studies. For each study, details on the type and location of recorded events and the number of events/number of patients included are shown in the right-hand column. (B) Results of the meta-analysis using a quantile estimation method. Data are expressed as median and interquartile range. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).
*For these two studies, the data are expressed as a mean (standard deviation). These studies were excluded from further analysis in B.

Our results confirm that thrombotic and bleeding events are staggered in time, with thrombotic events occurring primarily in the first ten days after admission. Although some events were reported within the first few days of hospitalisation, bleeding events occurred most often late. These findings are consistent with previously published biological data [10]. Hardy et al. observed an increase in thrombin generation associated with a decrease in overall fibrinolytic capacity during the first week of hospitalisation, resulting in a strong procoagulant state. After this early stage of the disease, inflammatory markers progressively decreased, as did D-dimer levels in survivors, probably in relation to a decrease in the intensity of processes leading to microthrombosis.

Data on bleeding events are difficult to interpret correctly: (i) some bleeding is spontaneous while others are related to invasive techniques (central venous or arterial catheters, renal replacement therapy, ECMO) ; (ii) some bleeding is directly related to anticoagulation (*e.g.*, overdose) while others would have occurred independently of anticoagulation status; (iii) some patients require anticoagulation anyway for identified medical reasons (identified thrombosis, atrial fibrillation, extracorporeal circuits, etc.). Thus, data on bleeding events should be analysed not only by considering all bleeding events but also by taking into account the imputability between anticoagulation exposure and bleeding events.

These results raise the question of the optimal duration of anticoagulation (therapeutic or intermediate dose) in COVID-19 patients. Increased-dose prophylactic anticoagulation, if indicated, should be initiated very early in the course of the disease, when the thrombotic risk is high. Thereafter, in patients without a clear indication for curative anticoagulation, the dose of anticoagulation

should probably be gradually reduced to a standard prophylactic dose to limit the risk of bleeding, and possibly monitored by inflammatory or coagulation markers.

Conflicts of interest

CT, AM, A Godon and SS have no conflicts of interest to declare.

YG declares honoraria and travel fees from Aguettant, Bayer-Healthcare, Bristol-Myers-Squibb/Pfizer, CSL Behring, Octapharma, Roche, Sanofi, and Sobi.

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