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Thrombosis Research

Letter to the Editors-in-Chief

Thromboprophylaxis in COVID-19: Early initiation might be as important as optimal dosing

Letter to the Editor

Moll et al. recently published a retrospective analysis of COVID-19 patients admitted to intensive care unit (ICU) from a single tertiary-care academic hospital showing that there was no significant difference in death and venous thromboembolism events (VTE) in those on intermediate compared to standard dose thromboprophylaxis [1]. Despite the meticulous statistical approach of the authors (propensity score-matched methodology), their findings should be interpreted by taking into consideration the retrospective nature of the study, as well as the lack of details on thromboprophylaxis, especially time of initiation, before the ICU admission [1].

Severe COVID-19 is associated with increased VTE risk and current guidelines recommend thromboprophylaxis in all hospitalized patients [2–4]. The source of the evidence regarding the latter recommendation is derived from observational studies. However, the guidance on the optimal dosing of thromboprophylaxis is inconsistent and mainly based on expert opinion. It has been suggested that a dose-dependent anticoagulant benefit might be evident especially in high VTE risk patients [2–5]. Thus, several experts recommend intermediate intensity of thromboprophylaxis in high VTE risk patients and after individualized assessment of the VTE/bleeding risk [2–4].

Only recently, important evidence from randomized trials regarding the effect of different doses of anticoagulation in COVID-19 became available. The INSPIRATION trial compared intermediate versus standard dose thromboprophylaxis in ICU COVID-19 patients and failed to show a significant difference in the primary composite efficacy outcome or its major components, including all-cause mortality and VTE [6]. This was the first published randomized trial to address this important issue and provide evidence against routine empirical use of intermediate dose anticoagulation in unselected ICU COVID-19 patients. However, these findings should be interpreted in light of some methodological issues. First, the median duration of symptoms prior to hospitalization was 7 days and that of hospitalization before randomization was 4 days [6]. Details regarding the anticoagulation regimen of these patients before randomization were not reported and might have played a crucial role. Low molecular weight heparin exhibits not only anticoagulant, but also anti-inflammatory effects and early administration might be as well

important [7]. It might be argued that the benefit of a more aggressive strategy is obtained before the advent of critical disease and the establishment of irreversible pathology in lung vessels. Second, the rate of VTE events was 3.4% which was significantly lower compared to that reported in the literature, especially with systematic assessment/screening and in critically ill patients (ICU) [8,9]. As acknowledged by the authors, this might have been attributed to the lack of systematic routine screening or the underdiagnosis of less severe forms of VTE which did not translate to increased mortality [6]. However, VTE represents the most relevant endpoint regarding the anticoagulation therapy. Heterogeneity in the VTE phenotypes across different stages and types of COVID-19 might be an important confounding factor in such studies. Interestingly, in the INSPIRATION trial, pulmonary embolism was confirmed in 45% and 18% of the assessments in the standard and intermediate group respectively [6].

In addition to the INSPIRATION trial, preliminary but not peer-reviewed results were available from the interim analysis of a multi-platform with combined data from three randomized, open-label controlled trials (REMAP-CAP, ATTACC, and ACTIV4) regarding the safety and efficacy of therapeutic dose versus standard dose of thromboprophylaxis in 2895 hospitalized patients with moderate or severe disease (61% and 39% respectively) [10]. It should be mentioned that the randomization was performed within 72 h of admission. Interestingly, therapeutic dosing compared to standard thromboprophylaxis was associated with lower odds ratio for the primary outcome (organ support-free days) in patients with severe disease. In fact, a recommendation was given for discontinuation of enrolling patients, as the pre-specified futility stopping boundary for therapeutic anticoagulation had been achieved and the probability that therapeutic dosing was harmful compared to standard thromboprophylaxis was 98.5%. Moreover, there was a numeric increase in major bleeding events in the therapeutic arm, although the rate was in the predicted range for critically ill patients (3.7%). On the contrary, in patients with moderate disease, therapeutic dosing was more likely to improve the primary outcome, as well as morbidity and mortality components of the primary endpoint, whereas bleeding events were rare.

In conclusion, available data from randomized trials open the road for high-quality evidence regarding the optimal dosing of

thromboprophylaxis in patients with COVID-19. However, it seems that apart from the severity of the disease another important factor is the optimal timing of thromboprophylaxis. According to the promising experience with intermediate dose anticoagulation in hospitalized COVID-19 patients in the medical ward [7], we consider that the beneficial effects of such a strategy might be expected when administered before the development of critical illness. Earlier applications in high VTE patients, in the outpatient setting, warrant research attention.

CRediT authorship contribution statement

AK, GP, ED and KGK performed the research and drafted the manuscript.
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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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