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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Commentary

Thromboprophylaxis for medical inpatients with coronavirus disease 2019

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Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and the disease it causes, coronavirus disease 2019 (COVID-19), have put health-care and financial systems worldwide under tremendous pressure. At present, COVID-19 has afflicted millions globally and the death toll is rapidly rising. Awaiting the development of effective and safe vaccines and antiviral therapies, researchers are struggling to better understand the disease and optimize supportive treatment.

Individuals hospitalized with COVID-19 are often immobilized with serious respiratory failure and have a remarkable procoagulant biochemical profile with elevated D-dimer levels and hyperinflammation. This has raised concern about increased risk of venous thromboembolism (VTE). Only a few studies specifically address this complication in COVID-19 and risk estimates range from 1% in ward patients to 35% in intensive care units [1,2]. However, most of these studies are hampered by small sample sizes in selected study populations treated in intensive care units at tertiary-care facilities with very short and incomplete follow up. Moreover, some of the studies also include VTEs with uncertain significance for risk of death, such as asymptomatic VTEs diagnosed by screening and subsegmental pulmonary embolisms. In conjunction with high mortality in previous studies, cumulative incidence findings of VTE may be inflated. Still, recent VTE estimates have garnered considerable media attention and are currently extrapolated to all hospitalized individuals with COVID-19, while data on potential major bleeding complications and risk–benefit of anticoagulant therapy in COVID-19 are sparse.

Two recent retrospective observational studies have evaluated the effect of anticoagulation (AC) on mortality in individuals hospitalized with COVID-19.

Paranjpe et al. studied 2773 individuals hospitalized within the Mount Sinai Health System, New York City [3]. Overall, 786 individuals received treatment-dose AC during their hospital course and median time from admission to AC initiation was 2 days (interquartile range 0–5 days). Study participants were followed from hospital admission (T0) until discharge, death, or end of study. The authors compared mortality among AC users versus non-users and found similar mortality (22.5% versus 22.8%). In a sub-analysis among individuals receiving mechanical ventilation, AC was associated with greater benefit (mortality 29.1% versus 67.2%). However, as T0 was date of admission and AC initiation was delayed, the authors introduced immortal person-time among AC users, thereby conferring an artificial survival advantage to the AC group. Immortal time bias (or survivor treatment selection bias) can occur in survival analyses where patients who live longer are more likely to receive treatment than patients who suffer an early death [4]. As an example, Kaplan–Meier survival curves in the paper by Paranjpe et al. give the false illusion of improved survival among AC users when in fact ~25% of AC users were not at risk of death until after day 5 and all non-users were at risk from day 0.

A frequently cited study by Tang et al. examined the effect of AC, primarily enoxaparin 40–60 mg daily, on 28-day mortality in 449 hospitalized individuals with severe COVID-19 [5]. Exclusion criteria included hospitalization for <7 days and the AC group was defined as receiving AC for ≥7 days. In the primary analysis, the authors found no effect of AC on mortality (30.3% versus 29.7%). However, among individuals with sepsis-induced coagulopathy and in those with more than six-fold elevated D-dimer, mortality was lower among the individuals treated with AC. The study by Tang et al. is also at risk of immortal time bias unless everyone in the AC group initiated therapy on the day of admission, which is unclear. Of greater relevance, neither VTE events nor bleeding risk was detailed and the generalizability was limited on account of the inclusion criteria, meaning that just 449 of 1786 screened patients

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were included in the analysis. The authors sensibly conclude that AC may not benefit unselected COVID-19 patients, but should be considered in certain high-risk patients, for example those with sepsis-induced coagulopathy and markedly elevated D-dimer.

Of note, recent evidence from Italy suggests that deep venous thrombosis is an infrequent occurrence during COVID-19 and that filling defects on computed tomography angiography may be related to local pulmonary thrombi, and not to embolism, in which case heparin therapy is of questionable benefit [6].

Heparin therapy and thromboprophylaxis with heparin for individuals with infection and medical inpatients in general remains controversial [7,8]. Previous studies on thromboprophylaxis with low-molecular-weight heparin (LMWH) have found limited effect on clinically relevant outcomes in hospitalized medical patients with a number-needed-to-treat of approximately 250 to prevent symptomatic pulmonary embolism and a similar number-needed-to-harm in the form of major bleeding, resulting in little or no net benefit [7]. Moreover, thromboprophylaxis with LMWH has never been shown to prevent death in hospitalized medical patients including those with severe infection [9]. Prolonged thromboprophylaxis has been considered of potential benefit, but AC extended beyond hospital discharge for medical illness was not found to have an effect on risk for symptomatic VTE or death [10].

Guidelines on thromboprophylaxis and AC therapy in COVID-19 are rapidly emerging with differing recommendations. A recent position paper endorsed by several international societies suggested VTE risk stratification for all individuals with COVID-19 and pharmacological VTE prophylaxis in many cases [11]. The International Society for Thrombosis and Haemostasis has pushed the case for thromboprophylaxis with LMWH to all patients hospitalized with COVID-19 [12]. Other authorities have suggested intermediate or therapeutic doses of LMWH for hospitalized patients and extended VTE prophylaxis for up to 45 days post-discharge [11].

Although the COVID-19 pandemic confers a strong incentive on the medical community to act, we must remain adherent to evidence-based medicine and ethical considerations before changing guidelines from common practice, especially in prophylactic treatment of individuals. Consequently, there is a need for high-quality observational studies to better detail the incidence of VTE and bleeding events in individuals with COVID-19. There is also a need for information on risk factors and development of validated VTE and bleeding risk prediction models to identify those individuals with COVID who might benefit most from thromboprophylaxis. Even more importantly, we need well-conducted clinical trials on thromboprophylaxis in COVID-19 that explore clinically meaningful outcomes including symptomatic VTE, major bleeding events and death. These studies are needed to ensure that we do not harm patients, and may inform physicians and policy-makers of the most efficient use of already heavily strained health-care resources.

Transparency declaration

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Author contributions

MDP is lead and corresponding author. Conceptualization and investigation were by MDP and JB. The original draft was written by MDP and both MDP and JB contributed to reviewing and editing.

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