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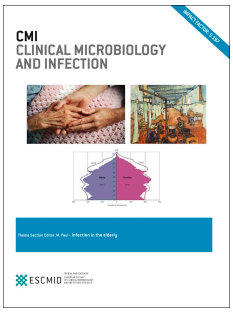

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Thromboprophylaxis for medical inpatients with COVID-19

Michael Dalager-Pedersen[1,2], Jacob Bodilsen[1,2]

[1]Department of Infectious Diseases, Aalborg University Hospital, Mølleparkvej 4, 9000 Aalborg, Denmark
[2]Department of Clinical Medicine, Aalborg University, Søndre Skovvej 15, 9000 Aalborg, Denmark

Comment.

Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) and the disease it causes, Corona Virus Disease 2019 (COVID-19), has put healthcare 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 optimise supportive treatment.

Patients hospitalised with COVID-19 are often immobilised with serious respiratory failure and have a remarkable pro-coagulant biochemical profile with elevated D-dimer levels and hyperinflammation. This has raised concern about increased risk of venous thromboembolism (VTE). Thus far, 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 (ICU) [1,2]. However, the majority of these studies are hampered by small sample sizes in selected study populations treated in ICUs at tertiary care facilities with very short and incomplete follow-up. Moreover, some of the studies also include VTEs of uncertain significance on 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 hospitalised COVID-19 patients 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 patients hospitalised with COVID-19.

Paranjpe et al. studied 2,773 patients hospitalised within the Mount Sinai Health System, New York City [3]. Overall, 786 patients received treatment-dose AC during their hospital course and median time from admission to AC initiation was 2 days (IQR 0-5). Study subjects 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 patients 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 hospitalised patients with severe COVID-19 [5]. Exclusion criteria included hospitalisation for <7 days and 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% vs. 29.7%). However, among patients with sepsis induced coagulopathy (SIC) and in those with more than 6-fold elevated D-dimer, mortality was lower among patients 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 day of admission, which is unclear. Of greater relevance, neither VTE events nor bleeding risk was detailed and the generalisability was limited on account of the inclusion criteria meaning that just 449 of 1786 screened patients 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, *e.g.* those with SIC and markedly elevated D-dimer.

Of note, recent evidence from Italy suggest 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 embolism, in which case heparin therapy is of questionable benefit [6].

Heparin therapy and thromboprophylaxis with heparin for patients 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 hospitalised 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 hospitalised medical patients including those with severe infection [9]. Prolonged thromboprophylaxis has been considered of potential benefit, but anticoagulation extended beyond hospital discharge for medical illness was not found to have an effect on risk for symptomatic VTE or death [10].

Still, guidelines on thromboprophylaxis and anticoagulant 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 COVID-19 patients and pharmacological VTE prophylaxis in many cases [11]. The International Society for Thrombosis and Haemostasis have pushed the case for thromboprophylaxis with LMWH to all patients hospitalised with COVID-19 [12]. Other authorities have suggested intermediate or therapeutic doses of LMWH for hospitalised patients and extended VTE prophylaxis for up to 45 days post-discharge [11].

Although the COVID-19 pandemic infers a strong incentive in 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 patients. Consequently, there is a need for high-quality observational studies to better detail the incidence of VTE and bleeding events in COVID-19 patients. There is also a need for information on risk factors and development of validated VTE and bleeding risk prediction models to identify those COVID patients 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 healthcare resources.

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