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Weekly Journal Scan

Therapeutic-dose heparin should integrate the standard of care of moderately ill patients with COVID-19 admitted to hospital

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Comment on 'Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with covid-19 admitted to hospital: RAPID randomised clinical trial' published in the *British Medical Journal* (https://doi.org/10.1136/bmj.n240).

Key Points

- The Therapeutic Anticoagulation versus Standard Care as a Rapid Response to the COVID-19 Pandemic (RAPID) was an investigator-initiated, randomised, controlled, adaptive, open-label, international trial.[1] The trial examined the benefits of administering therapeutic-dose versus prophylactic-dose heparin [either unfractionated or low molecular weight (LMWH)] to moderately ill patients admitted to hospital ward level of care for COVID-19 (not already mechanically ventilated, and not imminently requiring mechanical ventilation or critical care) with laboratory-confirmed SARS-CoV-2 infection and elevated D-dimer levels ($\geq$2 times the upper limit of normal, or above the upper limit of normal in the presence of an oxygen saturation $\leq$93% on room air) within the first five days of admission.
- The intention-to-treat analysis included 465 patients (mean age, 60 years; 57% men; mean body mass index (BMI), 30 kg/m^2) enrolled at 28 hospital sites in six countries and randomly assigned to receive therapeutic full-dose heparin (n = 228; mean treatment duration, 6.5 days; LMWH in 98%) or prophylactic low-dose heparin (n = 237; mean treatment duration, 6.3 days; LMWH in 94%) between 29 May 2020 and 12 April 2021.
- The primary outcome was a composite of death, invasive mechanical ventilation, non-invasive mechanical ventilation, or intensive care unit (ICU) admission, assessed up to 28 days. The secondary outcomes included all-cause death, the composite of all-cause death or any mechanical ventilation, and venous thromboembolism. The trial also assessed major bleeding as defined by the International Society on Thrombosis and Haemostasis, as a safety outcome. Outcomes were blindly adjudicated.
- At 28 days, the primary outcome occurred in 37 (16%) patients in the therapeutic arm and in 52 (22%) in the prophylactic arm [odds ratio (OR) 0.69; 95% confidence interval (CI), 0.43-1.1; P = 0.12]. Four patients (1.8%) in the therapeutic arm died versus 18 patients (7.6%) in the prophylactic arm (OR 0.22; 95% CI, 0.07–0.65; P = 0.006). Major bleeding occurred in 2 patients (0.9%) in therapeutic arm and in 4 (1.7%) in the prophylactic arm. No fatal bleeding events or intracranial haemorrhage occurred.

Comment

Endothelial injury and microvascular/macrovascular thrombosis, driven by an excessive inflammatory response,[2,3] are common pathophysiological features of COVID-19, affecting the severity of illness, the progression of respiratory failure and pulmonary fibrosis, and mortality. A variety of antithrombotic agents, doses, and durations of therapy are being assessed in ongoing randomised controlled trials across the spectrum of disease severity.[4] However, the optimal antithrombotic regimen(s) remain unknown. Current treatment guidelines recommend using prophylactic-dose heparin on hospital admission of COVID 19 patients.[5,6]

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In the RAPID trial,[1] among moderately ill hospitalized patients with elevated D-dimer levels (as an indicator of thrombo-inflammation), therapeutic intensity anticoagulation with heparin/LMWH was not significantly associated with a reduction in the primary outcome but the odds of all-cause death at 28 days was decreased as compared to prophylactic heparin, with a low risk for major bleeding. The early initiation of therapeutic heparin could reduce the thrombo-inflammatory process and risk for critical illness or death due to its anticoagulant, anti-inflammatory and potential anti-viral effects.[7] This might also help explain why heparin was effective in non-ICU level patients, whereas other antithrombotic agents, including direct oral anticoagulants, were not. Therapeutic-dose rivaroxaban, for example, failed to show a benefit in hospitalized patients.[8]

The unexpectedly large effect size for the secondary outcome of mortality should be viewed within the context of other randomized trials. In particular, the data of multiplatform trial integrating ATTACC, ACTIV-4a, and REMAP-CAP have been recently reported in 2 studies investigating therapeutic-dose anticoagulation compared with usual-care thromboprophylaxis in hospitalized patients with COVID-19.[9,10] In non-critically ill patients hospitalized with COVID-19, therapeutic-dose heparin increased the probability of survival to hospital discharge and reduced the need for cardiovascular or respiratory organ support compared with usual-care thromboprophylaxis (adjusted OR 1.27; 95% CI, 1.03–1.58).[9] However, therapeutic-dose heparin was found to have no benefit in patients with severe COVID-19, and was associated with a higher risk of bleeding.[10]

Limitations of RAPID include its open-label design, although relevant outcomes were blindly adjudicated by an independent clinical events committee. The observed primary outcome event rate was much lower than expected (22% vs. 50%), with no adjustment of sample size at the second interim analysis; therefore the trial was largely underpowered to detect as statistically significant a 30% reduction in risk.[1] Moreover, only 12% of screened patients were randomized, limiting. generalizability of the findings. Despite these limitations, the results of the RAPID trial,[1] in concert with the ATTACC, ACTIV-4a, and REMAP-CAP multiplatform trial,[9] provide a reasonably high probability of clinically meaningful benefits of therapeutic heparin in moderately ill COVID-19 patients, thus integrating the standard of care in this setting.

The role of antiplatelet and other pharmacological treatments that could modulate the prothrombotic state of hospitalized COVID-19 patients remains to be established. The phenotypic characterization of moderate and severe disease should be better defined, particularly when it comes to oxygen requirements. The transition of patients between non-ICU and ICU settings represents a time when the intensity of anticoagulation therapy needs to be revisited. Finally, it remains to be determined whether a prolonged course of anticoagulation is required after hospital discharge, particularly for patients who have been hospitalized with a more severe clinical course of COVID-19, or who have persistently elevated D-dimer levels.

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