Correspondence

Is Rivaroxaban Superior to Enoxaparin for Thromboprophylaxis in Hospitalized Patients of COVID-19?

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Sir,

We read with great interest the article titled “Oral Rivaroxaban in the Prophylaxis of COVID-19 Induced Coagulopathy” by Kumar et al.¹ We sincerely congratulate the authors for conducting a randomized clinical trial, especially during the COVID-19 pandemic. In this single-center, open-label, prospective, randomized, superiority trial, the efficacy of rivaroxaban as compared to enoxaparin for thromboprophylaxis in mild to moderate cases of COVID-19 was studied. The primary efficacy outcome occurred in 3.5% of patients in the rivaroxaban arm as compared to 14.2% of patients in the enoxaparin arm with a
hazard ratio of 0.207 (95% CI 0.069–0.621; \( p \) 0.005). The minimum required sample size calculated was 300, however, only 230 patients could be recruited resulting in an underpowered study. As the study was underpowered for the primary outcome itself, it was far more underpowered for the subgroup analysis which led to inconclusive results. The randomization was carried out using a computer-generated sequence, however, it is not clear if the allocation was concealed. Randomization prevents selection bias and controls for all known and unknown confounding variables. Failure to conceal allocation negates all the beneficial effects of randomization and introduces a high risk of bias.\(^2\) The open-label design further amplifies bias in the above study. An intention to treat analysis has been traditionally described as “once randomized always analyzed.” All the patients that are randomized into a study arm must be included in the final analysis and analyzed as per the initial allocation irrespective of whether they received the treatment or are lost to follow-up. It preserves the benefit of randomization, minimizes type I error, and avoids attrition bias. In the above study only those patients who received at least a single dose of the drug after randomization were included in the analysis. The exclusion of participants post-randomization introduces bias and compromises randomization. Though used in many studies, we should be cautious in interpreting results of a modified intention to treat analysis.\(^3\) It is unclear if the consent was taken pre- or post-randomization. The methodology section states patients were randomized after taking consent however figure 1 states that two patients refused consent after randomization into the treatment arm. It is unclear from the study: how missing data were addressed. The way in which missing data is addressed like the use of single imputation methods–last observation carried forward, best observation carried forward, etc. can introduce bias. Ideally, the authors should use several approaches to address missing data and carry out a sensitivity analysis so that the impact of missing data on effect estimates is known.\(^4\) The RECOVERY trial and ACTIV-4a trial have not shown any beneficial effect of adding antiplatelet therapy to standard thromboprophylaxis or anticoagulant therapy.\(^5,6\)

Despite the shortcomings, the study raises an important signal that rivaroxaban can be used instead of enoxaparin for thromboprophylaxis in patients of COVID-19 and provides a background on which future studies with larger sample size and better design can be planned.

References