Response to letter by Gratz et al

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We thank Dr Gratz and colleagues for their comments [1] on the heparin thromboprophylaxis section of our Challenging Dogma article [2]. The newly published systematic review/meta-analysis by Fernando *et al* does include more recent studies assessing thromboprophylaxis strategies [3]. However, none of these compared heparin against placebo, reinforcing the dogma that *assumes* an impact from this intervention. Diagnosis of deep venous thrombosis was generally ultrasonographic; clinically identifiable thrombosis was rarely reported. As with the few older placebo-controlled trials, no impact was seen on either the very low incidence of recognized pulmonary embolism nor mortality. An analogy can be made to air travel; DVT risk is significantly increased, especially with longer flights, yet major sequelae are rare despite few passengers taking specific preventative measures [4].

Of note, Fernando *et al* highlighted the poor quality of evidence for preventing pulmonary embolism and even acknowledged that the data do not rule out the possibility of important harm [3]. Even with COVID-19 disease, where pulmonary thromboembolism was a prominent feature, a recent Cochrane review on the benefits of heparin thromboprophylaxis was plagued with uncertainty, with no clear signal on the benefits of higher over lower doses, nor even between use and non-use [5].

Dr Gratz and colleagues rightly make the point that achieving an optimal anti-Factor Xa (anti-FXa) range to reduce the risk of venous thromboembolism also represents an unproven dogma in itself. The utility of this particular biomarker remains a topic of debate among haematologists, and alternatives such as viscoelastic methods also remain unproven. However, at least anti-FXa is a functional assay representing a measure of drug activity rather than an empiric fixed-dose LMWH prophylaxis regimen which, as far as we can ascertain, has never been validated in a critically ill population. As we pointed out in our article [2], multiple studies report anti-FXa levels are below the desired range in many ICU patients – including those with COVID-19 disease - and to a far greater extent than general ward populations [2]. Dr Gratz and colleagues refer to their interesting, recently-published retrospective

study of 1352 critically ill patients who had anti-FXa levels measured between 2015-18 [6]. Despite many patients failing to achieve recommended anti-FXa thresholds, venous thromboembolism was documented in only 19 cases and they found with no relationship to anti-FXa levels. Four questions thus arise. As they note in their paper, anti-FXa thresholds protective of VTE still need to be determined for a critically ill population receiving prophylactic LMWH. The second is to find a superior alternative monitoring technique that can be readily employed to personalize dosing regimens that will impact on outcomes. The third question is to identify truly at-risk populations where LMWH could make a difference, and to spare low-risk patients the pain, cost and any unrecognized harm. The final question is to query whether a LMWH prophylactic strategy actually works in the first place, particularly so in the present era considering the many changes in fluid, sedation, mobilization and other practices that have occurred 20-30 years on from the initial low-evidence studies.

References

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