

Mortality benefits of thromboprophylaxis

We thank John Eikelboom for his comments. We investigated his concern and observed no significant change in treatment effects on venous thromboembolism or mortality after re-analysing studies according to the year of publication.¹ These results are illustrated by plotting the mean study-specific risk ratios sorted by year, together with robust locally weighted regression lines and 95% CIs (appendix p 1).

More broadly, we disagree with the conclusions drawn from the meta-analysis by Collins and colleagues,² and are concerned about its enduring effects on medical practice.³ Most of the trials included in this previous meta-analysis² had a significant risk of bias. Even though over 70 trials were included, only 31 were placebo-controlled, and of these, heparin neither reduced the incidence of fatal pulmonary embolisms, nor did it improve survival.

Additionally, the so-called one-step Peto method used by Collins and colleagues² has important limitations. This method cannot incorporate data from trials with no events (51 trials reported no fatal embolisms), and is asymptotically biased when study-stratum-specific odds ratio parameters are not constant and equal. Finally, the Peto method is biased when effect sizes are large.⁴

We are specifically concerned that statistical bias was introduced into the meta-analysis by Collins and colleagues² by the inclusion of two unblinded trials^{5,6} published in 1975. These trials had unprecedented effect sizes on fatal pulmonary embolism and mortality; the magnitude of which has never been seen before or since (appendix p 2). Without these two trials, the meta-analysis² would have shown no significant effects from perioperative heparin administration on the incidence of fatal embolism or

mortality.

Most trials included in the meta-analysis by Collins and colleagues² had results consistent with estimates from our meta-analysis,¹ and show that prevention of venous thromboembolism does not detectably influence mortality.¹ The two trials^{5,6} published in 1975 are clear outliers, both relative to contemporary trials in the previous meta-analysis² and to modern trials included in our meta-analysis.¹ For this reason, the results of these two trials^{5,6} should not continue to exert a disproportionate influence on medical practice.

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