

INVICTUS trial: unusual curve behavior and anticoagulant drug effects.

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To the Editor

The results of the INVICTUS trial are hard to understand on the basis of clinical and pathophysiological grounds. In this trial of anticoagulants, the incidence of bleeding was similar in the two treatment groups, with fewer fatal bleeding events in the rivaroxaban group than in the vitamin K antagonist group. Kaplan–Meier curves for death overlapped until month 20 after randomization and then diverged, with higher mortality in the rivaroxaban group than in the vitamin K antagonist group. Interestingly, curves for stroke or systemic embolism overlapped until much later (month 32), which suggests that stroke did not contribute to higher mortality. A sudden and steep change in the slope at that time resulted in increased risk of stroke with rivaroxaban (number needed to harm, 263 per year). Furthermore, the authors confirmed that the increase in mortality with rivaroxaban was not driven by a higher rate of embolism: “The difference in mortality was almost entirely due to lower rates of sudden cardiac death and of death due to mechanical or pump failure in the vitamin K antagonist group than in the rivaroxaban group.” These are end points for which anticoagulants have an unproven effect. Reasons for the highly unusual change in slope for the stroke curve, requiring specific statistical handling,¹ and the effect of anticoagulants on sudden death and pump failure remain to be explained.

References

1. Andersen PK, Perme MP. Pseudo-observations in survival analysis. *Stat Methods Med Res* 2010;19:71-99.