

Editorial Focus

Methodological issues affecting estimates of bleeding risks and consequences after venous thromboembolism

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Evidence-based treatment guidelines rely critically on reliable estimates of the risks and benefits of treatment. Further, application of guidelines to specific populations requires information on the way these risks vary according to patient characteristics and time after disease onset and treatment initiation. New information from the population-based Worcester Venous Thromboembolism Study (1) provides compelling evidence that most previous estimates of the risks of bleeding after venous thromboembolism (VTE) substantially underestimate this risk in some patients. Specifically, the 6% risk of bleeding within 30 days after diagnosis in residents of the Worcester metropolitan area is substantially larger than bleeding risks seen among patients in randomised trials (2), and also more than twice the 90-day risk of bleeding after initiation of anticoagulant therapy in the RIETE registry (3). The size of the Worcester study excludes chance as an explanation for these differences, and the definition of bleeding outcomes precludes inflation of the estimate by inclusion of minor bleeds. Differences in study inclusion criteria are the most likely explanation for the heterogeneity in bleeding risks across studies. In particular, the Worcester study included many patients near death as well as complicated, actively bleeding patients who would not be included in randomised trials or registry studies drawing from anticoagulation clinics.

Population selection

Unbiased estimates of treatment effects require randomised evidence. However, in the design of randomised trials investigators often have to make trade-offs between generalisability and validity. In order to obtain a valid estimate of a treatment effect among patients who maintain adherence to study therapy, eligibility criteria exclude potential subjects who are unlikely to survive or to adhere to therapy for the duration of the trial. Because adherence and commitment are difficult to measure, a run-in period is

often used to better identify participants who will maintain a long-term commitment to randomised treatment. This strategy can enhance the validity of the trial, but it reduces the generalizability of estimates of absolute risk within treatment groups (4). Further, if risk declines by time after an index event, delayed randomization also leads to lower observed rates of adverse events.

Estimates of bleeding risk based on registries typically find higher risks than those obtained from randomised trials, but registries also usually impose some eligibility criteria. For example, the RIETE registry excluded patients enrolled in randomized trials with a blinded treatment and those not expected to be available for three-month follow-up.

Time-varying risks

The risk of bleeding is highest at the time of VTE onset due to both the many active comorbid conditions that trigger VTE as well as the immediate response to anticoagulation (2). The findings of the Worcester Venous Thromboembolism Study further quantify the magnitude of the early risk. Just over half (115 of 228 cases) of the patients who bled during the three-year follow-up period, had incident bleeding within 30 days of their VTE. For adverse events with such highly variable risks by time, care is needed to quantify risk by time interval. It is unclear whether risk factors associated with early bleeding after VTE are the same as those related to later bleeding. Further, studies designed to quantify this risk among all VTE cases need to pay particular attention to inclusion of the most impaired patients from the time of VTE onset.

The role of prior bleeding

Several previous studies have found that prior bleeding is the best predictor of bleeding after VTE (2, 3). A challenge to the de-

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sign of the Worcester Venous Thromboembolism Study based on retrospective review of hospital records relates to the potential difficulty in determination of the time of onset of bleeding relative to the occurrence of VTE. While the study identified important determinants of bleeding risk including impaired renal function and trauma, detailed measures of prior bleeding were not considered. Study designs to distinguish the temporal sequence of bleeding and VTE in patients with multiple other illnesses are needed.

Competing risks

Results of the Worcester Venous Thromboembolism Study also highlight the high prevalence of comorbid conditions in patients with VTE and the substantial death rates and rates of recurrence in these patients. The death rates observed in this Worcester study are quite consistent with those from the earlier, population-

based Worcester DVT Study which reported a 12% in-hospital case fatality rate in VTE patients and that 30% of patients who were discharged alive later died within three years (5). In the setting of high rates of the competing risk of death, estimates of the risk of bleeding need to account for this censoring and other losses to follow-up (6, 7). Also, in the presence of high in-hospital death rates, studies that enroll patients after discharge need to acknowledge the differential exclusion of the frailest patients.

Conclusion

It is very likely that the high absolute risk of bleeding found in the Worcester Venous Thromboembolism Study is attributable to the inclusion of a substantial number of frail patients, many near death, who are typically excluded from randomised trials and registry studies. Additional studies seem warranted to clarify optimal treatment strategies in such patients.

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