Major Bleeding Risks Are Associated with Long-Term Oral Anticoagulation for Venous Thromboembolism

Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. Ann Intern Med 2003;139:893–900.

Study Overview

Objective. To determine a reliable estimate of the clinical impact of major bleeding complications of long-term oral anticoagulation for venous thromboembolism.

Design. Meta-analysis of 33 randomized controlled trials and prospective cohort studies.

Study selection. Randomized controlled trials and prospective cohort studies of warfarin or warfarin derivatives were gathered from English language MEDLINE index, Cochrane controlled trial registry, topic experts, and reference lists. Analyzed studies investigated the treatment of venous thromboembolism with oral anticoagulation therapy of greater than 3 months with a target international normalized ratio (INR) of 2.0–3.0 and with reported outcomes of major bleeding and death. Two reviewers extracted data on the number of major and intracranial bleeds and whether these events were fatal.

Main results. Data on 4374 patient-years of oral anticoagulant therapy were extracted from 33 studies. Among all patients, major bleeding occurred at a rate of 7.22 per 100 patient-years (95% confidence interval [CI], 7.19–7.24), fatal bleeding occurred at a rate of 1.31 per 100 patient-years (95% CI, 1.30–1.32), and the rate of intracranial bleeding was 1.15 per 100 patient years (95% CI, 1.14–1.16). Following the initial 3 months of anticoagulation, the rate of major bleeding was 2.74 per 100 patient-years (95% CI, 2.71–2.77), the rate of fatal bleeding was 0.63 per 100 patient-years (95% CI, 0.61–0.65), and the rate of intracranial bleeding was 0.65 per 100 patient-years (95% CI, 0.63–0.68).

Conclusion. Major bleeding complications of warfarin therapy in venous thromboembolism are frequent and severe. Physicians should consider these risks when deciding whether to begin extended oral anticoagulation on patients with venous thromboembolism.

Commentary

The use of oral anticoagulation for prevention of recurrent venous thromboembolism (ie, deep venous thrombosis and pulmonary embolism) has been the subject of many high-quality clinical trials. A consensus recommendation has emerged, which is to treat patients for at least 3 months in the absence of contraindications to warfarin therapy. Consistently, the risk of recurrent thromboembolism without anticoagulation exceeds the risk of major bleeding complications. However, the estimates of major bleeding and subsequent deaths are imprecise in any one trial because of the lower frequency of these events. By pooling the bleeding risk data of every major prospective trial of warfarin therapy for thromboembolism since 1989, the authors have calculated a very precise estimate of oral anticoagulation risks. Two results are noteworthy: the absolute risk of major bleeding across the entire anticoagulation course is 7%, and approximately 1 in 7 of these episodes result in the most devastating complications—death or intracranial bleeding. Furthermore, the authors demonstrated that major bleeding complications are clustered toward the initiation of therapy suggesting that warfarin loading is particularly risky, or that patient susceptibility to bleeding is exposed early in the course of warfarin therapy. Additional research could explore this safety issue by calculating a "time to major bleeding episode." If devastating bleeds usually occur within a limited time frame, additional monitoring or quality improvement efforts could be targeted to this critical period.

The findings of this meta-analysis do not change the balance of risks and benefits that favor oral anticoagulation in the average patient. However, it helps physicians make difficult decisions in patients at higher than average risk for anticoagulant-related bleeding such as the elderly or patients with a history of gastrointestinal bleeding. What is not in question is the appropriate intensity of oral anticoagulation. Recent studies have shown a target INR of 1.5–2.0 increases recurrence rates of venous thromboembolism without significantly decreasing bleeding rates [1]. Likewise,

studies of target INRs greater than 3.0 show increased bleeding without added prophylaxis against thromboembolism.

Applications for Clinical Practice

Good evidence supports oral anticoagulation for patients with venous thromboembolism. However, both patient and physician should recognize the relatively high frequency and risk of major bleeding.

–Review by Josh F. Peterson, MD, MPH

References

1. Ridker PM, Goldhaber SZ, Danielson E, et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med 348:1425–34.