Reducing Risk of Bleeding in Anticoagulated Patients

Beyth RJ, Quinn L, Landefeld CS. A multicomponent intervention to prevent major bleeding complications in older patients receiving warfarin. A randomized controlled trial. Ann Intern Med 2000;133:687–95.

Study Overview

Objective. To implement a multicomponent program of warfarin management and to determine if it can affect the rate of major bleeding in elderly patients on warfarin.

Design. Randomized controlled trial. Analysis was by intention to treat.

Setting and participants. Patients hospitalized at the University Hospital in Cleveland, Ohio, who were older than 65 years, resided in Cuyahoga County, Ohio, and were scheduled to receive warfarin for 10 days or more. Recruitment of study subjects took place between September 1992 and October 1995. Patients were excluded if they had been treated with warfarin in the previous 6 months, did not speak English, were admitted from a nursing home, were enrolled in another clinical trial, were too ill or otherwise unable to give consent, or had a primary care physician who refused to participate in the study. Of the patients screened, 426 were eligible and 3161 were not enrolled because of exclusion criteria.

Patients were stratified according to their baseline risk of bleeding, as determined by the Outpatient Bleeding Risk Index [1]. This measure includes 4 independent risk factors: age older than 65 years, history of gastrointestinal bleeding, history of stroke, and 1 or more of 4 specific comorbid conditions (creatinine concentration greater than 1.5 mg/dL, hematocrit less than 30%, diabetes, and recent myocardial infarction). Patients with 1 or 2 risk factors for bleeding were considered at intermediate risk, while those who had 3 or more risk factors were considered at high risk. The frequency of major bleeding events at 6 months was estimated at 6% in the intermediate-risk group and 35% in the high-risk group.

Intervention. Patients were randomized to receive either usual care (n = 162) or the intervention treatment (n = 163). The intervention consisted of 2 main elements: (1) a guideline-based consultation, in which researchers provided specific recommendations concerning modifiable risk factors (eg, nonsteroidal anti-inflammatory drug use) and directed warfarin dosing and INR testing after hospital discharge; and (2) a patient education program, in which lay educators provided patients with 1-on-1 teaching on different aspects of anticoagulation, including warfarin use, and on self-monitoring prothrombin time using a portable monitor. Patients were instructed to check their INR 3 times a week during the first week after discharge, weekly for the remainder of the first month, and then monthly thereafter depending on their results. Shortly after discharge, patients were visited at home to ensure that they were using the monitor properly. Self-testing results were discussed with a coach, and adjustments to warfarin dosing were made over the telephone. After 6 months, management of warfarin treatment reverted back to the patients' personal physicians. At 1, 3, and 6 months, blinded and trained abstractors collected data on patient demographics as well as reasons for anticoagulation, complications, bleeding, and thromboembolic events. Every event was reviewed, and follow-up was completed for all patients.

Main outcome measures. The primary endpoint was the first major bleeding episode during the 6-month study period. Major bleeding was defined as a loss of at least 2 units of blood over a 1-week period or a life-threatening bleeding event, such as intracranial bleeding. Secondary outcomes were death and recurrent venous thromboembolic events at 6 months, major bleeding after 6 months, and control of anticoagulation therapy as assessed by INR measurements.

Main results. Baseline patient characteristics were similar in both study groups. The mean age of participants was 75 years (range, 65 to 94 years). The primary indication for warfarin treatment was venous thromboembolism in 38%, atrial fibrillation in 17%, cerebrovascular disease in 15%, heart prosthesis in 11%, and other indications in 19% of the study cohort. The baseline risk for bleeding was identified as intermediate in 85% of patients and high in 15% of patients.

Among the 163 patients randomized to the intervention, 132 participated and 31 declined the intervention. Of the total intervention cohort, 28% self-monitored their INR; 31% had a spouse, family member, or visiting nurse helping to monitor their prothrombin time; and 22% were monitored conventionally. The 31 patients who did not participate in the intervention were monitored by their personal physicians. A statistically higher risk of bleeding was reported in the conventional-treatment arm at 1, 3, and 6 months (7%, 12%, and 12%, respectively, versus 4.6%, 4.6%, and 5.6% in

the intervention group; $P = 0.048$). Eight major bleeding events occurred among intervention patients, 6 of which occurred in patients who declined the study intervention, while 17 events occurred among patients receiving conventional care. Half of the bleeding episodes (12 out of 25) occurred during hospitalization; of these, 3 occurred in the intervention group and 9 in the usual-care group. The most common site of bleeding was the gastrointestinal tract.

After 6 months, major bleeding occurred in 2 intervention-group patients and 3 usual-care patients, but the difference was not statistically significant ($P > 0.2$). More patients in the intervention group maintained a therapeutic INR (56%) during the study period than did those in the usual-care group (32%, $P < 0.001$). At 6 months, 21 patients in the intervention group had died versus 26 in the conventional-treatment group, although this difference was not statistically significant ($P > 0.2$). In addition, a nonsignificant trend toward a higher rate of recurrent thromboembolism was seen in the usual-care group (13%) versus the intervention group (8.6%, $P = 0.2$).

Conclusion

A multicomponent program of warfarin management reduces the risk of major bleeding in patients older than 65 years.

Commentary

This study by Beyth et al was well conducted. The authors addressed a problem that has been not well examined in the past: how to prevent bleeding in elderly patients who are anticoagulated. The risk of bleeding while on anticoagulation therapy is well known, yet data are somewhat conflicting as to whether age is an independent risk factor. In a study by Fihn and colleagues [2], no association between age and bleeding risk was observed except in patients older than 80 years; however, another study [3] demonstrated a relationship between these 2 factors, with rates of major bleeding at 1.7% per year for patients younger than 75 years and 4.2% per year for patients older than 75 years. Beyth and colleague's research suggests that a multicomponent comprehensive anticoagulation program is feasible and can significantly reduce the risk of bleeding in elderly patients. The strengths of the study include no differences in clinical or sociodemographic variables between study groups at enrollment, adequate follow-up, and a heterogeneous study population. The number of deaths in both groups was not significant; unfortunately, the authors do not provide any information on the causes of death aside from 1 patient who had a fatal hemorrhage. Few details were given on the practical aspects of implementing the anticoagulation management program (eg, potential difficulties in teaching self-management techniques, the time needed for adequate instruction), and there was no discussion regarding characteristics of the 31 patients who were enrolled in the intervention group but refused to participate. Furthermore, it is unclear why so many patients (101) out of the 426 eligible were not enrolled in the trial at all.

Applications for Clinical Practice

This study shows that reducing the risk of bleeding episodes is possible in anticoagulated patients who are older than 65 years. Overall, this intervention seems promising, but further studies will be necessary to address some important issues. A previous study reviewed in *The Lancet* showed that self-management of chronic oral anticoagulation is feasible [4]. In the future, larger studies that involve community settings and/or private practice should be conducted to determine if a program similar to the one used in the study can be implemented on a large scale. The cost-effectiveness of such a program should also be analyzed, along with the question of whether third-party payers will provide reimbursement.

References

1. Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. Am J Med 1998;105:91–9.
2. Fihn SD, Callahan CM, Martin DC, et al. The risk for and severity of bleeding complications in elderly patients treated with warfarin. The National Consortium of Anticoagulation Clinics. Ann Intern Med 1996;124:970–9.
3. Bleeding during antithrombotic therapy in patients with atrial fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators. Arch Intern Med 1996;156:409–16.
4. Cromheecke ME, Levi M, Colly LP, et al. Oral anticoagulation self-management and management by a specialist anticoagulation clinic: a randomised cross-over comparison. Lancet 2000;356:97–102.