Bleeding in Very Old Patients on Vitamin K Antagonist Therapy

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A common topic in clinical anticoagulation research used to be bleeding risk in old age. Times have changed, as well as the population of patients on anticoagulants, and the topic now is bleeding risk in very old patients. What is it about age that stimulates clinical investigators to launch studies of age and bleeding risk with vitamin K antagonist (VKA) therapy? First, the decision to initiate a VKA must always follow a consideration of the risks and benefits of therapy, regardless of age, and one should have a reasonable knowledge of the risk of bleeding at various age intervals. Second, the elderly, however defined, are the major users of oral anticoagulants because the 2 most common indications for such treatment, atrial fibrillation (AF) and venous thromboembolism, are most prevalent in the elderly. Third, a number of studies suggest that older individuals are at greater risk of bleeding than their younger counterparts with similar diagnoses.1–4 Fourth, the perception, real or not, that older age is associated with a greater risk of bleeding represents a barrier to the treatment of the elderly with oral anticoagulants for well-established indications. Multiple studies document that individuals with AF are undertreated or not treated at all with VKA therapy, thus denying one of the most effective stroke prevention therapies to a large segment of the population most in need.5–8 The consequence of this paradox is exemplified by the recent Apixaban versus Acetylsalicylic Acid to Prevent Strokes (AVERROES) study with a new direct factor Xa inhibitor, apixaban, in which investigators randomized patients with AF who were thought to be poor candidates for a VKA (mean age, 70±10 years) to apixaban versus aspirin.9 The principal criticism of this study was the rationale behind the decisions not to treat patients with a VKA, which in many cases was that they were thought to be at too high a risk for such therapy.10 The outcome overwhelmingly favored the anticoagulant, as was the case in trials of warfarin versus aspirin in AF,11 without an increased incidence of major bleeding compared with aspirin alone, thus indicating that anticoagulation therapy really is safe for these individuals. Finally, there are ongoing debates and contradictory evidence12 as to whether older age is a risk factor for major bleeding and, if so, if it is an independent risk factor for major bleeding. A number of bleeding risk indexes incorporate age as an independent risk factor and have been validated prospectively such as the Outpatient Bleeding Risk Index,13 the HEMORR2HAGES score,14 and the HAS-BLED index.15

In the current edition of Circulation, Poli et al16 add to this debate by demonstrating in a large, prospective, observational study of 4039 individuals ≥80 years of age who were newly started on VKA therapy for either AF (74%) or venous thromboembolism (26%) an absence of an increased incidence of major bleeding with age. Dose management of VKA was conducted by centers of the Italian Federation of Anticoagulation Clinics, and the presumption is that all patients had high-quality dose management consistent with the reported time in therapeutic range of 62% among all participants. Because the study included all international normalized ratios from the beginning of therapy, this number is likely to be artificially low compared with other studies in which the first 1 to 3 months after the start of therapy are often excluded from the time-in-range calculation. The median age of the population was 84 years, and the mean age of those who bled was 85 years. The investigators found an incidence of major bleeding of 1.87 per 100 patient-years of observation. The average time to a major bleed was 14.2 months (range, 0.1 to 109 months), and there was a higher incidence of major bleeding in the first 3 months (3.87%) than later (1.63%), as noted by others.17,18 The median international normalized ratio at the time of bleeding was 2.5 (range, 1.0 to 13.8), and 82% of bleeds occurred with the international normalized ratio in the therapeutic range. Thirty percent of these were intracranial (0.55 per 100 patient-years), and 14.5% of major bleeds were fatal (0.27 per 100 patient-years). Of note, the rate of bleeding was higher in patients with venous thromboembolism than in those with AF (relative risk, 1.4; 95% confidence interval, 1.1 to 1.8; P=0.03). On univariate analysis, male sex, age >85 years, venous thromboembolism versus AF, history of bleeding, renal failure, active cancer, history of falls, and comedications were significantly associated with bleeding, but on multivariate analysis, only history of bleeding, active cancer, and history of falls were independently associated with bleeding risk. The major limitation of this study, as the authors acknowledged, was the possibility of selection bias in that all patients were referred to the anticoagulation clinics for management, and many of the higher-risk or unsuitable patients may have already been excluded. The overall incidence of major bleeding in this very elderly population was similar to that seen in other well-designed prospective studies such as the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) trial19 in which major bleeding on warfarin was 1.9% in patients ≥75 of age.
The BAFTA investigators noted an increased incidence of bleeding with age, but the trial was not powered to detect significant differences, nor was age assessed as an independent risk factor.

What should we conclude from this study and from the many others that investigate the effect of age on the risk of hemorrhage? Is age simply a marker for an increased risk of bleeding, and are the correlates of aging such as comorbidities and polypharmacy the real culprits? The study of a large Kaiser Permanente database by Fang et al\textsuperscript{2} showed that, regardless of whether individuals were on oral anticoagulants, progressive age increased the risk of major bleeding, but the concomitants of aging were not considered in this study.

The outcomes of oral anticoagulant therapy are also highly dependent on the quality of dose management. Robust prospective clinical trials and anticoagulation clinics where high-quality dose management is practiced are often associated with low rates of bleeding in both elderly and younger cohorts compared with the usual management of VKA therapy by individual physicians.\textsuperscript{20,21} When the model of VKA management is taken into consideration, age loses its impact on bleeding risk in many trials in which dose management is overseen by an anticoagulation service compared with other means of management, but this finding is not consistent.\textsuperscript{12} Patient management in the Poli et al trial\textsuperscript{16} was performed entirely by specialized anticoagulation services. Another factor influencing outcome may have been the high rate of patients living at home in this Italian population (77.5%), with only 7.9% in nursing homes, whereas in the United States, \(\approx 15\)% of individuals \(\geq 80\) years of age live in nursing homes.\textsuperscript{23}

Comparing or aggregating the results from the numerous trials addressing age and the risk of bleeding is fraught with problems such as trial design, trial size, age groups, indications for anticoagulation, target therapeutic range, quality of dose management, and consideration of comorbidities, polypharmacy, and living environment.\textsuperscript{24}

Older age, even in those not on anticoagulant therapy, appears to be a marker for a greater risk of bleeding, and age most surely represents a higher risk for those on oral anticoagulants unless certain aspects of patient/dose management are optimized,\textsuperscript{20} but the more difficult question of whether age is an independent risk factor remains unsettled. This study, unfortunately, does not solve the debate, but the findings may still help to allay the fear that physicians have about treating the elderly, and it may reduce the barriers to VKA use in the elderly.\textsuperscript{5,7} Hopefully, this study will also support the delivery of high-quality dose management of VKA therapy as delivered by specialized anticoagulation services, especially for the elderly.

Finally, how do we translate the findings from this study and the whole debate about age and risk of bleeding on oral anticoagulants to the new targeted thrombin and factor Xa inhibitors? In the 2 large AF trials published to date,\textsuperscript{25,26} a focused analysis of age as a risk for major bleeding has not been done, but the overall incidence of major bleeding was found to be similar to that of warfarin, although with the lower dose of study drug in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, it was reduced. Of particular interest is the consistently lower incidence of intracranial hemorrhage seen with the new agents, which is a key benefit given the increased rate of intracranial hemorrhage seen with warfarin.\textsuperscript{3} In the RE-LY trial, however, dabigatran was also associated with an increased risk of gastrointestinal bleeds compared with warfarin, and this might be accentuated in older individuals. The anticoagulant predictability of the new agents eliminating the need for monitoring may appear to be a benefit, but the importance of this pharmacokinetic attribute may be limited, given that \(>80\)% of the bleeds in the Poli et al\textsuperscript{16} trial occurred when the international normalized ratio was in the therapeutic range.

The take-home message from this large prospective study and other studies in the literature is that VKA therapy should not be withheld from the very old simply because of age. Such therapy can be optimized when managed by a specialized anticoagulation service, but this is also true at any age. As we enter a new era of oral anticoagulant therapy, it will be interesting to see how age affects the use of therapy and outcomes in the very old.

Disclosures

None.

References


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