HHS Public Access

Author manuscript

Blood Coagul Fibrinolysis. Author manuscript; available in PMC 2016 January 01.

Published in final edited form as:

Blood Coagul Fibrinolysis. 2015 January ; 26(1): 110–112. doi:10.1097/MBC.0000000000000186.

Risk of Bleeding During Long-term Anticoagulation with Warfarin: A Tertiary Care Center Experience

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Abstract

The risk of recurrent venous thromboembolism (VTE) must be weighed against the risk of bleeding in deciding to keep patients on extended anticoagulation with vitamin K antagonists (VKA). Most of the studies of risk of bleeding on VKA are randomized controlled trials of highly selected patients followed for less than one year. We sought to determine the rate of bleeding in "real world" patients on long term anticoagulation with VKA for VTE. We conducted a retrospective cohort study of patients monitored at our anticoagulation clinic who were treated with prolonged anticoagulation (>1 year) for secondary VTE prevention to assess the incidence of significant bleeding in this population. We found that most of our patients had serious comorbidities, including diabetes, cancer and solid organ transplantation. The overall rate of bleeding was 10 episodes per 100 person-years, with major bleeding 5.2 episodes per 100 person-years. The rate of significant bleeding while on long-term warfarin may be higher than what is anticipated based on outcomes from closely controlled trials.

Introduction

Extended anticoagulation with Vitamin K antagonists (VKA) remains the standard of care for patients requiring extended anticoagulation for venous thromboembolism (VTE) [1]. The most common adverse effect associated with use of VKA is bleeding, the severity of which may vary from minimal, self-limited bleeding to fatal hemorrhage. In deciding the duration of anticoagulation for an individual patient, the risk of recurrent VTE must be weighed against the risk of bleeding. There is great variation in the reported incidence of VKA-related bleeding between studies. This has been attributed to methodologic differences such as the lack of standardized definitions to classify bleeding [2]. In a meta-analysis of randomized controlled trials for patients treated with VKA for venous thromboembolism, the incidence of major bleeding was reported at 1.69–1.80% [3]. However, the risk of bleeding may be different outside of the context of a randomized controlled trial. The ISCOAT study by Palareti et al [4], an inception cohort study that recruited patients started on anticoagulation for all indications from 34 Italian centers, reported incidences of 1.1 and 0.25 per 100 patient-years of follow-up for major and fatal bleeding [4]. They also found that more than one-third of the bleeding episodes occurred within the first 90 days of

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initiation of anticoagulation. There is a paucity of real-time data regarding the risk of bleeding after the first year of anticoagulation. Most studies on long-term anticoagulation have been conducted in the context of atrial fibrillation and represent a study population that is less likely to have multiple co-morbidities [5].

Methods

We conducted a retrospective cohort study of patients treated with prolonged anticoagulation (>1 year) for secondary VTE prevention to assess the incidence of significant bleeding in this population. The study was carried out at the University of Minnesota Medical Center-Fairview, a tertiary care academic medical center, with the approval of the institutional review board. Patients with one or more episodes of deep venous thrombosis at any site, pulmonary embolism, or VTE or stroke related to antiphospholipid antibody syndrome that were on long term anticoagulation with warfarin were identified from the database of patients followed by the medication monitoring clinic. Exclusion criteria included duration of anticoagulation less than one year and an indication for anticoagulation other than the aforementioned eligibility criteria such as atrial fibrillation, mechanical heart valves, left ventricular assist devices, stroke, or peripheral vascular disease. Demographic and clinical data was collected, including gender, age, and medical co-morbidities, bleeding episodes, INR or factor II activity at the time of bleeding, and surgical procedures requiring interruption of anticoagulation. Bleeding episodes were classified as major or ‘clinically significant’ according to the ISTH Subcommittee for Control of Anticoagulation recommendations[6]. A major bleed was defined as fatal bleeding and/or symptomatic bleeding in a critical area or organ and/or bleeding associated with a decrease in the hemoglobin level of at least 2.0 g/dl or bleeding that required transfusion of two or more units of packed red cells. Bleeding episodes that were not clinically significant, such as minor bruising or epistaxis, were also recorded.

Results and Discussion

Data was collected for 187 patients for a total of 953 patient-years (Table 1). The average number of years on anticoagulation followed by the medication monitoring clinic was 5.0 ± 2.1 (SD) with a range of 1.0–10.5 years. There were 96 documented episodes of bleeding in 70 patients for a rate of 10 per 100 person years. There were fifty episodes of major bleeding, at a rate of 5.2 per 100 person years. Four episodes of major bleeding occurred in the first 6 months of anticoagulation, four occurred in the second six months of anticoagulation, and 42 occurred after 12 months of anticoagulation. There were no episodes of fatal bleeding reported. For major bleeds, the gastrointestinal tract was the most common site of bleeding, followed by internal or muscle hematomas. Epistaxis was the most common site of non-significant bleeding reported. Twelve patients had more than one episode of major bleeding. Recurrent bleeds were most frequently of gastrointestinal origin, and fewer than half of recurrent bleeding episodes were related to significant over-anticoagulation. Overall, 24 bleeding episodes occurred when the patients were over-anticoagulated, with INR was >4 (therapeutic range 2.0–3.0) or Factor II activity <12% (therapeutic range 15–25%). Only 10 patients stopped warfarin indefinitely due to bleeding, and 3 of the 10 patients were eventually restarted on anticoagulation with VKA due to recurrent VTE.

The rate of significant bleeding in our “real world” cohort was higher than the 0.9–1.1 per 100 person-years that has previously been reported in randomized trials. The number of patients in this study was too small to comment on specific risk factors for bleeding. However, as has been previously shown, we did find trends suggestive of higher rates of bleeding in patients with malignancies (OR= 2.06, 95% CI =0.9298 to 4.5857) and other co-morbidities such as coronary disease (OR =1.2, 95% CI= 0.44–3.36) and diabetes (OR= 4.3, 95% CI= 1.4 to 12.9). We also observed a higher incidence of major bleeding in our cohort of solid-organ transplant recipients (OR= 2.38, 95% CI= 0.84 to 6.73). The higher incidence of bleeding observed in our cohort can be explained by the large number of patients in this study that had numerous co-existing medical conditions (Table 1). Warfarin remains a reasonably safe option for most patients with VTE requiring long term anticoagulation. However, the rate of significant bleeding while on long-term warfarin may be higher than what is anticipated based on outcomes from closely controlled trials. Further, while the risk of bleeding is highest in the initial few months after initiation of anticoagulation [4, 7], it likely does not become negligible with prolonged anticoagulation.

Acknowledgments

Funding: This work was supported by the National Institutes of Health Hematology Research Training Program 5T32HL007062-37. Also Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health Award Number UL1TR000114. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Table 1

Bleeding status stratified by risk factors

	No Bleeding	Minor Bleeding	Major Bleeding
Sex			
Female	63 (53.4%)	23 (67.7%)	21 (60%)
Male	55 (46.6%)	11 (32.3%)	14 (40%)
Age (years)			
≤50	54 (45.8%)	10 (29.45%)	8(22.8%)
51–69	45 (38.1%)	16 (47%)	19 (54.3%)
≥70	19 (16.1%)	8 (23.5%)	8 (22.8%)
Mean duration of anticoagulation (person-years)	4.7	5.8	6.1
Co-morbid conditions			
Malignancy	14 (11.8%)	5 (14.7%)	10 (28.6%)
History of solid organ transplant	7 (5.9%)	1 (2.9%)	8 (22.8%)
Autoimmune disorder	22 (18.6%)	13 (38.2%)	9 (25%)
Hepatic disease	0	0	1 (2.8%)
Hypertension	3 (2.5%)	6 (17.6%)	5 (14.3%)
Coronary disease	10 (8.5%)	3 (8.8%)	4 (11.4%)
Diabetes mellitis	5 (4.2%)	3 (8.8%)	8 (22.8%)
Renal disease	15 (12.7%)	2 (5.9%)	6 (17.1%)
History of stroke	4 (3.4%)	2 (5.9%)	1 (2.8%)