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Bleeding complications associated with warfarin treatment in ischemic stroke patients with atrial fibrillation: a population-based cohort study

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Abstract

Background—Bleeding events are the major obstacle to the widespread use of warfarin for secondary stroke prevention. Previous studies have not examined the use of risk stratification scores to estimate lifetime bleeding risk associated with warfarin treatment in a population-based setting. The purpose of this study is to determine the lifetime risk of bleeding events in ischemic stroke patients with atrial fibrillation (AF) undergoing warfarin treatment in a population-based cohort and to evaluate the use of bleeding risk scores to identify patients at high-risk for lifetime bleeding events.

Methods—The resources of the Rochester Epidemiology Project Medical Linkage System were used to identify acute ischemic stroke patients with atrial fibrillation undergoing warfarin treatment for secondary stroke prevention from 1980 to 1994. Medical information for patients seen at Mayo Clinic and at Olmsted Medical Center were used to retrospectively risk-stratify stroke patients according to bleeding risk scores (including the HAS-BLED and HEMORR₂HAGES scores) prior to warfarin initiation. These scores were reassessed one and five years later, and compared with lifetime bleeding events.

Results—One hundred patients (mean age, 79.3 years; 68% women) were studied. Ninety-nine patients were followed to death. Major bleeding events occurred in 41 patients at a median of 19 months following warfarin initiation. Patients with a history of hemorrhage before warfarin treatment were more likely to develop major hemorrhage (15% vs 3%, $p=0.04$). Patients with baseline HAS-BLED scores ≥ 2 had a higher lifetime risk of major bleeding events compared with

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those with scores 1 (53% vs 7%, $p<0.01$), while those with HEMORR₂HAGES score 2 had a higher life-time risk of major bleeding events compared with those with scores 1 (52% vs 16%, $p=0.03$). Patients with an increase in the HAS-BLED and HEMORR₂HAGES scores during follow-up had a higher remaining lifetime risk of major bleeding events compared to those with no change.

Conclusions—Our findings indicate high lifetime bleeding risk associated with warfarin treatment for patients with ischemic stroke. Risk stratification scores are useful to identify patients at high-risk of developing bleeding complications and should be recalculated at regular intervals to evaluate the bleeding risk in anticoagulated patients with ischemic stroke.

Keywords

stroke; atrial fibrillation; warfarin; bleeding complications

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in 1-2% of the general population [1,2]. In the United States, 5% of individuals >65 years of age have AF and this proportion is expected to double over the next 50 years [3]. The risk of stroke in the setting of AF increases with age, affecting up to 23.5% of patients aged 80 to 90 years [4]. AF confers a 5-fold risk of stroke and one in five of all strokes is attributable to AF [5]. Recognition of comorbidities associated with increased stroke risk has led to the publication of various stroke risk schemes such as the CHADS₂ and, recently, the CHA₂DS₂-VASc scores [6,7]. Compelling data support the use of warfarin to lower the risk of stroke from AF. In a meta-analysis, the relative risk reduction with warfarin compared to placebo was 64%, corresponding to an absolute annual risk reduction for all strokes of 2.7% [8]. Despite a class 1 recommendation in major treatment guidelines [1,2,9], the utilization of warfarin remains suboptimal and a significant proportion of high-risk individuals with prior stroke or transient ischemic attack do not receive anticoagulation [10].

A major obstacle to the widespread use of warfarin lies in its propensity to cause hemorrhage. Despite modest bleeding risk reported in clinical trials [11-23], it has been suggested that the frequency of bleeding is higher in general clinical practice [24-28]. One population-based study (which included AF and non-AF patients) observed a temporal increase in the incidence of intracranial hemorrhage and attributed this rise to the frequent use of warfarin in the elderly [29]. Using data from the Medicare's National Stroke Project, Shireman and colleagues observed a 1.3% incidence of major bleeding events among warfarin users within the first 30 days of warfarin treatment [30]. Compared to patients who take warfarin for primary stroke prevention, patients with stroke prior to the start of warfarin treatment are usually older and have numerous comorbidities. A substantial proportion of these patients are considered high-risk for stroke recurrence; the same comorbidities that confer an increased stroke risk also render them vulnerable to developing bleeding events with anticoagulation. The CHADS₂ score, used primarily to predict stroke risk, has been shown to correlate closely with bleeding events associated with warfarin treatment [25,31].

Several risk stratification scores have been developed to estimate bleeding risk associated with warfarin treatment: the HAS-BLED [32], HEMORR₂HAGES [33], Bleeding Risk Scores [30,34], Outpatient Bleeding Risk Index [35] and the ATRIA Risk Score [36]. To date, the HAS-BLED score has been incorporated in the European and Canadian guidelines for the management of AF [37]. These scores are predictive of subsequent bleeding risk when calculated at the time of initiation of anticoagulation. As certain risk factors can become present or change over time, the value of serial updating of the scores has not been previously explored.

Lifetime risk considers the absolute cumulative risk of an individual developing a given disease during an individual's lifespan and is easier to understand than relative risk. In this study, we examine the lifetime risk of developing major bleeding events associated with warfarin treatment in a population-based cohort of stroke patients with atrial fibrillation and compare the validity of different risk stratification schemes, determined prior to warfarin treatment, to predict their lifetime bleeding risk. Whenever possible, these bleeding risk scores were reassessed, one and five years later, and the predictive value of a change in the bleeding risk score to the remaining lifetime risk of major bleeding events was determined.

METHODS

The Rochester Epidemiology Project Medical Record Linkage System provides resources to identify nearly all new cases of stroke and TIA in our community. Virtually all medical care in the community of Rochester is supplied by Mayo Clinic and its 2 hospitals or at Olmsted Medical Center and Olmsted Community Hospital. All medical diagnoses for patients seen at Mayo Clinic and at Olmsted Medical Center are entered into a central computer index. The index has been expanded to include medical practices in nearby communities such as the University of Minnesota and the Veterans Administration Hospital in Minneapolis. The comprehensive Mayo Clinic medical record includes all inpatient and outpatient data, emergency room visits, nursing home care and autopsy or death certificate information. In 1990, Rochester, Minnesota, had a population of approximately 70,000 with a strong predominance of non-Hispanic whites (96%).

All incident strokes occurring from 1980 through 1994 in residents of Rochester, Minnesota, were previously identified and entered into the Rochester Stroke and TIA Registry [38]. The method of ascertaining stroke in the Rochester population using the medical record linkage system and resources of the Rochester Epidemiology Project has been previously described [38,39]. For this analysis, the medical records for patients with ischemic strokes were reviewed; patients with amaurosis fugax and transient ischemic attack were excluded. Eligible patients had persistent atrial fibrillation or flutter or two or more episodes of atrial fibrillation or flutter, as documented by electrocardiography, at least 2 weeks apart in the 12 months before enrollment. Screening for AF using Holter monitoring was not routinely performed for all patients. Information on demographics, medical risk factors and laboratory features was collected in these patients prior to initiation of warfarin treatment, to derive the HAS-BLED, HEMORR₂HAGES and Bleeding Risk Scores, Outpatient Bleeding Risk Index and ATRIA Risk Scores [30,32-36]. Further details of these scores are summarized in Supplemental Table 1. Uncontrolled hypertension was defined as systolic blood pressure

exceeding 160 mmHg prior to warfarin treatment, a “history of malignancy” to carry a similar significance as “current malignancy”, ethanol abuse as alcohol consumption >20 alcoholic beverages per week, renal disease as creatinine clearance <50 ml/min, a low platelet count as less than the lower limit of normal and anemia as hemoglobin content less than the lower limit of normal. Genetic information was not available in the current cohort. Previous bleeding was defined as a history of bleeding events >3 months prior to warfarin treatment.

All patients were maintained either within the therapeutic international normalized ratio (INR) range of 2 to 3 (after 1990) or prothrombin times (PT) 1.5-2 times greater than control values (before 1990). Follow-up visits were typically scheduled every 2 to 4 weeks for INR or PT monitoring. All patients were followed up for anticoagulation management by specialist nurses and attending neurologists or their primary care provider. The bleeding risk scores of eligible patients, who tolerated and were continued on warfarin, were reassessed based on review of the comprehensive medical record one and five years after initiation of warfarin treatment. Reasons for warfarin discontinuation were recorded. The CHADS₂ and CHA₂DS₂VASC scores were calculated for each patient.

Each patient was followed until death or until August 31, 2011. End-points of death and bleeding were collected previously and verified by review of the medical records. Major bleeding was defined as fatal or clinically overt bleeding associated with either transfusion of ≥2 units of blood or ≥20 g/l decrease in hemoglobin or bleeding involving a critical anatomic site. Intracranial hemorrhage was counted as major bleeding event. Fatal bleeding was defined as death within a week of a major bleeding.

Statistical analysis

Statistical analyses were performed using the SPSS software (version 17.0; SPSS Inc, Chicago, Ill). Data are presented as mean (standard deviation) or median (interquartile range) for continuous measures, and counts and percentages for categorical variables. The study covariates were compared according to bleeding events (major and fatal) and the risk categories of the bleeding scores were compared with lifetime risk of bleeding events. Whenever possible, the bleeding risk scores were reassessed one and five years following initiation of warfarin treatment and these scores were compared with their remaining lifetime risk of major bleeding. Statistical significance was considered when $p < 0.05$.

RESULTS

Among 303 ischemic stroke patients who presented with atrial fibrillation during the study period, 100 (33%) patients were treated with warfarin for secondary stroke prevention and formed the study cohort. Warfarin was prescribed more frequently with time (1980-1984, 9/106 [8%]; 1985-1989, 37/101 [37%]; 1990-1994, 54/96 [56%]). Seventy-four percent of patients not treated with warfarin received antiplatelet therapy. Follow-up was complete for all patients and no patient was lost to follow-up from January 1985 through August 2011 (total, 419 person-years). Ninety-nine patients died prior to August 2011. Mean (standard deviation) age of the study cohort at stroke onset was 79.3 (11.5) years; 68% were females and 100% whites. Baseline characteristics of the study population are summarized in Table

1. Mean CHADS₂ and CHA₂DS₂VASC scores were 3.43 (0.81) and 5.36 (1.29) respectively. Median duration of warfarin treatment was 2.4 years (interquartile range, 0.4-6.6 years) and median duration from stroke onset to death was 3.7 years (1.1-8.8 years). Twenty-one patients had prior warfarin use but were not on warfarin at the time of stroke. Sixty-one patients were continued on warfarin for at least one year. Warfarin was discontinued in 39 patients due to death (n=24, 3 hemorrhage-related), patient-physician decision (n=13) and increased fall risk (n=2). Five years after stroke onset, 36 patients remained on warfarin: 24 patients died from non-hemorrhage causes and one patient stopped warfarin due to increased fall risk (mean 3.2 years from stroke onset). Five patients developed stroke recurrence while on active warfarin treatment (1.21 stroke recurrence per 100 patient-years).

Major bleeding events occurred in 41 patients (9.79 bleeds per 100 patient-years) at a median of 19 months (interquartile range, 5-58 months) following warfarin initiation. Cumulative major bleeding events were 14% at year one and 26% at year five following warfarin treatment. These events included intracranial hemorrhage (n=9), gastrointestinal tract bleeding (upper, n=14; lower, n=8), gross hematuria (n=4), gluteal/thigh hematoma (n=4), retroperitoneal (n=1) and pulmonary hemorrhage (n=1). Apart from two patients with trauma-related limb hematoma (both patients suffered accidental falls at home and presented with INR>3), these bleeding events occurred spontaneously. INR at the time of hemorrhage was most often within therapeutic range (INR 2-3, n=34; INR >3, n=7). Seven patients (17%) died within a week of these bleeding events. Patients with a history of any previous hemorrhage prior to warfarin treatment were more likely to develop major and fatal hemorrhage compared to those without history of bleeding (Table 2).

Sixteen major bleeding events occurred within a year of treatment, 25 events occurred between years 1-5, and 14 events in patients treated for >5 years. Overall, the HAS-BLED and HEMORR₂HAGES were more predictive of major bleeding events compared with the Bleeding Risk Score, Outpatient Bleeding Risk Index and the ATRIA score (Tables 3). An increase in the HAS-BLED and HEMORR₂HAGES scores over time predicted a higher bleeding risk (Table 4). Patients with baseline HAS-BLED scores ≥2 had higher lifetime risk of major bleeding events compared with those with scores ≤1 (53% vs 7%, p=0.002), while those with HEMORR₂HAGES score ≥2 had higher lifetime risk of major bleeding events compared with those with scores ≤1 (52% vs 16%, p=0.03). Patients with an increase in the HAS-BLED score over time had a higher remaining lifetime risk of major bleeding events compared to those with no change (year one, 64% vs 34%, p=0.04; year five, 75% vs 29%, p=0.02). Similarly, patients with an increase in the HEMORR₂HAGES scores over time had higher remaining lifetime risk of major bleeding events compared to those with no change (year one, 57% vs 33%, p=0.06; year five, 71% vs 10%, p<0.001). Comparisons between the CHADS₂ and CHA₂DS₂VASC scores with lifetime bleeding events are summarized in Table 5. Neither of these scores reliably predicted lifetime bleeding events.

DISCUSSION

These data provide additional insights into the long-term risk of warfarin treatment for stroke patients with atrial fibrillation: (1) two in five elderly stroke patients developed

lifetime bleeding events following warfarin treatment for atrial fibrillation, (2) stroke patients with a higher baseline HAS-BLED and HEMORR₂HAGES scores had a higher incidence of lifetime bleeding events, (3) patients who had an increase in the HAS-BLED and HEMORR₂HAGES scores over time were more likely to develop bleeding complications. To our knowledge, this is the single largest series of patients with atrial fibrillation treated with warfarin for secondary stroke prevention with a meticulously documented lifetime bleeding risk, based on the longitudinal surveillance of a community-based cohort.

Data derived from clinical trials suggest that major bleeding events associated with warfarin treatment range from 0.01 to 4.1 per 100 patient-years [11-23], while those from prospective cohort studies report major bleeding events from 1.1 to 9.8 per 100 patient-years [24-28]. This study, which included older patients (many of whom had prior ischemic stroke), reported bleeding risks that were up to 10 times higher than previous estimates. Advanced age has been shown to increase the risk of major hemorrhage in warfarin-treated patients. In the AFFIRM trial (Atrial Fibrillation Follow-up Investigation of Rhythm Management), for example, the risk of major bleeding increased by approximately 5% per year of age [37]. “Danger periods” for warfarin treatment (during which time complications rates are highest) are known to occur immediately following warfarin initiation, especially when warfarin is administered for the first time or used in combination with antiplatelet therapy [40,41]. Other treatment- and person-related risk factors associated with bleeding events in patients undergoing anticoagulation have been previously reviewed [37,42,43,44].

In the current study, increased bleeding rates were observed in patients with higher HAS-BLED and HEMORR₂HAGES scores at baseline. Furthermore, patients with an increase in HAS-BLED and HEMORR₂HAGES scores at one and five years following warfarin treatment had a higher remaining lifetime risk of developing major bleeding events. These data support the use of risk stratification scores to inform bleeding risk associated with warfarin treatment and emphasize the merits of interval reassessment of bleeding risk in patients receiving long-term anticoagulation. This cautious approach is necessary because of the higher frequency of bleeding events among stroke patients undergoing warfarin treatment and high mortality associated with these bleeding complications.

This study also highlights considerable differences in the performance of bleeding risk scores in identifying patients at high-risk for developing major bleeding events. We found that the HAS-BLED and HEMORR₂HAGES scores were useful to stratify the bleeding risk of warfarin-treated patients, but in our cohort the Bleeding Risk Score, Outpatient Bleeding Risk Index and ATRIA Risk Score were less helpful for identifying stroke patients who were at high risk of major bleeding events. Differences in the performance of these risk scores may, in part, be explained by the variables included in each score. For example, a history of previous bleeding constitutes a component of the HAS-BLED and HEMORR₂HAGES scores, but not of the other two scores. The lower age cutoff used in the Bleeding Risk Score and Outpatient Bleeding Risk Index may affect their accuracy in distinguishing high from low-risk individuals. Despite incorporating a higher age cutoff (>75 years) and other risk components common to previous bleeding schemes, the newer ATRIA score did not perform as well as the HAS-BLED and HEMORR₂HAGES scores in

identifying patients at risk for bleeding events. This may be explained by the different weight attributed to each component for the calculation of the ATRIA score as compared to the HAS-BLED and HEMORR₂HAGES scores.

The population-based design and completeness of follow up are the main strengths of our study. However, we also acknowledge it has limitations. First, as patients were followed from 1985-1995 through 2011, changes in clinical practice (such as selection of patients for warfarin treatment and treatment of warfarin-related hemorrhage) may have affected our findings. The indication, intensity, and monitoring of anticoagulation with warfarin did not change considerably during this follow-up period, apart from very recent advances in outpatient anticoagulation monitoring. Whether more effective treatment of hypertension and peptic ulcer disease may have reduced the risks of bleeding from warfarin remains speculative. Second, the current study included a cohort of older stroke patients who were closely monitored in the outpatient setting and it remains possible that different event rates may be observed in younger stroke patients and in patients living in areas with limited access to comprehensive medical care. Our high lifetime rate of bleeding may be related to the characteristics of our cohort and lower rates could be found by studying other populations. Third, an operational case definition of major bleeding events adopted by major clinical trials was employed in this study. These bleeding rates may therefore vary in studies that incorporate different definitions of bleeding events. Furthermore, the study population was predominantly white and our findings may not be generalized to non-white individuals. Fourth, the sample size of the study population was relatively small (which is further reduced over time), thereby limiting our abilities to perform further post-hoc analyses.

Our findings indicate high lifetime bleeding risk associated with warfarin treatment for patients with ischemic stroke. They also support the use of risk stratification scores to identify patients at high-risk of developing bleeding complications. These scores, in particular HAS-BLED and HEMORR₂HAGES, can provide reliable estimates of the lifetime bleeding risks in warfarin-treated patients, but recalculation at regular intervals is necessary to optimize their performance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Patient characteristics

	Baseline (n=100)	Year 1 (n=61)	Year 5 (n=36)	P-values
Age, years, mean (SD)	79.3 (11.5)	77.1 (12.0)	76.8 (12.4)	0.92
Female gender, %	68 (68)	40 (66)	23 (64)	0.90
Medical history (%)				
Diabetes mellitus	10 (10)	15 (25)	8 (22)	0.90
Congestive heart failure	21 (21)	33 (54)	18 (50)	0.90
Myocardial infarction	16 (16)	31 (51)	18 (50)	0.66
Liver disease	0	1 (2)	1 (3)	0.93
Renal disease	14 (14)	26 (43)	13 (36)	0.40
Alcohol abuse	1 (1)	4 (7)	2 (6)	0.76
Previous hemorrhage	6 (6)	6 (10)	6 (17)	0.33
Antiplatelet use	0	1 (2)	1 (3)	0.75
Malignancy	8 (8)	15 (25)	10 (28)	0.90
Hypertension ^a	1 (1)	2 (3)	1 (3)	0.88
Prior warfarin use	21 (21)	61 (100)	36 (100)	0.04
Laboratory features (%)				
Anemia ^b	3 (3)	12 (20)	13 (36)	<0.001 [†]
Low hematocrit ^c	4 (4)	9 (15)	7 (19)	0.79
Elevated creatinine ^d	9 (9)	24 (39)	12 (33)	0.20
Platelet count ^e	4 (4)	4 (7)	2 (6)	0.96

^aSystolic blood pressure >160 mmHg;

^bhemoglobin <13.5g/dL in men, <12 g/dL in women;

^chematocrit <30%;

^dcreatinine >1.5 g/dL;

^eplatelet count <150 × 10⁹/L.

[†]The rate of anemic patients on warfarin increased over time.

Table 2

Baseline characteristics of study cohort according to bleeding status

	Major bleeding			Fatal bleeding		
	Yes (n=41)	No (n=59)	P-values	Yes (n=7)	No (n=93)	P-values
Age, years, mean (SD)	79.3 (11.5)	76.5 (11.5)	0.24	75.4 (11.9)	77.8 (11.5)	0.60
Female gender, %	28 (68)	34 (58)	0.28	4 (57)	58 (62)	0.78
Medical history (%)						
Diabetes mellitus	10 (24)	16 (27)	0.76	2 (29)	24 (26)	0.87
Congestive cardiac failure	21 (51)	30 (51)	0.97	5 (71)	24 (50)	0.26
Myocardial infarction	16 (39)	28 (48)	0.40	5 (71)	39 (42)	0.13
Liver disease	0	2 (3)	0.23	0	2 (2)	0.69
Renal disease	14 (34)	18 (31)	0.70	2 (29)	30 (32)	0.84
Alcohol abuse	1 (2)	3 (5)	0.51	0	4 (4)	0.57
Previous bleed [†]	6 (15)	2 (3)	0.04	3 (43)	5 (5)	<0.001
Antiplatelet use	0	1 (2)	0.40	0	1 (1)	0.78
Malignancy	8 (20)	16 (27)	0.38	2 (29)	22 (24)	0.77
Hypertension ^a	1 (2)	1 (2)	0.79	0	2 (2)	0.69
Prior warfarin use	7 (17)	14 (24)	0.56	1 (14)	20 (22)	0.35
Laboratory features (%)						
Anemia ^b	3 (7)	4 (7)	0.92	1 (14)	6 (7)	0.43
Low hematocrit ^c	4 (10)	11 (19)	0.22	1 (14)	14 (15)	0.96
Elevated creatinine ^d	9 (22)	17 (29)	0.44	1 (14)	25 (27)	0.46
Platelet count ^e	4 (10)	3 (5)	0.37	1 (14)	6 (7)	0.43

^aSystolic blood pressure >160 mmHg;^bhemoglobin <13.5g/dL in men, <12 g/dL in women;^chematocrit <30%;^dcreatinine >1.5 g/dL;^eplatelet count <150 × 10⁹/L;[†]p<0.05.

Table 3

Comparison between bleeding scores at baseline and life-time risk of major bleeding

	Major bleeding		
	Yes (n=41)	No (n=59)	C-statistic
HAS-BLED score [32]			0.72
1 (n=27)	2 (7%)	25 (93%)	
2 (n=41)	22 (54%)	19 (46%)	
3 (n=28)	15 (54%)	13 (46%)	
4 (n=4)	2 (50%)	2 (50%)	
HEMORR₂HAGES score [33]			0.76
1 (n=31)	5 (16%)	26 (84%)	
2 (n=35)	12 (34%)	23 (66%)	
3 (n=23)	15 (65%)	8 (35%)	
4 (n=9)	7 (78%)	2 (22%)	
5 (n=2)	2 (100%)	0	
Bleeding Risk Score [34]			0.49
Low risk (0) (n=4)	2 (50%)	2 (50%)	
Intermediate risk (1-2) (n=72)	34 (47%)	45 (63%)	
High risk (3) (n=24)	9 (37%)	15 (63%)	
Outpatient Bleeding Risk Index [35]			0.49
Low risk (0) (n=0)	0	0	
Intermediate risk (1-2) (n=26)	12 (46%)	14 (54%)	
High risk (3-4) (n=74)	29 (39%)	45 (61%)	
Shireman et al [30]			0.54
Low risk (< 1.07) (n=75)	30 (40%)	45 (60%)	
Intermediate risk (1.7-2.19) (n=23)	9 (39%)	14 (61%)	
High risk (>2.19) (n=2)	1 (50%)	1 (50%)	
ATRIA Risk Score [36]			0.56
Low risk (0-3) (n=75)	28 (37%)	47 (63%)	
Intermediate risk (4) (n=3)	2 (67%)	1 (33%)	
High risk (5-10) (n=22)	11 (50%)	11 (50%)	

Table 4

Reassessment of bleeding risk scores one and five years following initiation of warfarin treatment and remaining lifetime risk of major bleeding events.

	Major bleeding events (%)		P-values
	Yes	No	
HAS-BLED score [32]			
Year one reassessment			0.04
Increase (n=14)	9 (64%)	5 (36%)	
No change (n=47)	16 (34%)	31 (66%)	
Year five reassessment			0.02
Increase (n=8)	6 (75%)	2 (25%)	
No change (n=28)	8 (29%)	20 (71%)	
HEMORR₂HAGES score [33]			
Year one reassessment			0.06
Increase (n=21)	12 (57%)	9 (43%)	
No change (n=40)	13 (33%)	27 (68%)	
Year five reassessment			<0.001
Increase (n=17)	12 (71%)	5 (29%)	
No change (n=19)	2 (10%)	17 (90%)	
Bleeding Risk Score [34]			
Year one reassessment			0.81
Increase (n=2)	1 (50%)	1 (50%)	
No change (n=59)	24 (41%)	35 (59%)	
Year five reassessment			0.30
Increase (n=3)	2 (67%)	1 (33%)	
No change (n=33)	12 (36%)	21 (64%)	
Outpatient Bleeding Risk Index [35]			
Year one reassessment			0.79
Increase (n=2)	1 (50%)	1 (50%)	
No change (n=59)	24 (41%)	35 (59%)	
Year five reassessment			0.84
Increase (n=3)	1 (33%)	2 (67%)	
No change (n=33)	13 (39%)	20 (61%)	
Shireman et al [30] <u>ENREF 20 ENREF 20</u>			
Year one reassessment			0.26
Increase (n=18)	10 (56%)	8 (44%)	
No change (n=43)	16 (37%)	27 (63%)	
Year five reassessment			<0.001
Increase (n=15)	11 (73%)	4 (27%)	

	Major bleeding events (%)		P-values
	Yes	No	
No change (n=21)	3 (14%)	18 (86%)	
ATRIA Risk Score [36] <u>ENREF_14</u> <u>ENREF_14</u>			
Year one reassessment			0.55
Increase (n=17)	8 (47%)	9 (53%)	
No change (n=44)	17 (39%)	27 (61%)	
Year five reassessment			0.04
Increase (n=9)	6 (67%)	3 (33%)	
No change (n=27)	8 (30%)	19 (70%)	

Table 5

Comparison between the CHADS₂ and CHA₂DS₂VASC scores at baseline and life-time risk of major bleeding

	Major bleeding		
	Yes (n=41)	No (n=59)	C-statistic
CHADS₂ score			0.54
2 (n=10)	3 (7%)	7 (12%)	
3 (n=47)	19 (46%)	28 (48%)	
4 (n=33)	15 (37%)	18 (31%)	
5 (n=10)	4 (10%)	6 (10%)	
CHA₂DS₂VASC score			0.52
2 (n=2)	1 (2%)	1 (2%)	
3 (n=7)	1 (2%)	6 (10%)	
4 (n=13)	8 (20%)	5 (9%)	
5 (n=31)	11 (27%)	20 (34%)	
6 (n=28)	11 (27%)	17 (29%)	
7 (n=19)	9 (22%)	10 (17%)	