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ORIGINAL RESEARCH ARTICLE

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Warfarin prescription in patients with nonvalvular atrial fibrillation and one non–gender-related risk factor (CHA_2DS_2VASc 1 or 2): A treatment dilemma

Gentian Denas[1] | Giacomo Zoppellaro[1] | Seena Padayattil Jose[1] | Emilia Antonucci[2] | Francesco Marongiu[3] | Daniela Poli[4] | Sophie Testa[5] | Armando Tripodi[6] | Gualtiero Palareti[2] | Vittorio Pengo[1]

[1]Department of Cardiac, Thoracic and Vascular Sciences, Cardiology Clinic, University of Padua, Padua, Italy

[2]Arianna Anticoagulation Foundation-START Register Section, Bologna, Italy

[3]Department of Medical Sciences, University Hospital of Cagliari, Cagliari, Italy

[4]Department of Heart and Vessels, Thrombosis Centre, University Hospital, Florence, Italy

[5]Department of Laboratory Medicine, Hemostasis and Thrombosis Centre, District Hospital, Cremona, Italy

[6]Department of Clinical Sciences and Community Health, Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre, University of Milan, Milan, Italy

Correspondence
Vittorio Pengo, Department of Cardiac, Thoracic and Vascular Sciences, Cardiology Clinic, Padua University Hospital, Padua, Italy.
Email: vittorio.pengo@unipd.it

Summary

Introduction: The issue of anticoagulation in individuals with nonvalvular atrial fibrillation (NVAF) and 1 non–gender-related (NGR) risk factor is subject to debate. The reported risk of stroke in untreated individuals is not uniform, and the rate of hemorrhage associated with anticoagulation in this group of individuals is not well defined. To this end, we assessed the rate of stroke and major hemorrhage in individuals treated with warfarin.

Materials and Methods: individuals were extracted from the START register, an observational, multicenter, dynamic inception cohort study that collects data on NVAF individuals starting anticoagulation therapy. Risk of stroke is stratified using the CHA_2DS_2VASc score upon entry into the registry.

Results: Overall, 431 individuals with 1 NGR risk factor were followed up for 604 person-years. One nonfatal ischemic stroke was recorded (0.17 per 100 person-years) during follow-up. On the other hand, there were 9 major bleeding events (1.49 per 100 person-years), with 4 being intracranial hemorrhage (0.66 per 100 person-years), 1 of which was fatal. No difference in patient characteristics, bleeding risk factors, and quality of treatment were found between individuals who bled versus those who did not. However, a trend toward more bleeding events was observed in individuals <65 years old.

Conclusion: We found an elevated risk of major bleeding and intracranial hemorrhage in NVAF individuals treated with warfarin with 1 NGR risk factor for stroke. These data call for caution when treating with warfarin these individuals.

KEYWORDS

Atrial fibrillation, Hemorrhage, Risk factors, Stroke, Warfarin

1 | INTRODUCTION

Oral anticoagulation treatment (OAT) is recommended in most individuals with nonvalvular atrial fibrillation (NVAF) for stroke prevention.[1-3] The risk of stroke in NVAF is not uniform, and it rather depends on the presence of other associated risk factors that confer an incremental risk of up to 15.2% per year.[4] The score used by European and American guidelines, the CHA_2DS_2VASc score[4] (congestive heart failure, hypertension, age >75 years, diabetes mellitus, stroke/transient ischemic attack [TIA], vascular disease, age 65-74 years, sex category) aimed at a better stratification of low-risk individuals identified with the $CHADS_2$ score[5] (congestive heart failure, hypertension, age >65 years, diabetes

mellitus, stroke/transient ischemic attack [TIA]). However, its introduction posed an important issue on what is the lowest score for OAT initiation.[6] In the absence of risk factors ($CHA_2DS_2VASc = 0$), individuals forego anticoagulation, while in the presence of at least 2 non–gender-related (NGR) risk factors, anticoagulation is warranted.[3,7,8] Even with the results of the more recent studies comparing warfarin with the non-VKA oral anticoagulants (NOACs), the risk-benefit profile of OAC agents in the lowest-risk individuals could not be settled. In fact, these randomized trials did not include individuals with a CHA_2DS_2VASc score of 1. These uncertainties are reflected in the guideline recommendations. The recommendations for anticoagulation differ between AHA/ACC/HRS guidelines[8] and the 2012 ESC guidelines.[2] According to the ESC guidelines,[2] OAT was *recommended* in NVAF individuals with one or more risk factors (score of 1 assessed by CHA_2DS_2VASc). On the other hand, the AHA/ACC/HRS guidelines[8] recommend anticoagulation in individuals with a score of 2. The latest ESC guidelines on atrial fibrillation[7] reconsidered their position (lowering the level of evidence from IIA to IIB) in light of new data.[9,10] Under these circumstances, the true risk-benefit ratio is difficult to predict in these individuals. Current CHA_2DS_2VASc validation trials, despite having large numbers, have been performed by retrospective collection of data and post hoc analysis, with results pointing in opposite directions.[9,11] Considering the drawbacks of retrospective validation cohorts, we extracted and analyzed data on individuals with one NGR risk factor (male individuals with CHA_2DS_2VASc of 1 and female with a CHA_2DS_2VASc of 2), from a prospective registry of naïve atrial fibrillation individuals[12] starting OAT. The aim of our study was to assess the incidence of stroke and bleeding in an inception cohort of prospectively recorded data of warfarin-treated NVAF individuals with 1 NGR risk factor for stroke.

2 | METHODS

We used data collected in the START (Survey on anTicoagulated pAtients RegisTer).[12] START is an independent, inception cohort, observational, collaborative database aimed at recording prospectively the clinical history of adult individuals starting anticoagulant treatment for any reason and using whatever drug. Participants insert prospectively consecutive individuals without any a-priori exclusion criteria other than life-expectancy or geographical inaccessibility. The web-based electronic record collects data on: demographic and clinical characteristics of individuals, associated risk factors for stroke and bleeding, laboratory routine data, clinical indication for treatment, and therapeutic range (in case of treatment with vitamin K antagonists-VKAs), concomitant medication. For individuals on VKA, time spent in the therapeutic range (TTR, computed according to the Rosendaal's method) is recorded every 3 months for the first year and annually thereafter. Patient comorbidities such as congestive heart failure, diabetes mellitus (types I, II, and unclassified), history of stroke or thromboembolism (stroke, transient ischemic attack, or systemic embolism), and vascular disease (myocardial infarction [MI] or peripheral artery disease [PAD]) are recorded in the registry by the treating physician using a clinical diagnosis code.

The follow-up is mandatory for at least 1 year and data on the quality of treatment (for individuals on VKAs), bleeding complications, thrombotic events, and the onset of any type of associated disease are all reported on set deadlines. Data are also reported even if anticoagulants were interrupted before 12 months.

We used the records collected in the START to identify all anticoagulation-naïve individuals with NVAF and one NGR risk factor for stroke recorded in the register between May 2011 and May 2016 and receiving warfarin. Individuals were considered naïve if at the time of inclusion were receiving anticoagulation therapy for no more than 30 days. Stroke risk stratification was based on guideline-established risk factors and computed using the CHA_2DS_2VASc score upon entry into the registry. Thus, the final cohort consisted of individuals with NVAF and one NGR risk factor (male individuals with CHA_2DS_2VASc of 1 and female with a CHA_2DS_2VASc of 2). Follow-up lasted until an endpoint occurred, death, or May 30, 2016, whichever came first. The risk of bleeding was assessed using HASBLED (Hypertension, Abnormal renal/liver function, Stroke/thromboembolism, Bleeding history, Elderly [age >65 years], Drug consumption/alcohol abuse) score.[13] All individual risk factors for stroke and bleeding were available for the final analysis.

Endpoints included the incidence of stroke or systemic embolism, and major bleeding including intracranial hemorrhage. The diagnosis of stroke was made based on clinical and imaging criteria. It required the abrupt onset of focal neurological symptoms lasting at least 24 hours and supported by congruent ischemic lesions in the absence of cerebral hemorrhage at CT or MRI scan. Diagnosis of systemic embolism required symptoms consistent with an acute loss of blood flow to a peripheral artery, which is supported by objective evidence of embolism.

Major hemorrhage was defined according to the ISTH criteria.[14] It included bleeding causing death, bleeding at critical sites (intracranial, retroperitoneal, intraocular bleeding causing blindness, joint hemorrhage), or bleeding associated with a fall in hemoglobin level of ≥2 g/dL in 24 hours and requiring transfusion of ≥2 units of packed red blood cells. INR at the time of event (within 7 days) was recorded.

Total follow-up time for each individual was calculated as the number of days from the start of OAC until censoring. Individuals were censored when an endpoint occurred, death (from a cause other than a stroke endpoint), or last date of data collection.

3 | STATISTICS

Rates of events are calculated as events per 100 person-years. Baseline characteristics are presented as appropriate and compared in individuals who bled versus those who did not using Fisher's exact test. Kaplan-Meier survival analysis was used to determine the cumulative incidence of major bleeding events; data were compared using the Log-rank test for comparison. Cutoff for statistical significance was set at $P < .05$. The assessed patient characteristics for statistical analysis were patient demographics: age, sex, and single CHA_2DS_2VASc and HASBLED risk factors. Baseline characteristics and incidence rates are provided in detail; comparative statistical analysis data are presented in results only in case of significance ($P < .05$).

4 | RESULTS

Starting May 2011 until May 2016, of the 7497 individuals recorded into the register, 431 (5.7%) fulfilled the extraction criteria. The mean age of the cohort was 63 years, and 160 (37%) were female. Age (65-74 years) was the only thromboembolic risk factor in 187 individuals, while hypertension (n = 223), diabetes (n = 10), congestive heart failure (n = 10), and vascular disease (n = 1) were the single remaining risk factors (n = 244). Mean CHA_2DS_2VASc score of the cohort was 1.4, while the mean HASBLED score was 0.9. The clinical characteristics of the studied cohort are illustrated in Table 1.

The follow-up extended for 604 person-years. During follow-up, 1 nonfatal ischemic stroke was recorded (0.17 per 100 person-years). The event occurred in a female patient with hypertension as an adjunctive risk factor; her TTR was 42%, and the INR at the time of event was 1.8.

There were 9 major bleeding events (1.49 per 100 person-years) as illustrated in Table 2. Of the 9 events, 2 occurred in female individuals with hypertension and 7 in males, 5 of which with hypertension and 2 with age ≥65 as the single thromboembolic risk factor. HASBLED score was 1 in all but one case. The INR at the time of event was within therapeutic range in all but two individuals (INR = 3.9 in a patient with gastrointestinal bleeding; INR = 4.2 in a patient with genitourinary

TABLE 1 Characteristics of 431 patients with 1 NGR risk factor

Clinical characteristic	No. (%) or Mean ± SD
Age, y	62.9 ± 8.0
Age <65 y	244 (56.6)
Female	160 (37.1)
Past medical history	
CHF	10 (2.3)
HTN	223 (51.7)
DM	10 (2.3)
Vascular disease/CAD	1 (0.2)
Abnormal renal/Liver function	25 (5.8)
History or predisposition to bleeding	5 (1.2)
Medication predisposition to bleeding	30 (7.0)
Labile INR	139 (32.3)
Drugs	
ACEi/ARB	111 (25.8)
BB/CCB	244 (56.6)
Antiplatelet	22 (5.1)
Steroids	17 (3.9)
Statins	42 (9.7)
CHA2DS2VASc score	1.4 (±0.5)
1 (men)	271
2 (women)	160
HASBLED	0.9 (±0.8)
Mean follow-up, days	512 (±367)

TABLE 2 Major bleeding events on warfarin

No.	Age	Sex	TE risk factor	HASBLED items	Type of bleeding	INR at event	Time to event (d)	Notes
1	59	F	HTN	Aspirin	Acute anemia (post-traumatic)	2.1	175	Myeloproliferative disease
2	64	M	HTN	Labile INR	ICH	2.7	334	ACEi, well-controlled HTN; permanent OAC discontinuation
3	68	M	Age	Age	ICH	N/A	316	No concomitant therapy
4	74	M	Age	Age	Acute anemia (post-traumatic)	2.4	1269	permanent OAC discontinuation
5	62	M	HTN	Labile INR	ICH	2.5	266	Deceased
6	62	F	HTN	Labile INR	Acute anemia (GI)	3.9	980	
7	62	M	HTN	Labile INR	Acute anemia (hematuria)	4.2	672	CCB and BB, well-controlled HTN
8	64	M	HTN	Abnormal renal function; aspirin	Acute anemia (hematuria)	2.9	249	
9	58	M	HTN	None	ICH	2.4	169	Well-controlled HTN; permanent OAC discontinuation

TE, thromboembolic; HTN, hypertension; ICH, intracranial hemorrhage; GI, gastrointestinal; OAC, oral anticoagulant; ACEi, angiotensin-converting enzyme inhibitor; BB, beta-blocker; CCB, calcium channel blocker.

bleeding). Patient characteristics and the HASBLED score in major bleeding did not differ from the rest of the cohort (mean HASBLED score 1.0 ± 0.5 vs 0.9 ± 0.8, respectively). The quality of treatment was not related to major bleeding. Major hemorrhage occurred in 4 of 139 individuals with labile INR and 5 of 244 individuals with stable INR (2.9% vs 2%, $P = .74$). More bleeding events occurred in individuals <65 years old as compared to individuals in the 65-74 age-group (7 vs 2, respectively; $P = .31$). Major bleeding incidence was more frequent among individuals with hypertension (7 vs 2 cases, respectively; $P = .17$).

There were 4 intracranial hemorrhages (0.66 per 100 person-years) all in male individuals; 1 with age ≥65 and 3 with hypertension as the sole risk factors. On Cox regression, hypertension was the only predictor of major bleeding (HR = 21.9, 95% CI 1.6-400; $P = .027$).

5 | DISCUSSION

In this study, we found that in individuals categorized at the lower-risk end of the CHA_2DS_2VASc score (CHA_2DS_2VASc 1 for males and 2 for females) and treated with warfarin, the rate of major bleeding was 1.49 per 100 person-years, and 0.66 per 100 person-years for intracranial hemorrhage (ICH). On the other hand, the incidence of stroke was 0.17 per 100 person-years.

Starting oral anticoagulation in NVAF individuals requires a careful evaluation of the risk-benefit profile of any anticoagulation therapy.[9] In individuals with a $CHA_2DS_2VASc > 2$, this profile is in favor of anticoagulation, as is against anticoagulation in individuals with a CHA_2DS_2VASc of 0. The risk threshold for which NVAF individuals should receive anticoagulation is >1% per year, and there is uncertainty whether individuals with 1 NGR factor meet this requirement. This group of individuals is not represented in the pivotal trials evaluating novel anticoagulants in NVAF population. Available data come from nationwide registries health insurance databases, reporting conflicting rates of ischemic stroke in this patient group.[9-11,15-19] These diversities reflect differences in the methodology with results conditioned by several issues[6] regarding the definition of stroke used and the influence of the quarantine period,[9] if any, set at different time points by different studies.[11] The 2010 ESC guidelines recommended anticoagulation in $CHA_2DS_2VASc = 1$ individuals based on post hoc calculated stroke risk of 1.3%,[20] while latest data have reported a lower (0.8%) incidence rate of ischemic stroke at CHA2DS2-VASc 1 individuals.[10] The rate of stroke (0.17 per 100 person-years) in our inception cohort of treated individuals is in line with the expected reduction in individuals treated with warfarin,[21] while major bleeding incidence (1.49 per 100 person-years) is of concern. The reported rate of ICH in the general population is 0.01 per 100 person-years in the <75 year age-group.[22] In the ATRIA study,[23] an NVAF cohort with a mean age of 72 years, the reported rate of ICH in nonanticoagulated individuals was 0.29 per 100 patient-years. In light of these data, anticoagulation conferred a markedly increased risk of ICH in our population (mean age 63 years) of NVAF individuals. Surprisingly, we found more major bleeding and ICH in individuals <65 years old. These data deserve attention, as age 65-74 years is a more powerful ischemic stroke risk factor than the others weighted as 1 on CHA_2DS_2VASc score,[2] thus individuals with only 1 of the other factors not only may be below the 1% per year ischemic threshold but may be at higher risk for major and ICH according to our data. Furthermore, our results suggest that another single risk factor, such as hypertension, not only is a "minor" ischemic risk factor but also might significantly expose warfarin-treated individuals to major bleeding. We had also more individuals below 65 years of age experiencing major bleeding. Taken together, these data urge caution in the decision to treat with warfarin individuals with 1 NGR risk factor.

Strengths of the present study lie in its design. First, in contrast to retrospective studies based on data regarding dispensing of medications, the present study suggests a causal relationship rather than temporal association. Second, the gathered information allowed researchers to comment on the clinical importance of the bleeding events, excluding clinically insignificant bleeding with the bleeding outcome data. Third, we could calculate the HASBLED score (which includes labile INR) rather than HASBLED, used in administrative data studies.

Limitation of this study is the relatively low number of individuals assessed, although this population (1 NGR risk factor) is also poorly represented in other NVAF studies. Arguably, the relatively short follow-up might have tipped the balance in favor of the side effects (side effects develop early with the treatment, while complications of the disease may take longer to develop). However, long follow-up is not suitable for this kind of population because NVAF is not a "static" healthcare state due to changes in risk factors change over time.[24] As time goes by, age and other risk factors develop more frequently; thus, longer follow-up times switch the patients to higher thromboembolic risk category, where anticoagulation would be justified. Under these premises, our relatively shorter follow-up is favorable when assessing this specific (1 NGR risk factor) population.

The major clinical implications of this work are that the risk of bleeding should not be underestimated in younger individuals without significant bleeding risk factors. By treating these individuals with warfarin, not only we had a low impact in ischemic risk, but also a high impact on major bleeding incidence. Our data need confirmation from larger prospective registries, but this study might serve as a pivotal work for further research.

Other robust analysis points against the use of anticoagulation with warfarin in this group of individuals,[10] and our data on major bleeding further support this point. NOACs may be a more suitable treatment option for those at lower stroke risk, but data are still scant, and importantly, this patient group is not represented in the pivotal NOAC trials.

In conclusion, we found an elevated risk of major bleeding and intracranial hemorrhage in NVAF individuals treated with warfarin with 1 NGR risk factor for stroke. These data call for caution when treating with warfarin these individuals.

AUTHOR CONTRIBUTION

G.D. and V.P. conceived and designed the research and drafted the manuscript. G.Z. and S.P.J. performed statistical analysis. E.A. acquired and processed the data. G.Z., F.M., D.P., S.T., and A.T. made critical revision of the manuscript for key intellectual content.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

ORCID

Vittorio Pengo http://orcid.org/0000-0003-2064-6071

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