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Warfarin persistence among atrial fibrillation patients – why is treatment ended?

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Abstract

Background and Aim

Warfarin treatment discontinuation is significant among patients with atrial fibrillation (AF). Studies mainly focused on whether the proportion of warfarin persistence and discontinuation are clinically appropriate are absent. This study evaluates warfarin persistence with focus on predictors for, and reasons to, warfarin discontinuation in AF patients.

Methods

From the national quality register AuriculaA, all AF patients in Sundsvall, Sweden, on warfarin treatment on January first, 2010 were included. These 478 patients were followed until discontinuation or study-stop December 31, 2013. By going through each patient's medical record risk factors for thromboembolism, bleeding and causes of discontinuation were obtained.

Results

Proportion of warfarin persistence was 0.91 (95% confidence interval (CI) 0.89 to 0.93) after one year and 0.73 (95% CI 0.69 to 0.77) after four years. *Previous intracranial bleeding, excessive alcohol use, anemia* and *pulmonary or peripheral emboli* were each associated with over two times higher risk of discontinuation (hazard ratio (HR) 5.66, CI 2.23-14.36, HR 2.54, CI 1.48-4.37, HR 2.40, CI 1.38-4.17, and HR 2.13, CI 1.02-4.46). Among patients discontinuing, 50.5% were due to questionable causes, such as *sinus rhythm* (33.9%), *patients demand* (10.1%) and *falls* (8.2%). The majority (43.1%) of treatment discontinuers were changed to aspirin, while 40.4% of them were left without medical stroke prophylaxis.

Conclusions

Although persistence to warfarin among AF patients proves higher than previously reported, there is room for improvement since half of the discontinuers have questionable reasons for treatment stop and the majority of them receive no other efficient stroke prophylaxis.

Keywords

Atrial fibrillation, discontinuation, persistence, stroke prophylaxis, treatment, warfarin.

Introduction

Atrial fibrillation (AF), a significant risk factor for ischemic stroke, is diagnosed in about three percent of the adult population in Sweden and the prevalence increases with age [1-3]. Presence of concomitant risk factors for stroke such as heart failure, hypertension, diabetes mellitus, age, previous stroke/thromboembolism, vascular disease or female sex confer a risk of stroke up to 18% per year [4]. This risk can be reduced by two thirds with oral anticoagulation treatment such as warfarin [5]. However, treatment with oral anticoagulants is also associated with an increased risk of bleeding [6, 7]. Initiation of antithrombotic therapy therefore requires an individual assessment of the risk of thromboembolism as well as the risk of bleeding [8].

According to national guidelines all AF patients with one point or more according to risk score CHA₂DS₂-VASc should be offered treatment with warfarin or any of the new oral anticoagulants (NOACs) [9]. Warfarin is in the era of NOACs still the most common anticoagulant in Sweden [10, 11]. From year 2013 Swedish national guidelines equals NOACs and warfarin as thromboembolic prophylactic treatment among AF patients [9].

Studies on warfarin treatment persistence among AF patients clearly points to a significant discontinuation rate [12-17]. Such discontinuation is associated with male sex, homelessness, susceptibility to adverse side effect of drugs and cognitive impairment. However, until now, there are no consistent predictors established [18, 19]. Previous studies that mainly focus on whether the proportion of warfarin persistence and reasons for discontinuation are clinically appropriate are absent.

The aim of this study was to elucidate predictors for warfarin treatment discontinuation in AF patients and to determine to what extent treatment discontinuations were clinically motivated.

Materials and Methods

AuriculA is a Swedish national quality register, administering patients with AF or anticoagulation. The register has existed since 2006 and contains today over 110 000 patients [11].

From AuriculA, all patients in Sundsvall, Sweden with AF and warfarin treatment on January first, 2010 were included. Information about risk factors according to CHADS₂ [4], CHA₂DS₂-VASc [20] and HAS-BLED [21] was collected by going through each patient's medical records looking both at the set diagnoses according to ICD codes and the free text for both primary and hospital care. See appendix for definitions used. Concurrent medications were obtained from the list of prescribed drugs found in the medical record. The reason for discontinuation, as documented in the medical record, was noted. These reasons were later categorised by the authors.

Clinically motivated treatment discontinuation was defined as *bleeding complications*, *advanced comorbidity* (where risk/benefit of further warfarin treatment is negative, i.e. liver failure, advanced cancer and palliative care), *acute need for platelet inhibition therapy*, *problematic monitoring* and/or *no indication for warfarin* (CHA₂DS₂-VASc = 0 p). Clinically questionably treatment discontinuations was regarded for *sinus rhythm*, *falls*, *risk of falls* and *normal echocardiography*. Patients demand was regarded as an own category, since clinically motivated arguments here can be hard to apply.

INR values were not obtained and thus labile INR was excluded from the HAS-BLED score. The study population was followed from January 1, 2010 to December 31, 2013, or until discontinuation of warfarin, whichever occurred first. Persistence to warfarin treatment was defined as on-going treatment until end of study, moving out of the region or death.

All tests were performed two-tailed, and a p-value of < 0.05 was considered significant. All analyses were performed using SPSS statistics (Version 21; SPSS Inc., IBM Corporation, NY, USA). Confidence interval (CI) was set to 95%.

Results

In total 478 individuals, 33.7% females, with a mean age at study start of 69.5 years (± 8.9) were included. The mean CHADS₂, CHA₂DS₂-VASc and HAS-BLED score at start were 2.06 (± 1.27), 3.41 (± 1.77) and 2.18 (± 1.07) respectively (Table 1).

Of the 478 patients, 369 (77.2%) were persistent to warfarin treatment. During the study period 22 (4.6%) patients died and 14 (2.9%) patients moved out of the region. The overall proportion of warfarin treatment persistence was 0.91 (95% CI 0.89 to 0.93) after one year, 0.85 (95% CI 0.81 to 0.89) after two years and 0.73 (95% CI 0.69 to 0.77) after four years (Table 2).

Baseline data showed that patients with previous intracranial bleeding were most likely to discontinue warfarin treatment. They had more than five times higher risk of discontinuation (hazard ratio (HR) 5.66, CI 2.23-14.36). Patients with excessive alcohol use, anemia or pulmonary or peripheral emboli had more than two times higher risk of treatment discontinuation than others (HR 2.54, CI 1.48-4.37, HR 2.40, CI 1.38-4.17, and HR 2.13, CI

1.02-4.46). Females and patients with history of stroke/TIA were more likely to persist on warfarin (HR 0.50, CI 0.31-0.81, and HR 0.44, CI 0.23-0.82) (Table 3).

No significant association was seen between the risk scores CHADS₂, CHA₂DS₂-VASc or HAS-BLED and warfarin treatment discontinuation.

Among the 71 individuals with additional indications for warfarin treatment, 58 continued and 13 discontinued during the study period. No significant difference in risk of discontinuation was found between those that did and did not have additional indications.

Warfarin treatment was discontinued in 109 individuals. In 54 individuals the discontinuation was clinically motivated and in 55 questionable. The most common causes of discontinuation were sinus rhythm (31.2%), problematic monitoring (16.5%) and bleeding (14.7%) (Table 4).

Of the 109 patients discontinuing warfarin 44 (40.4%) received no thromboembolic medical prophylaxis, while 65 (59.6%) received another antithrombotic agent (Figure). The most commonly obtained agent was aspirin (43.1%).

Discussion

Warfarin treatment persistence

This study found a warfarin treatment persistence of 91% and 73% after one and four years, respectively. This is higher than what has been previously described, where prior studies have shown persistence between 65.1% and 78.8% at one year, 45% and 60% at two years, and 35% to 39.7% at five years [13, 16, 22-24]. Most of these studies defined discontinuation according to whether a new prescription was fulfilled within a certain time period after which

the patient is thought to be out of pills [13, 16, 22, 24-26]. One of these studies used self-reported discontinuation via surveys [23]. In difference to these, this study identified discontinuation by going through the medical records to find date and cause of discontinuation. Looking only at the filling of prescriptions, persistence may be underestimated since patients may have saved pills. On the other hand, with self-reported persistence, there is a risk of overestimation. Most other studies included only treatment naïve patients whereas this study starts at a specific date, with both warfarin naïve and treatment experienced patients included. This might have contributed to the higher persistence found since patients have been shown to discontinue more frequently early in their treatment period [24].

Only one study found a higher one-year persistence of 92.9% [26]. This study, like ours, included both treatment naïve and experienced individuals. However, in their study, discontinuation was considered only when a supposed gap in warfarin supply of 90 days occurred and individuals with documented contraindications to anticoagulation, such as risk of bleeding, were excluded.

Out of the discontinuers, four patients received NOACs. One can therefore argue that these individuals did not actually discontinue adequate stroke prophylaxis but rather changed to a different one. This would give a slightly higher persistence, if changing the definition of treatment persistence to on-going warfarin *or* shift to NOACs.

Predictors of warfarin treatment discontinuation

The variables found to be associated with increased risk of discontinuation on Cox regression analysis were *intracranial bleeding*, *excessive alcohol use*, *anemia* and *pulmonary or peripheral emboli*.

Suh et al. has shown higher risk of warfarin discontinuation among AF patients with a bleeding event within 90 days, compared with AF patients free from recent bleeding events [25], which support our finding of increased risk of discontinuation for patients with previous intracranial bleeding. However, we did not separate bleeding events according to time passed since it occurred. It is further notable that other major bleedings were not associated with a significant risk for treatment discontinuation in our analysis.

Patients with excessive alcohol use are known to be less likely to adhere to medical treatment and anticoagulation treatment is no exception [18]. No previous study has described *anemia* as a predictor of warfarin treatment discontinuation, but a true relation is probable when anemia clinically is often linked to feared or proven bleeding events.

Pulmonary and peripheral emboli was just about significant ($p=0.044$), why further analysis should be done with caution. These patients were overrepresented with both *excessive alcohol use* and *previous intracranial bleeding*, why interaction can be suspected.

Other studies have shown that higher CHADS₂ score is associated with better warfarin treatment persistence [13, 22, 24, 25]. A study by Hylek et al showed that among patients with CHADS₂ score three or higher, the rate of hemorrhage and discontinuation was higher

[27]. In our study neither CHADS₂, CHA₂DS₂-VASc nor HAS-BLED score was significantly associated with risk of discontinuation.

The variables associated with high warfarin treatment persistence in our study were female sex and history of stroke/TIA. Stroke/TIA patients with AF are probably more motivated to anticoagulant treatment than AF patients who have never experienced loss of cerebral function as a sign of the underlying treated disease. The association with female gender and persistence has been reported in some previous studies [13, 24, 25], but was contradicted by Skeppholm and Friberg [17]. Notable is that 92% of all patients with excessive alcohol use in our study were male.

Cause of warfarin treatment discontinuation

The most common cause of discontinuation was sinus rhythm. This corresponds with a previous study where sinus rhythm was the most common cause of discontinuation among patients younger than 80 years [27]. There were 37 patients (33.9%) discontinuing due to sinus rhythm in our cohort. Of these, three individuals had CHA₂DS₂-VASc zero which is classified as low risk of stroke and no indication for oral anticoagulation [8, 20]. For the remaining 34 patients, sinus rhythm as a cause of discontinuation can be questioned, since long-term anticoagulation is required for AF patients with identified high risk for thromboembolism even after sinus rhythm has been restored [8].

Previous fall has been questioned as a medically accurate reason to discontinue oral anticoagulation treatment in AF patients, since the risk of stroke almost always outweighs the risk of intracranial bleeding even in these patients [28]. There were 9 patients (8.3%) in our

cohort who stopped treatment due to fall or risk of fall, adding to questionable decisions to stop treatment.

According to a study by Bushnell et al, self-discontinuation is rare [23], while O'Brien et al reported 'patient refusal' as reason for discontinuation in as much as 21.1% [29]. In our study, patient demand was given as the main cause of discontinuation for 11 patients (10.1%).

Patient's demand as a cause for treatment-stop should be questioned. At least, these AF patients should receive extensive information about the risk-benefit ratio with anticoagulant treatment. If the patient's reluctance to warfarin treatment is based on practical issues, such as INR monitoring and dosage, alternative treatment like NOACs could be considered.

In our study a total of 55 patients (50.5%) discontinued due to a medically questionable cause or patients demand, indicating that there still is room for improvement in anticoagulant treatment persistence.

Medications after discontinuation

The majority of treatment discontinuers changed to a different antithrombotic agent, where aspirin was the most commonly used. This is worrying since aspirin mono-therapy in AF is only recommended for those who refuse oral anticoagulants or do not tolerate dual antiplatelet therapy with aspirin plus clopidogrel [8]. In addition, a recent study could not show any protective effect of aspirin mono-therapy as stroke prophylaxis in atrial fibrillation patients [30]. Dual antiplatelet therapy was given to 6.4% of the discontinuers, the risk of bleeding with this therapy is substantial and most patients do not benefit from this change [9].

Limitations and strengths

This is a relatively small, retrospective non-inception cohort study. The patients were followed from a specified date. Therefore both warfarin naïve and experienced patients were included which can partly explain the high warfarin persistence found. In the entire Auricula cohort the vast majority of the patients (64%) have atrial fibrillation as indication for oral anticoagulation, the remaining indications are mostly venous thromboembolism or mechanical heart valves. When comparing baseline variables of patients on anticoagulants due to atrial fibrillation as in this study, our cohort is representative of the entire Auricula cohort (data not shown).

The HAS-BLED score was calculated excluding labile INR. Intensity of anticoagulation plays an important role in the balance between risk of thrombosis and bleeding and poor INR control has a negative effect on persistence [24]. The intake of over-the-counter drugs such as non-steroidal anti-inflammatory drugs (NSAID) may affect the risk of bleeding but could not be controlled. The study also did not consider other drugs that may affect the platelet function. All patients were controlled at a single specialized anticoagulation clinic with a high treatment quality as measured by time in target range, which may affect persistence. It is possible that these patients are better informed and are under closer control, furthermore they may have more comorbidity or risk factors than patients controlled within the primary health care. However, studies from Sweden have shown that there is no difference in bleeding risk between patients treated at anticoagulation clinics and primary health care centers [31, 32].

Despite the presence of some limitations, this study also has several strengths. A major strength is the method by which it is performed. Rather than looking at whether the individuals fulfilled their prescription within a certain time period, discontinuation was

identified by going through the medical records. The risk factors were identified the same way and did not only include set diagnoses but also diagnoses and descriptions found in the medical records. Another advantage was that the patients that moved their monitoring to a primary health care center within the same region were still followed until end of the study period or discontinuation. Because of this, only a small number was lost to follow-up. The patients were not prospectively randomised with inclusion- or exclusion criteria, which makes the study more applicable.

Conclusion

This study shows persistence to warfarin treatment among AF patients much higher than previously reported. Although persistence was proven better than anticipated there still is room for improvement. This since for half of the non-persisters, the adequacy of the decision to stop treatment can be questioned. AF patients with concomitant risk factors are at a significant risk of stroke. Clinicians should think twice when discontinuing an adequate stroke prophylaxis and individual potential risks and benefits with oral anticoagulation must be considered in each patient. This can hopefully increase caution with warfarin discontinuation and result in more individuals remaining on adequate stroke prophylaxis.

Ethics

This study was approved by the regional ethical review board in Umeå, Sweden (EPN nr 2014-175-31M) and conforms to the declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

AS and FB designed the study. AE, FB and AS extracted and analysed data. FB and AE drafted the manuscript. All authors reviewed the manuscript, contributed to its revision, and approved the final version submitted.

Legends of tables

Table 1. Baseline characteristics of 478 patients with atrial fibrillation on warfarin treatment.

Presented as n (%), if other not indicated.

Table 2. Persistence to warfarin treatment for 478 patients with atrial fibrillation, presented in a Life Table. CI= confidence interval.

Table 3. Cox regression analysis on baseline variables impact on warfarin treatment non-persistence for patients with atrial fibrillation. HR= hazard ratio, CI= confidence interval.

Table 4. Main cause of discontinuation for the 109 patients stopping warfarin treatment during the study period.

Legends of figure

Figure. Medical stroke prophylaxis after stopping warfarin treatment.

Given as percent of the total number of discontinuers (n= 109). NOACs= new oral anticoagulants, LMWH= low molecular weight heparin.

Appendix.

Table 1.

Baseline variables	n (%)
Age (years)	
Mean (SD)	69.5 (± 8.9)
<65	138 (28.9)
65-74	212 (44.4)
≥ 75	128 (26.8)
Sex	
Male	317 (66.3)
Female	161 (33.7)
Hypertension	405 (84.7)
Chronic heart failure	171 (35.8)
Vascular disease	112 (23.4)
Diabetes mellitus	99 (20.7)
Thromboembolism	
Stroke	76 (15.9)
TIA	28 (5.9)
Pulmonary or peripheral emboli	22 (4.6)
Renal failure	29 (6.1)
Liver failure	0 (0.0)
Anemia	56 (11.7)
Antiplatelet drugs	37 (7.7)
Excessive alcohol use	36 (7.5)
Cognitive impairment	12 (2.5)
Previous major bleeding	
Gastrointestinal	41 (8.6)
Intracranial	11 (2.3)
Other	19 (4.0)
CHA₂DS₂-VASc	
Mean (SD)	3.41 (± 1.77)
0	20 (4.2)
≥ 1	458 (95.8)
CHADS₂	
Mean (SD)	2.06 (± 1.27)
0	38 (8.0)
≥ 1	440 (92.1)
HAS-BLED	
Mean (SD)	2.18 (± 1.07)
0-2	308 (64.4)
≥ 3	170 (35.6)

Table 2.

Year	Patients on treatment (n)	Discontinuers of treatment (n)	Ending study (n)	Cumulative proportion persistent to treatment at end of interval	95 % CI for cumulative proportion
0	478	44	10	0.91	0.89–0.93
1	424	28	10	0.85	0.81–0.89
2	386	21	8	0.80	0.76–0.84
3	357	16	341	0.73	0.69–0.77

Table 3.

	HR	95% CI for HR			p
Age	1.01	0.99	-	1.04	0.230
Female sex	0.50	0.31	-	0.81	0.005
Hypertension	0.69	0.41	-	1.16	0.159
Chronic heart failure	1.01	0.67	-	1.53	0.970
Vascular disease	1.49	0.94	-	2.38	0.090
Diabetes mellitus	0.91	0.56	-	1.49	0.707
Stroke/TIA	0.44	0.23	-	0.82	0.010
Pulmonary or peripheral emboli	2.13	1.02	-	4.46	0.044
Renal failure	0.87	0.40	-	1.88	0.717
Anemia	2.40	1.38	-	4.17	0.002
Antiplatelet drugs	1.09	0.56	-	2.10	0.805
Excessive alcohol use	2.54	1.48	-	4.37	0.001
Cognitive impairment	1.21	0.35	-	4.18	0.768
Previous gastrointestinal bleeding	1.07	0.55	-	2.08	0.853
Previous intracranial bleeding	5.66	2.23	-	14.36	<0.001
Previous other major bleeding	1.28	0.56	-	2.90	0.558

Table 4.

	n (%)
Clinically motivated discontinuations	54 (49.5)
Bleeding	16 (14.7)
Comorbidity	12 (11.0)
Problematic monitoring	
Instable INR	12 (11.0)
Excessive alcohol use	4 (3.7)
Cognitive impairment	2 (1.8)
Acute need for platelet inhibition therapy	
AMI* + PCI**	3 (2.8)
PCI**	2 (1.8)
No indication (CHA ₂ DS ₂ -VASc = 0)	3 (2.8)
Patient's demand	11 (10.1)
Clinically questionable discontinuations	44 (40.4)
Sinus rhythm	34 (31.2)
Risk of fall	7 (6.4)
Fall	2 (1.8)
Normal echocardiography	1 (0.9)

* Acute Myocardial Infarction

** Percutaneous Coronary Intervention

Figure.

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Appendix.

Variables	Definitions
Congestive heart failure	Heart failure or an echocardiogram with ejection fraction < 50% described in the medical record.
Hypertension	Hypertension or antihypertensive medication described in the medical record.
Diabetes mellitus	Diabetes mellitus 1 or 2 described in the medical record.
Stroke	Ischemic or hemorrhagic stroke described in the medical record.
TIA	Transient ischemic attack (TIA) described in the medical record.
Pulmonary or peripheral emboli	Pulmonary emboli or peripheral arterial emboli.
Vascular disease	Peripheral vascular disease, myocardial infarction, aortic aneurysm, aneurysms and dissections of other peripheral arteries, occlusion of cerebral/precerebral arteries, and aortic plaques.
Liver failure	Diagnosis of liver failure described in the medical record.
Renal failure	Creatinine clearance < 50ml/min. The creatinine clearance closest to start and stop of the study period was used.
Anemia	Anemia described in the medical record. Including all types of anemia.
Gastrointestinal bleeding	Any bleeding from the gastrointestinal tract described in the medical record.
Intracranial bleeding	All forms of intracranial bleeding described in the medical record. Including intracerebral-, subdural- and epidural bleedings. Both traumatic and a-traumatic.
Major bleeding	Bleeding according to ISTH: A fatal bleeding, and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or bleeding with a fall in hemoglobin level of 20g/L or more, or leading to transfusion of two or more units of whole blood or red cells [33].
Antiplatelet drugs	Antiplatelet drugs concomitant with warfarin at start or during the study period. For example clopidogrel, aspirin and NSAID. Not including COX-2 inhibitors.
Cognitive impairment	Any form of cognitive impairment described in the medical record. No diagnosis required.
Excessive alcohol use	Excessive alcohol consumption described in the medical record.