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Prediction of unstable anticoagulation with acenocoumarol versus warfarin in atrial fibrillation

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Abstract

Background: *The SAMe-TT_2R_2 (sex female, age, medical history, treatment, tobacco use, race) score was developed in patients with atrial fibrillation (AF) on warfarin. The present study aimed to 1) compare the anticoagulation quality and management of AF patients treated with warfarin with those on acenocoumarol and 2) optimize the SAMe-TT_2R_2 score to detect AF patients at high risk of unstable anticoagulation with acenocoumarol and warfarin.*

Methods: *In a single-center retrospective study, 320 patients with AF, including 15 (5%) after valve replacement, aged 40–82 (median 70) years, including 203 (63%) receiving acenocoumarol and 117 (37%) treated with warfarin, were studied. The SAMe-TT_2R_2 score was modified based on the candidate factors retrieved from univariate regression and assessed using the receiver operating curves (ROC).*

Results: *A median SAMe-TT_2R_2 score was 2 (1–3). Proportions of patients with ≥ 2 points and 0–1 points in the SAMe-TT_2R_2 score who had the time in therapeutic range (TTR) ≤ 70% were similar (61 [67%] vs. 63 [56%], p = 0.11). A modified score, involving medical history (myocardial infarction [MI] and chronic obstructive pulmonary disease [COPD], 1 point), statin treatment (1 point) and tobacco use (2 points) had a higher area under the curve (AUC) in patients on acenocoumarol compared to SAMe-TT_2R_2 (0.66; 95% confidence interval 0.58–0.73 vs. 0.56; 0.48–0.64, p = 0.042); ≥ 1 point indicated TTR > 70% with a sensitivity and specificity of 61% and 63%, respectively.*

Conclusions: *The SAMe-TT_2R_2 score is less effective in predicting unstable anticoagulation with acenocoumarol versus warfarin. Adding statin use and highlighting COPD and previous MI increases a predictive value of this score for acenocoumarol.* (Cardiol J 2017; 24, 5: 477–483)

Key words: atrial fibrillation, anticoagulant therapy, acenocoumarol, warfarin

Introduction

The prevalence of atrial fibrillation (AF) has quadrupled over the last 50 years [1]. Although non-vitamin K antagonists have been introduced in therapy of AF, vitamin K antagonists (VKA) remained the only treatment with established safety in valvular AF [2]. Quality of anticoagulation with VKA, assessed by the time in therapeutic range (TTR), is closely associated with the risk of stroke [3, 4]. Recently, several factors have been incorporated by Apostolakis et al. [5] into a clinical prediction scheme with the acronym SAMe-TT_2R_2 (sex female, age > 60 years, medical history [more than two comorbidities], treatment [interacting drugs, e.g. amiodarone for rhythm control], tobacco use [doubled], race [doubled]).

The anticoagulants assessed by Apostolakis et al. [5] have been referred to as VKA; however, the population included in the AFFIRM (The Atrial Fibrillation Follow-up Investigation of Rhythm Management) study was treated only with war-

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farin [6]. The SAMe-TT_2R_2 score has been demonstrated to have a modest ability of predicting stable anticoagulation control in patients treated with acenocoumarol [7], but there are no reports on the comparison of clinical utility of SAMe-TT_2R_2 for warfarin and acenocoumarol. The differences observed in anticoagulation control dependent on the type of VKA may result from a shorter half-life of acenocoumarol compared to warfarin [8]. Apart from the pharmacokinetic profile, it has been shown that carriers of variant alleles for cytochrome P type 2C9 (CYP2C9) and gamma-glutamyl carboxylase genes required a lower dose of warfarin as compared with non-carriers; the effects of those polymorphisms have been absent with regard to acenocoumarol dose [9]. Arterial hypertension, use of statins and aspirin as well as older age were identified by Undas et al. [10] as the clinical factors responsible for improved anticoagulation control after switching from acenocoumarol to warfarin. Those observations might be especially interesting in regard to differences in utility of SAMe-TT_2R_2 for predicting stability of anticoagulation on warfarin and acenocoumarol, as the score is based on common clinical factors.

We aimed to: 1) compare the anticoagulation quality and management of AF patients treated with warfarin with those on acenocoumarol and 2) optimize the SAMe-TT_2R_2 score to detect AF patients at high risk of unstable anticoagulation with acenocoumarol and warfarin.

Methods

Study design

This single-center retrospective study included 320 consecutive patients with documented AF, from the databases who were referred to the John Paul II Hospital, Krakow, Poland between 2010 and 2012. All patients were on oral anticoagulation with VKA for at least 6 months prior to enrolment. Paroxysmal AF, persistent AF and permanent AF were defined according to the European Society of Cardiology guidelines [11]. The exclusion criteria were: signs of acute infection and C-reactive protein ≥ 10 mg/L, acute coronary syndrome within the preceding 12 months being treated with dual antiplatelet therapy, hepatic injury (alanine aminotransferase ≥ 1.5 times the upper limit of normal), chronic kidney disease stage 4 or more or known malignancy. The study was approved by the Ethical Committee of the Jagiellonian University. All participants gave informed consent.

Data on demographic characteristics, cardiovascular risk factors, comorbidities, prior valvular surgery and treatment were collected by the recruiting physician. Obesity was defined as body mass index ≥ 30 kg/m^2. Arterial hypertension was diagnosed based on a history of hypertension (consistent blood pressure ≥ 140/90 mm Hg). Diabetes mellitus was defined as according to the American Diabetic Association criteria [12]. Coronary artery disease was diagnosed based on positive results of cardiac stress tests, cardiac catheterisation, or coronary computed tomography angiography. Myocardial infarction (MI) was recognized according to the guidelines [13]. Heart failure was defined as the presence of relevant symptoms and signs and left ventricular ejection fraction ≤ 40%. Ischemic stroke prior to the enrollment was diagnosed based on the symptoms and positive finding of brain non-contrast-enhanced computed tomography [14]. Chronic obstructive pulmonary disease (COPD) was diagnosed based on the signs and symptoms and results of spirometry. Chronic kidney disease was defined according to the guidelines [15]. TTR during VKA treatment was calculated with Rosendaal's method [16]. Stable anticoagulation was defined as having the TTR of ≥ 70% [17]. The value of ≥ 2 points in SAMe-TT_2R_2 score (sex female, age > 60 years, medical history [more than two comorbidities], treatment [interacting drugs, e.g. amiodarone for rhythm control], tobacco use [doubled], race [doubled]) indicated the risk of unstable anticoagulation [5]. The CHA_2DS_2-VASc (cardiac failure, hypertension, age > 75 years, diabetes, stroke, vascular disease, age 65–74 and sex) score was used to assess the risk of stroke.

Statistical analysis

Categorical variables were presented as numbers and percentages. Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range. Normality was assessed by the Shapiro-Wilk test. Equality of variance was assessed using the Levene's test. Differences between groups were compared using the Student's or the Welch's t-test depending on equality of variance for normally distributed variables. The Mann-Whitney U test was used for non-normally distributed continuous variables. Categorical variables were compared by the Fisher's exact test for 2 × 2 contingency tables and Pearson's χ^2 test for other tables.

To assess the predictive ability of identifying the unstable patients with the SAMe-TT_2R_2 score, compared herein was the percentage of patients with

TTR ≤ 70% among patients with SAMe-TT_2R_2 ≥ 2 vs. 0–1. The univariate logistic regression was performed to calculate the odds ratio (OR) and 95% confidence interval (95% CI) of achieving TTR > 70% for the following factors. Covariates associated with TTR at levels of 0.1 in univariate analysis served as candidate factors to build the modified model, where each factor was given 1 or 2 points. The modified models were further tested in binary logistic regression models using a TTR cut-off at 70%. The predictive ability of the modified score was compared with SAMe-TT_2R_2 score using area under the receiver operating curve (AUC). The sensitivity and specificity were calculated. P-values < 0.05 were considered statistically significant. The study was powered to have a 80% chance of detecting a 2–4% TTR difference between groups stratified by SAMe-TT_2R_2 score of 0–1, 2–3 and ≥ 4 using a p-value of 0.05. In order to demonstrate such a difference or greater, 102 patients were required in each group. All calculations were done with JMP®, Version 9.0.0 SAS Institute Inc., Cary, NC, 1989–2007.

Results

The final analysis included 320 patients, 203 (63%) receiving acenocoumarol and 117 (37%) treated with warfarin. There were 305 patients with non-valvular AF, 11 (3%) subjects after mitral valve replacement, 3 (1%) following aortic valve replacement and 1 patient who underwent concomitant mitral and aortic valve replacement. The median age was 70 (minimum 46, maximum 89). The majority of the patients studied represented overweight women with permanent AF at high risk of ischemic stroke in CHA_2DS_2-VASc (Table 1). Patients treated with acenocoumarol were slightly younger, less frequently smoked cigarettes and were diagnosed with COPD compared to these receiving warfarin (Table 1).

SAMe-TT_2R_2

A median SAMe-TT_2R_2 score was 2 (1–3). Ninety one (45%) patients on acenocoumarol and 77 (66%) on warfarin had SAMe-TT_2R_2 ≥ 2 (p = = 0.0003). The median TTR was 66 (58–75.5)% with no differences related to the type of VKA. Median TTR of patients with SAMe-TT_2R_2 ≥ 2 (n = 186, 52%) was lower by 9.6% compared to those with SAMe-TT_2R_2 0–1 (64 [57–74]% vs. 70 [60–78]%, p = 0.002). There was a progressive decline in median TTR from the score of 0–1 to ≥ 4 in SAMe-TT_2R_2 score in the whole cohort of patients (70 [60–78]% vs. 65 [57–75]% vs. 61 [54.5–70]%, p = 0.007). The same was true for the patients treated with acenocoumarol (69 [59–77.5]% vs. 65 [57–75]% vs. 55.5 [45.75–61.75]%, p = 0.009) and warfarin (71.5 [63.25–79]% vs. 63 [56.5–73]% vs. 63.5 [58.25–72.25]%, p = 0.05) (Fig. 1).

124 patients (39%) had TTR > 70%. Among 168 (52%) patients with SAMe-TT_2R_2 ≥ 2 there were 115 (68%) individuals with TTR ≤ 70%. Among patients treated with acenocoumarol, there was a similar proportion of patients with TTR ≤ 70% among those SAMe-TT_2R_2 ≥ 2 points as well as 0–1 points (61 [67]% vs. 63 [56]%, p = 0.1). In contrast, taking into consideration only warfarin-treated patients, there were more subjects with TTR ≤ 70% among those with SAMe-TT_2R_2 ≥ 2 points in comparison to 0–1 points (54 [70]% vs. 18 [45]%, p = 0.01).

Modified SAMe-TT_2R_2

The following candidate factors found in the univariate regression analysis for TTR > 70% (Table 2) were included in the modified score for acenocoumarol-treated patients: medical history (MI — 1 point; COPD — 1 point), treatment (statins — 1 point), tobacco use (2 points). In acenocoumarol-treated patients, the modified score predicting the TTR > 70% had increased AUC compared to the SAMeTT_2R_2 (0.66; 95% CI 0.58–0.73 vs. 0.56; 95% CI 0.48–0.64, p = 0.04). The score of ≥ 1 point was associated with a TTR > 70% with a sensitivity and specificity of 61% and 63%, respectively. In the warfarin-treated patients, the AUC of identifying the TTR > 70% by the modified model was comparable with SAMe--TT_2R_2 (AUC 0.61; 95% CI 0.51–0.71 vs. 0.65; 95% CI 0.55–0.75, p = 0.3).

Discussion

According to the present research of available literature, this study is the first to compare the predictive ability of SAMe-TT_2R_2 score in AF patients treated with acenocoumarol versus warfarin on a long-term basis. This study showed that common and clinical risk factors incorporated in the SAMe-TT_2R_2 score are less effective in predicting unstable anticoagulation in AF patients on acenocoumarol as compared to warfarin. The modified score highlights the impact of statins, previous MI and COPD on the quality of acenocoumarol treatment in patients with AF.

Previously, Roldan et al. [18] validated the clinical value of the SAMe-TT_2R_2 score in a prospec-

Table 1. Baseline characteristics of patients with atrial fibrillation (AF) treated with acenocoumarol and warfarin.

Variable	Acenocoumarol (n = 203, 63%)	Warfarin (n = 117, 37%)	P
Demographic characteristics:			
Male	89 (44%)	53 (45%)	0.8
Age [years]	69 (62–73)	72 (65–78)	0.006
BMI [kg/m^2]	28 (24.6–32.6)	27.25 (24.5–31)	0.4
Tobacco use	23 (11)	58 (50)	< 0.001
Atrial fibrillation — type:			
Permanent	91 (44%)	54 (46%)	0.2
Persistent	55 (27%)	40 (34%)	
Paroxysmal	57 (28%)	23 (20%)	
Time since AF diagnosis [years]	5 (3-9)	4.0 (3–10)	0.8
Comorbidities:			
Coronary artery disease	60 (30%)	20 (17%)	0.02
Myocardial infarction	35 (17%)	19 (16%)	0.9
Peripheral artery disease	8 (4%)	28 (24%)	< 0.001
Arterial hypertension	118 (58%)	62 (53%)	0.4
Heart failure	50 (25%)	19 (16%)	0.09
Stroke	25 (12%)	20 (17%)	0.2
COPD	21 (10%)	34 (29%)	< 0.001
Diabetes mellitus type 2	34 (17%)	21 (18%)	0.9
Chronic kidney disease	25 (12%)	22 (19%)	0.1
Medication:			
VKA weekly dose [mg/week]	32.0 (23.0–42.0)	35.0 (21.0–48.0)	–
TTR [%]	66.5 ± 14.3	66.7 ± 13.3	0.09
Acetylsalicylic acid	60 (30%)	20 (17%)	0.02
Clopidogrel	10 (5%)	3 (3%)	0.4
Beta-blocker	113 (56%)	57 (49%)	0.2
ACEI	76 (37%)	40 (34%)	0.6
Statin	83 (41%)	44 (38%)	0.6
Amiodarone	26 (13%)	9 (8%)	0.2
Digoxin	29 (14%)	15 (13%)	0.9
Scores:			
SAMe-TT_2R_2	1 (1–2)	2 (1–3)	< 0.001
SAMe-$TT_2R_2 \geq 2$	38 (19%)	49 (42%)	< 0.001
CHA_2DS_2-VASc	3 (2–4)	3 (2–4)	0.5
CHA_2DS_2-VASc ≥ 2	164 (81%)	97 (83%)	0.1
CHA_2DS_2-VASc = 1	29 (14%)	17 (14%)	0.6
CHA_2DS_2-VASc = 0	10 (5%)	3 (3%)	0.5

Data are given as number (percentage) or mean ± standard deviation or median (interquartile range). Results are presented as the p-value for Fisher's exact test for categorical variables or t-Student's test for normally distributed variables or Mann-Whitney's test for other variables. BMI — body mass index; COPD — chronic obstructive pulmonary disease; VKA — vitamin K antagonists; TTR — time in therapeutic range; ACEI — angiotensin converting enzyme inhibitor; SAMe-TT_2R_2 — sex female, age, medical history, treatment, tobacco use, race score; CHA_2DS_2-VASc — cardiac failure, hypertension, age > 75 years, diabetes, stroke, vascular disease, age 65–74 and sex score

tive "real-world" cohort of 459 patients initiating oral anticoagulation with acenocoumarol. In a latter study patients with less than 2 points in SAMe-TT_2R_2 score had TTR lower by 6% than those with more than 2 points, indicated that the score properly identified the individuals on acenocoumarol [18].

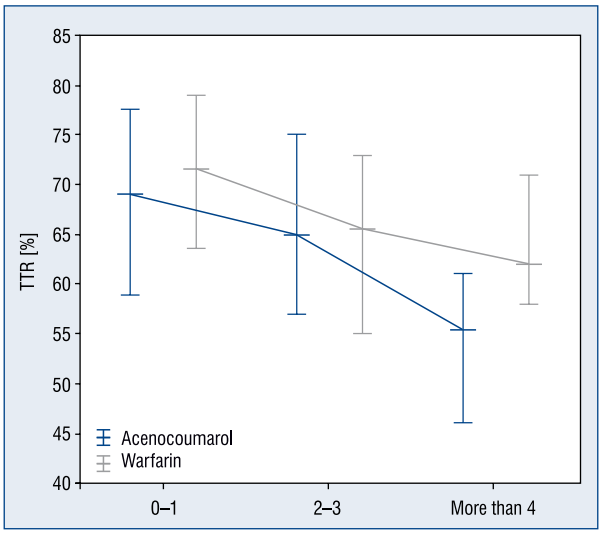

Figure 1. Comparison of the median time in therapeutic range (TTR) between patients treated acenocoumarol and warfarin with 0–1, 2–3 and more than 4 points in SAMe-TT_2R_2 (sex, age < 60 years, more than two comorbidities, interacting drugs, tobacco and race) score. Vertical lines extend from the 25th to the 75th percentiles, with the horizontal lines in the middle at the median value.

However, in a subsequent Spanish study involving 1524 patients, among them approximately 95% on acenocoumarol, the discriminating capability of the SAMe-TT_2R_2 score was modest (AUC 0.59) and did not improve after adding new factors [7].

In this study the percentage of AF patients with TTR less than 70% was comparable among individuals with SAMe-TT_2R_2 over 2 points and 0–1 points. It suggested that SAMe-TT_2R_2 score was not able to identify the AF patients treated with acenocoumarol at risk of poor anticoagulation control using the TTR cut-off value of 70%. It seems that the clinical factors predispose to unstable anticoagulation to a different extent during treatment with warfarin and acenocoumarol. It was found that COPD, reported to coexist in a considerable percentage of AF patients (10%) [19], strongly contributed to the prediction of the anticoagulation stability. A potential factor which might explain the association between COPD and stability of anticoagulation with acenocoumarol is drug–drug interaction. Patients with COPD exacerbation commonly receive corticosteroids and macrolides or fluoroquinolones [20], both interacting with the anticoagulant

Table 2. Factors associated with time in therapeutic range (TTR) > 70% in patients on acenocoumarol.

Variable	OR (95% CI)	P
Demographic data:		
Male gender	0.80 (0.45–1.41)	0.4
Age < 60 years	1.25 (0.60–2.56)	0.5
Tobacco use	0.13 (0.02–0.45)	< 0.001
Comorbidities:		
Arterial hypertension	0.92 (0.52–1.64)	0.8
Myocardial infarction	0.48 (0.20–1.06)	0.07
Peripheral artery disease	0.51 (0.07–2.28)	0.4
Heart failure	0.95 (0.49–1.82)	0.9
Stroke	1.53 (0.65–3.56)	0.3
COPD	0.07 (0.00–0.33)	< 0.001
Diabetes mellitus type 2	1.12 (0.52–2.36)	0.8
Chronic kidney disease	0.57 (0.21–1.39)	0.2
Medication:		
Acetylsalicylic acid	0.97 (0.52–1.79)	0.9
Clopidogrel	0.66 (0.14–2.45)	0.5
Beta-blockers	0.85 (0.48–1.50)	0.6
ACEI	0.79 (0.44–1.43)	0.4
Statin	0.53 (0.29–0.94)	0.031
Digoxin	1.13 (0.50–2.49)	0.8
Amiodarone	0.81 (0.33–1.88)	0.6

Data presented as the odds ratio (OR) and 95% confidence interval (CI) and p-value calculated using the logistic univariate regression analysis; COPD — chronic obstructive pulmonary disease; ACEI — angiotensin-converting enzyme inhibitor

treatment [21]. Here might be the point where the shorter half-live of acenocoumarol may not entirely justify but may exaggerate the effect of interacting drugs on the acenocoumarol pharmacokinetics in comparison to warfarin.

The present study emphasised the role of the previous MI in maintaining stable anticoagulation. MI is an established risk factor for AF, with AF occurring in 6% to 21% of patients following MI [22, 23]. The poor TTR control was an independent predictor of major adverse cardiovascular events including MI in a cohort of 627 AF patients on VKA patients followed by Pastori et al. [24]. We assume that a decreased TTR prior to the MI may reflect the overall worse anticoagulation control observed in that subset of patients not only prior to but also following the MI. Mechanisms linking a history of MI with anticoagulation control need to be further investigated.

Unexpectedly, in the present study, statin use has been identified to be a risk factor for unstable anticoagulation with acenocoumarol. Previously, statins have been associated with the 9% lower risk of bleeding during VKA therapy [25], which suggested beneficial influence of statins on the anticoagulation stability. Statins favourably modulate blood coagulation by exerting mild anticoagulant and antiplatelet effects [26, 27]. The results of statins on blood clotting can also be observed in patients with AF [28]. In the context of VKA, drug–drug interactions may be however of key importance. Simvastatin has been found to reduce warfarin dose requirement by 29% in the CYP2C9*3 allele carriers compared with 5% in non-carriers [29]. This effect may predispose unstable anticoagulation in patients carrying the CYP2C9*3 allele that represent 12% of Poles [9]. Further investigations are required to establish mechanisms behind the relationship between statin use and stability of anticoagulation with warfarin and acenocoumarol. Other postulated beneficial influences of statin is slowing the evolution of AF and reducing inflammation and fibrosis [30].

Limitations of the study

Several study limitations should be acknowledged. Firstly, baseline characteristics of the patients treated with acenocoumarol and warfarin in this study differed which could affect to some extent the differences observed in the discriminating ability of the scores. Secondly, the number of the studied patients was relatively low, although the study was sufficiently powered to show some intergroup differences. These findings cannot be reliably extrapolated to patients excluded from our analysis including those with advanced renal insufficiency or on dual antiplatelet therapy, as well as for predicting quality of anticoagulation with lower TTR out-offs [31]. Long-term follow-up to assess clinical impact of the scoring systems in terms of stroke and risk of bleeding was beyond the scope of the present study.

Conclusions

1. The SAMe-TT_2R_2 score appears less effective in predicting unstable anticoagulation with acenocoumarol compared with warfarin.
2. Adding the statin use and highlighting a role of COPD and previous MI in the modified score increase its predictive value for acenocoumarol.

Conflict of interest: None declared

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