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A new index to predict quality of anticoagulation control in patients on vitamin K antagonists: the DAFNE score

Vivencio Barrios[1], Carlos Escobar[2], Luis Prieto[3], Jose Polo[4], Javier Muñiz[5], Manuel Anguita[6] & Gregory Y H Lip[7]

[1] *Cardiology Department, University Hospital Ramon y Cajal, Madrid, Spain*

[2] *Cardiology Department, University Hospital La Paz, Madrid, Spain*

[3] *Medical Biostatistics, Universidad Católica San Antonio de Murcia, Murcia, Spain*

[4] *Primary Care Health Center Casar de Cáceres, Cáceres, Spain*

[5] *Instituto Universitario de Ciencias de la Salud, Instituto de Investigacion Biomédica de A Coruña (INIBIC), Universidade da Coruña, La Coruna, Spain*

[6] *Servicio de Cardiología, Hospital Universitario Reina Sofía, Cordoba, Spain*

[7] *Liverpool Centre for Cardiovascular Science, University of Liverpool & Liverpool Heart & Chest Hospital, Liverpool, United Kingdom & Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark*

Author for correspondence: vivenciobarrios@gmail.com

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Abstract

Aim: To derive a new clinical score to improve the prediction of those at risk of poor International Normalized Ratio control among patients with atrial fibrillation taking vitamin K antagonists. **Materials & methods**: The score was calculated using PAULA database and validated in the FANTASIIA population. **Results**: The DAFNE score (cardiovascular **D**isease, concomitant treatment with **A**miodarone, **F**ood/dietary transgression and taking ≥7 pills daily, f**E**emale sex) score was related to a higher probability of poor International Normalized Ratio control. C-indexes were 0.611 and 0.576 (De Long test, $p = 0.007$) for the DAFNE and SAMe-TT_2R_2 scores, respectively. **Conclusion**: The DAFNE score is a new clinical score which may potentially help determine those patients with atrial fibrillation who are at high risk of poor anticoagulation control with vitamin K antagonists.

Lay abstract

Patients with atrial fibrillation are often treated with a group of drugs called vitamin K antagonists. However, taking these drugs can result in poor anticoagulation control in certain patients. This paper aims to find a new way to predict which patients might have a higher risk of poor anticoagulation control. The authors suggest that the DAFNE score, which is shown to be bigger if there is a greater chance of poor anticoagulation control, could be used to help predict patients who might be at risk.

Keywords: anticoagulation; atrial fibrillation; control; INR; SAMe-TT_2R_2; vitamin K antagonists

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Although atrial fibrillation (AF) increases the risk of cardiovascular death and myocardial infarction, the most dramatic complication associated with AF is cardioembolic stroke, which is significantly reduced by anticoagulation [1].

Despite the introduction of direct oral anticoagulants in clinical practice, many patients globally are still treated with vitamin K antagonists (VKA) [2]. Importantly, about 40–50% of patients with nonvalvular AF who are taking VKA have a poor anticoagulation control [3] and such suboptimal anticoagulation is associated with an increased risk of stroke, bleeding and death [4].

Hence, the prior determination of those patients who are more likely to have a suboptimal anticoagulation control, for switching or choosing direct oral anticoagulants instead of VKA may help management. However, many clinical and nonclinical factors influence anticoagulation control while on VKA. In 2013, a simple clinical score, SAMe-TT_2R_2 was developed to predict those AF patients less likely to achieve good anticoagulation control on VKA [5]. The variables included in this score are female sex (1 point), age < 60 years (1 point), history of more than two of the following: hypertension, diabetes, coronary artery disease, peripheral artery disease, heart failure, stroke, pulmonary, hepatic or renal disease (1 point), interacting drugs such as amiodarone (1 point), tobacco use within 2 years (2 points) and non-Caucasian race (2 points). Those patients with a score 0–2 points are more likely to achieve a high time in therapeutic range (TTR) and may potentially be suited for VKA therapy. By contrast, those patients with a score of > 2 are more likely to have a poor International Normalized Ratio (INR) control and additional interventions to achieve acceptable anticoagulation control or starting/switching to direct oral anticoagulants should be encouraged [5].

Some studies have suggested that the SAMe-TT_2R_2 score could be very helpful for clinical decision making [6,7], but others have reported that utility of SAMe-TT2R2 may be low in some settings, especially where the population average TTR was good, with a narrow spread [8,9]. Indeed, the SAMe-TT_2R_2 performs best where the mean TTR is low, with a wide standard deviation. As a result, further research is warranted to refine the predictive scales for anticoagulation control among patients taking VKA.

The PAULA (Perspectiva Actual de la sitUación de la anticoaguLación en la práctica clínica de Atención primaria [Current perspective of anticoagulation in clinical practice in the primary care setting]) study was initiated to determine the situation of

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anticoagulation control over a long period among patients with nonvalvular AF treated with VKA in primary care setting in Spain [3]. In this study, our aim was to derive a new clinical score to improve the prediction of those at risk of poor INR control among patients with AF taking VKA, through the PAULA study database. In addition, the score was validated in the FANTASIIA population [10].

Materials & methods

The design and methods of the PAULA study have been previously described [3,11,12]. Briefly, the PAULA study was a multicenter, nationwide, observational and cross-sectional/retrospective study that included a total of 1524 patients with nonvalvular AF who had received treatment with VKA for the prevention of stroke in the primary care setting, for the last 12 months.

The inclusion criteria were: patients aged 18 years or older; with nonvalvular AF; anticoagulated with VKAs for at least one year before inclusion; followed in primary care setting according to clinical practice, for whom at least 80% of INR controls were available and who signed written informed consent. Exclusion criteria were: patients with cognitive impairment or participating in a clinical trial in the previous year before inclusion. The study was approved by the Clinical Research Ethics Committee of the University Hospital La Paz of Madrid, under the protocol number 3966 and was amended by the local Clinical Research Ethics Committees of each participating center.

The PAULA study data were recorded through a single visit coinciding with one of the patient's regular follow-up visits. The data were collected from the electronic medical history of the patients, completed during the physician interview and recorded into an electronic database. Biodemographic data, cardiovascular risk factors, cardiovascular disease, thromboembolic and bleeding risk, number of pills and INR determinations in the last 12 months previous inclusion were recorded. To assess patients' INR control, the TTR in the previous 12 months was calculated by the Rosendaal method at a core lab (inadequate control < 6 %). To determine if patients had dietary habits that could affect INR control, patients were specifically asked if they consumed large amounts of foods rich in vitamin K (cereals, broccoli, cabbage, carrots, etc), alcohol, cranberry juice or ginseng, if they were regular users of herbal medicine or if they had frequent dietary variations [3].

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The DAFNE (D: Disease; A: Amiodarone; F: Food; N: Number of pills; E: fEmale) score was externally validated in the FANTASIIA population, a multicenter and observational study, in which cardiologists, general practitioners, and internists recruited consecutive patients with nonvalvular AF receiving uninterrupted anticoagulant treatment for stroke prevention for > 6 months [10].

Statistical analysis

Univariate analysis was performed to assess the factors those may have an impact on the bad anticoagulation control assessed by the Rosendaal method. For categorical variables, the proportion of controlled patients with and without each factor was compared. For continuous variables, different cut-off points were calculated, in order to maximize the accuracy.

To control the possible confounding factors, a multiple logistic regression analysis was performed. At the beginning, the model contained all factors and in next steps, those variables with high p-value were eliminated. The quality of the fit of the model was measured with the value of 'Pseudo R2' (equivalent to the coefficient of determination of multiple linear regression), the value of the overall Chi-square with the number of degrees of freedom equal to the number of factors minus one and the corresponding p-value.

With the factors that showed a significant impact on the multivariate analyses, the predictive index was created, adding '1 point' for each factor involved and selecting the index with maximum accuracy, evaluated by the difference in the proportion of controlled patients between the group with zero and maximum score, encompassing in this group those patients having a score of 3 or more. Starting with the index with the highest discriminative capacity in Phase III, variables were tested by incorporating by turn each of the factors that in the multivariate analysis showed moderate relationship with the proportion of controlled patients. Then, search continued step by step until the maximum discrimination index was obtained. For the maximum discrimination index, 95% CI were calculated for the proportion of controlled patients in each level, using the asymptotic approximation to the normal distribution. The accuracy of the DAFNE score was compared with that of the SAMe-TT_2R_2 score using c-indexes, which were compared using the De Long test. To validate our score in the FANTASIIA population, a multiple logistic regression analysis was performed between INR control and DAFNE score. As

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dietary habits that could affect INR control were not recorded in the FANTASIIA study, the validation of the DAFNE score was performed according to 3 scenarios: 18.4, 0 and 100% of patients had dietary habits that could affect INR control.

Results

A total of 1524 patients with nonvalvular AF were included in the study. The main clinical characteristics at baseline were shown in Table 1. Mean age was 77.4–8.7 years, 48.6% were women, 80.2% had hypertension and 23.9% heart failure. Patients had at high thromboembolic risk (mean CHA_2DS_2-VASc 3.9–1.5) and 13.0% had a HAS-BLED ≥ 3. The total number of INR records in the previous 12 months was 21,982 and the mean number of INR readings recorded per patient in the past year was 14.4–3.8. The mean TTR was 69.0–17.7% according to the Rosendaal method. A total of 60.6% of patients had adequate INR control according to the Rosendaal method.

The proportion of patients with an adequate anticoagulation control assessed by the Rosendaal method according to the factors included in the SAMe-TT_2R_2 score (except for race, since in our cohort almost all patients were Caucasians), are summarized in Supplementary Table 1. Additionally, other 4 factors (number of pills ≥ 9, dietary transgression, glomerular filtration rate < 60 ml/ and bleeding) were also included, as in the univariate analysis these factors were significantly associated with anticoagulation control. Smoking and being less than 60 years were not associated with a worse anticoagulation control, but rather the converse. The logistic regression analysis confirmed these results (Supplementary Table 2).

The proportion of patients with an adequate anticoagulation control according to age, comorbidities, number of pills and renal function are shown in the Supplementary Table 3 and the multiple logistic regression analysis to identify those factors that predicted adequate INR control, adjusted for other factors in the Supplementary Table 4. These show that the association between anticoagulation control and renal dysfunction was moderate, but weak regarding comorbidities and bleeding

Based on these results, a new score, called DAFNE1, was created, adding ‘1 point’ for each of the 4 factors that showed a strong relationship with an adequate anticoagulation control in the multivariate analysis (female, use of amiodarone, comorbidities >2, dietary transgression and number of pills ≥ 9).

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The proportion of patients with an adequate anticoagulation control according to the score in the SAMe-TT_2R_2 and DAFNE1 scales was shown in Supplementary Table 5. As shown at the bottom of the table, the DAFNE1 scale discriminated more accurately than the SAMe-TT_2R_2 scale (32.0 vs 20.4%).

The proportion of patients with an adequate anticoagulation control according to different comorbidities was shown in Supplementary Table 6. As shown in the logistic regression analysis (Supplementary Table 7), these factors did not improve the accuracy of the DAFNE1 scale to predict a good INR control. A multiple logistic regression analysis to identify those comorbidities that may predict an adequate anticoagulation control, adjusted for different factors is reported in the Supplementary Table 8. Heart failure, renal insufficiency and hepatic insufficiency showed a negligible relationship with adequate anticoagulation control, but there were moderate associations with myocardial infarction and peripheral artery disease.

Hence, the DAFNE2 score was created by adding '1 point' for patients with previous myocardial infarction or peripheral artery disease (Table 2, column 3). Finally, the 'number of pills' was coded by adding '1 point' to the score if patient has taken 9 or more tablets per day. Although in the univariate analysis and the multivariate models, the cut-off point of 9 pills was the most efficient one, when included in the scale, the score improved by 1.2 points when the cut-off point was reduced to 7 or more pills (Table 2; column 4). This new index was called the DAFNE score. The proportion of patients (95% CI) with an adequate anticoagulation control according to each score level was also reported in Table 2 (p for the linear trend test of proportions, Armitage's test < 0.001).

The accuracy of the DAFNE score was compared with that of the SAMe-TT_2R_2 score (Table 3), showing a small but significant higher precision with the DAFNE score (C-indexes were 0.611 and 0.576; De Long test, $p = 0.007$, for the DAFNE and SAMe-TT_2R_2 scores, respectively).

In the FANTASIIA study, a total of 1640 patients were taking VKA. As INR values were not available in seven patients, the final validation was performed in 1633 patients. The clinical characteristics of the FANTASIIA population are shown in Table 1 and the validation of the DAFNE score in Table 4. In FANTASIIA, c-index for the DAFNE score was modest (0.52) but the score correctly classified more than 50% of patients.

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Discussion

In our study, a new index, with the acronym DAFNE score, was defined to determine which patients are more likely to have a poor INR control under VKA treatment and consequently, to ascertain which patients would benefit less from this treatment. In our cohort of patients, the variables that better discriminated an adequate anticoagulation control and thus, included previous myocardial infarction or peripheral artery disease (1 point), concomitant treatment with amiodarone (1 point), female sex (1 point), dietary transgression (1 point) and taking 7 or more pills daily (1 point) into the DAFNE score. Those patients without any of these factors are more likely to have a good INR control and the likelihood of poor INR control progressively decreased as the score increases.

Despite some studies having validated the SAMe-TT_2R_2 score [6,7] but other works have reported discouraging results [8,9], warranting the search for new and more accurate scores. Our index showed a small but significantly higher accuracy than the SAMe-TT_2R_2 to detect those patients at higher risk of poor anticoagulation control with VKA in our cohort of patients.

Many factors may explain the disparities concerning the utility of the SAMe-TT_2R_2 in clinical practice. First, the latter score was developed in a specific cohort of patients that may be different to others [6,9]. In the SAMe-TT_2R_2 score, being non-Caucasian scored 2 points and directly indicates a high risk of poor INR control, regardless other clinical characteristics. Indeed, race, together with the tobacco use, are the two variables with the highest weights in the SAMe-TT_2R_2 score [5].

Second, the SAMe-TT2R2 score was developed in stable AF patients, but these data may be different in other clinical settings (i.e., AF patients after hospitalization for acute decompensated heart failure) [9]. This was also evident in our cohort of patients. As a result, both, the SAMe-TT_2R_2 and the DAFNE scores should be applied to stable AF outpatients, but not in other clinical settings, such as hospitalization.

Third, the SAMe-TT_2R_2 score was developed among patients taking warfarin. Although one study has validated this score in patients taking acenocoumarol [13], there are some differences between warfarin and acenocoumarol (i.e., renal elimination, anticoagulation stability or half-life time) that could modify the utility of the SAMe-TT_2R_2 score according to the type of VKA [13]. In our study, approximately 95% of patients were taking acenocoumarol and only 5% warfarin; however, the validity of the DAFNE score

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was independent of the type of VKA (data not shown), suggesting that it could be used among patients not only on acenocoumarol, but also taking warfarin.

As the SAMe-TT_2R_2 score has some limitations, other authors have tried to develop new scores with a better capacity to detect those patients at higher risk of poor INR control. For example, a new clinical prediction model for TTR while on warfarin in newly diagnosed AF patients has been proposed, even with a better predictive performance than the SAMe-TT_2R_2 score, but 15 different factors were included in the final validated model, making this new index very difficult to implement [14]. By contrast, the DAFNE index included only 5 variables, easily recorded in a routine visit, making this score feasible in clinical practice.

With regard to the variables included in the DAFNE score, previous studies have shown that peripheral artery disease and cardiac disease [15], treatment with amiodarone [16], female gender [3], dietary habits [3] and polymedication [17] were independently associated with a worse INR control, hence enhancing the validity of our results.

With regard to the variables included in the SAMe-TT_2R_2 score that performed differently to the DAFNE index. Although some studies have reported poorer anticoagulation control among patients age under 60 years [18], other studies have shown just the opposite [15]. In the SAMe-TT_2R_2 score, tobacco use within 2 years is one of the most important factors associated with an inadequate anticoagulation control. Although some studies have corroborated this [19], in other studies this association was nonsignificant [20].

Although renal insufficiency, particularly severe renal dysfunction has been associated with a higher INR variability, thromboembolic and bleeding risks, inclusion of this point to the SAMe-TT_2R_2 score might slightly improve its accuracy to assess the likelihood of adequate anticoagulation control, but only in patients without chronic kidney disease and not in patients with chronic kidney disease [8].

The DAFNE study was externally validated in the FANTASIIA study [10], showing that the DAFNE score correctly classified more than 50% of patients taking VKA. However, dietary factors were not recorded in the FANTASIIA study. This means than in clinical practice, in addition to the well documented variables, including history of cardiovascular disease, concomitant treatment with amiodarone, polymedication and female sex, dietary habits should also be recorded.

Limitations

As the DAFNE score was generated from a specific cohort of patients (a European and old population with nonvalvular AF), this index should be applied only to patients with the same clinical characteristics. However, this cohort of 'real-life' patients may be representative of most of the Western countries. On the other hand, since the majority of patients were taking acenocoumarol (95%), the highest accuracy of this index was achieved with this VKA, despite no significant differences were obtained between warfarin and acenocoumarol in our study.

Conclusion

The DAFNE score is a new clinical score which may potentially help determine those patients with AF who are at high risk of poor anticoagulation control. Such patients could be targeted for additional measures to improve anticoagulation control (e.g., education, counselling, more frequent INR checks) or to swop for direct oral anticoagulants.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fca-2020-0122

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.
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Table 1. Baseline clinical characteristics of the PAULA and FANTASIIA study populations.

Variables	PAULA study (n = 1524)	FANTASIIA study (n = 1633)
Biodemographic data		
Age (years)	77.4 ± 8.7	74.0 ± 9.4
Gender, women (%)	48.6	43.0
Number of tablets	7.0 ± 3.8	4.5 ± 1.5
Dietary habits potentially affecting anticoagulation control with VKAs (%)	18.4	–
Cardiovascular risk factors		
Hypertension (%)	80.2	80.8
Diabetes (%)	31.0	30.5
Smoking (%):		
Smokers	5.1	5.1
Ex-smokers <1 year	1.5	2.2
Ex-smokers ≥1 year	26.0	30.1
Nonsmokers	67.4	62.5
Vascular disease		
Heart failure (%)	23.9	30.6
History of stroke/transient ischemic attack (%)	13.7	16.0
History of myocardial infarction (%)	9.6	19.1
Peripheral artery disease (%)	6.5	6.1
Renal failure (%)	6.0	20.9
Thromboembolic/bleeding risk		
$CHADS_2$	2.3 ± 1.2	2.2 ± 1.2
CHA_2DS_2-VASc	3.9 ± 1.5	3.6 ± 1.5
HAS-BLED	1.6 ± 0.9	2.0 ± 1.0
Anticoagulant treatment:		
Acenocoumarol (%)	94.8	90.7
Warfarin (%)	5.2	9.3b
Percentage time within therapeutic range, Rosendaal method (%)	69.0 ± 17.7	61.3 ± 24.9
Adequate INR control, Rosendaal method (%)	60.6	47.2
INR determinations per patient	14.4 ± 3.8	6.0 ± 0.1

VKA: Vitamin K antagonist.

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Table 2. Proportion of patients (95% CI) with an adequate anticoagulation control according to each score level.

	DAFNE1	DAFNE2[†]	DAFNE (95% CI)
Previous myocardial infarction or peripheral artery disease		+1	+1
Amiodarone	+1	+1	+1
Women	+1	+1	+1
Dietary transgression	+1	+1	+1
Number of pills ≥9	+1	+1	(≥7) +1[‡]
DAFNE score:	Proportion of patients (95% CI) with an adequate anticoagulation control		
0	393	333	247
	73.5%	76.3%	77.7% (72.4–83.3)
1	669	628	565
	61.6%	62.3%	64.1% (60.1–68.1)
2	343	398	504
	49.3%	51.8%	55.4% (51.0–59.8)
3 or more	53	99	142
	41.5%	41.4%	41.6% (33.3–49.9)
Difference DAFNE score 0–3	32.0	34.9	36.1

[†] The DAFNE2 score was created by adding '1 point' for patients with previous myocardial infarction or peripheral artery disease.

[‡] The 'number of pills' was coded by adding '1 point' to the score if patient was taken 9 or more tablets per day. Although in the univariate analysis and the multivariate models, the cut-off point of 9 pills was the most efficient one, when included in the scale, the score improved by 1.2 points when the cut-off point was reduced to 7 or more pills.

DAFNE: Disease, Amiodarone, Food, Number of pills, fEmale.

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Table 3. Accuracy of the DAFNE and SAMe-TT_2R_2 scores.

	DAFNE (95% CI)	SAMe-TT_2R_2 (95% CI)
< 60 years		+1
Smoking		+2
Comorbidities > 2		+1
Previous myocardial infarction or peripheral artery disease	+1	
Amiodarone	+1	+1
Women	+1	+1
Dietary transgression	+1	
Number of pills ≥7	+1	
DAFNE score:		
0	247	423
	77.7%	70.4%
	(72.4–83.3)	(63.3–75.2)
1	565	730
	64.1%	58.8%
	(60.0–68.0)	(54.5–61.8)
2	504	234
	55.4%	56.0%
	(50.9–59.8)	(49.9–62.4)
3 or more	142	71
	41.6%	50.7%
	(33.3–49.9)	(38.6–62.8)
Difference DAFNE score 0–3	36.1	19.7
Linear Coef.: Mean decreasing by step	-11.3–1.4%	9.5–1.8%
PseudoR^2	0.031	0.014
Average OR	0.61	0.67
Wald Stat	-7.6	-5.24
c-indexes	0.611	0.576
De Long test H0: equal C with both scores (AUC)	p = 0.007	
Correctly classified	62.8%	61.1%
McNemar + test	p = 0.037	
H0: equal Correctly classified		

AUC: Area under the curve; OR: Odds ratio.

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Table 4. Validation of the DAFNE score in the FANTASIIA population (n = 1633).

		DAFNE (95% CI)	
Dietary habits potentially affecting anticoagulation control with VKAs	18.4%	0%	100%
DAFNE score:			
0	446	555	
	49.8%	49.5%	
	(45–54.5)	(45.3–53.8)	
1	767	804	555
	47.2%	47.5%	49.5%
	(43.6–50.8)	(44–51)	(45.3–53.8)
2	337	229	804
	46.0%	42.4%	47.5%
	(40.6–51.5)	(35.9–49)	(44–51)
3 or more	83	45	274
	37.3%	35.6%	41.2%
	(27–48.7)	(21.9–51.2)	(35.4–47.3)
Difference DAFNE score 0–3	12.43	13.99	
Linear Coef.: Mean decreasing by step	-11.5 ± 6.0%	-15.1 ± 6.6%	-15.2 ± 7.2%
PseudoR^2	0.0016	0.0023	0.002
Average OR	0.89	0.86	0.86
Wald Stat	-1.91	-2.28	-2.11
c-index	0.523 (0.497–0.549)	0.527 (0.502–0.553)	0.527 (0.501–0.552)
Correctly classified	52.7%	52.5%	52.5%

OR; Odds ratio; VKA: Vitamin K antagonist.