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Evaluation of genotype-guided acenocoumarol dosing algorithms in Russian patients

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Abstract

Background: Acenocoumarol dose is normally determined via step-by-step adjustment process based on International Normalized Ratio (INR) measurements. During this time, the risk of adverse reactions is especially high. Several genotype-based acenocoumarol dosing algorithms have been created to predict ideal doses at the start of anticoagulant therapy.

Materials and methods: Nine dosing algorithms were selected through a literature search. These were evaluated using a cohort of 63 patients with atrial fibrillation receiving acenocoumarol therapy.

Results: None of the existing algorithms could predict the ideal acenocoumarol dose in 50% of Russian patients. The Wolkanin-Bartnik algorithtm based on European population was the best-performing one with the highest correlation values ($r = 0.397$), mean absolute error (MAE) 0.82 (± 0.61). EU-PACT also managed to give an estimate within the ideal range in 43% of the cases. The two least accurate results were yielded by the Indian population-based algorithms. Among patients receiving amiodarone, algorithms by Schie and Tong proved to be the most effective with the MAE of 0.48 ± 0.42 mg/day and 0.56 ± 0.31 mg/day, respectively.

Conclusions: Patient ethnicity and amiodarone intake are factors that must be considered when building future algorithms. Further research is required to find the perfect dosing formula of acenocoumarol maintenance doses in Russian patients.

Keywords: acenocoumarol; *CYP2C9*; *CYP4F2*; dosing algorithms; *GGCX*; *VKORC1*.

Introduction

Acenocoumarol is a widely used and effective vitamin K antagonist (VKA). Its popularity stems from the large number of patients with high risk of thrombotic events. However, coupled with the narrow therapeutic range of acenocoumarol, that is, cases where the dose is slightly different from optimal, either the effect might not be reached or side effects may occur. VKA are most often prescribed to patients suffering from atrial fibrillation to prevent thromboembolic complications [1, 2]. Clotting factors synthesis inhibition is the mechanism behind both the therapeutic effect and adverse reactions of VKA: 25% of patients develop hemorrhage, including 1.5%–5% patients with major, life threatening bleeding episodes [3]. The current standard for reaching maintenance dose is step-by-step adjustments based on consecutive International Normalized Ratio (INR) measurements. That process, however, is quite time-consuming and can lead to the discussed complications. Determining the correct dose of acenocoumarol has become even more complicated, because, as far as we know from research, many factors weigh in on the optimal dose, including age, gender, body mass index, pharmacological interactions, and genetic factors [4].

P450 2C9 (CYP2C9) is the key enzyme involved in acenocoumarol metabolism in the liver. It is encoded by the *CYP2C9* gene located on chromosome 10 at 10q24.1. Many studies have already shown that genetic variations of the *CYP2C9* gene significantly influence the optimal dose [5]. The target molecule for acenocoumarol is vitamin K epoxide reductase complex subunit 1 (VKORC1, 16p11.2), which is part of the vitamin K cycle. Polymorphisms in the *VKORC1* gene affect the maintenance dose of indirect anticoagulants [6]. Cytochrome P-450 4F2 is also thought to be part of vitamin K metabolism based on a similar reaction with vitamin E, where P-450 4F2 (CYP4F2) catalyzes

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hydroxylation. Another argument for CYP4F2 involvement states that V433M polymorphism is associated with variations in II, VII, IX, and X clotting factor levels after acenocoumarol intake [7, 8]. Another key enzyme that matters in this pharmacological response is γ-Glutamyl carboxylase (*GGCX*), which regulates carboxylation. It oxidizes vitamin K hydroquinone (the active form of vitamin K1) to vitamin K 2,3 epoxide, which is later reduced back to the active K1H2 form by the vitamin K epoxide reductase complex (*VKORC1*) [9].

Thus far, several acenocoumarol-dosing algorithms that factor in not only the clinical, but also genetic variations have been created. We believe it is crucial to validate the accuracy of these algorithms in the populations where they are to be implemented. This has already been successfully done for warfarin dosing algorithms [10, 11]. Choosing the best fitting algorithm will allow us to make the treatment both more safe and effective. We have already published the results of our research on the influence of patient genotypes on doses and hemorrhage risk with acenocoumarol therapy as a separate study done on 50 patients earlier [12, 13]. For the current study, we have increased the patient number to 63. To the best of our knowledge, no similar studies have been performed in Russian populations before.

Materials and methods

Patients

The retrospective cohort study included 63 participants, mean age 60 ± 8 years, 41 (65%) men and 22 (35%) women, all of Russian nationality and all taking acenocoumarol at mean dose of 2.8 ± 1 mg (Table 1).

Included in the study were patients suffering from non-valvular atrial fibrillation, permanently receiving acenocoumarol (Syncumar, ICN Hungary Co. Ltd., Hungary) as a measure of thrombosis prophylaxis. All subjects signed an informed consent. The inclusion criteria were as follows: patients with permanent atrial fibrillation, same dose of acenocoumarol (1–6 mg per day) for at least 1 month with INR target values 2–3. Patients were excluded from the study if they had any of the counter indications to receiving acenocoumarol (according to the National Pharmaceuticals Registry Instruction Manual) or had a medical condition that could influence acenocoumarol distribution, metabolism, or elimination (oncological diseases, diabetes mellitus, kidney and liver diseases). Another exclusion criterion was incompliance with monthly INR measurements in accordance with clinical guidelines [14]. INR measurement was performed with thromboplastin (Technological Standard Company, Russia) with international sensitivity index of 1.3.

Table 1: Characteristics of patients.

Cohort (n = 63)	
Age, years[a]	59.7 ± 8.3
Males, %	41 (65)
Height, cm[a]	170.6 ± 7.6
Weight, kg[a]	85.4 ± 11
Use of amiodarone, %	5 (7.9)
Maintenance dose, mg/day	2.8 (1.0–6.0)

[a]Mean ± SD.

CYP2C9 (*2 *3), *VKORC1* (rs9923321), *CYP4F2* rs2108622, and *GGCX* genes were screened in all patients. Genotyping was performed using the PCR-RFLP method. PCR primers were designed using "PrimerSelect" 4.05©1993-2000 DNASTAR, Inc. software and synthesized by Syntol Company (Russia). All the enzymes were produced by SybEnzyme (Russia). Restriction fragment division was performed using electrophoresis in 10% acrylamide gel [15].

The authors obtained appropriate institutional review board approval and have followed the principles outlined in the Declaration of Helsinki for all in-human investigations. For investigations involving human subjects, informed consent was obtained from the participants involved.

Selections of algorithms

A literature search was performed using pubmed.com for eligible studies published in the past 11 years (2006–2017) on genotype-guided acenocoumarol algorithms, using the search terms "acenocoumarol", "pharmacogenetic algorithm". Nine algorithms were selected. Two of them [16, 17] used genotypes other than *VKORC1*, which were not available in our cohort data. However, as these polymorphisms yielded minimal impact on the calculated dose value, these algorithms were included in the study anyway (Table 2).

Evaluation of selected algorithms

We used the following parameters to evaluate the performance of the selected algorithms: 1) mean absolute error (MAE), which is the mean of the absolute value of the difference between the predicted dose and the maintenance dose chosen via small adjustments based on consecutive INR measurements; 2) correlation coefficient of maintenance dose and estimated dose; and 3) percentage of estimated dose in relation to ideal dose. Estimated dose was calculated using data for both genetic and non-genetic factors in all of the algorithms tested. MAE was calculated by subtracting the maintenance dose from the estimated dose. Patients were divided into three groups as follows: underestimated dose (patients whose estimated dose was >20% below the maintenance dose), ideal dose (patients whose estimates dose was within 20% of the maintenance dose), and overestimated dose (patients whose estimated dose was >20% above the maintenance dose). These criteria have been successfully used in a similar study [11]. SPSS software was used to analyze all data. Maintenance dose distribution analysis showed a non-normal distribution of values, which led to us using the Spearman correlation method.

Table 2: Characteristics of acenocoumarol dosing algorithms evaluated in the study.

Algorithm	Ethnicity	Incorporated factors	Ref.
1. Tong et al. 2016	Caucasian	Age, weight, enzyme inducer status, amiodarone use, *CYP2C9* (*2 *3), *VKORC1* (rs9923231), *CYP4F2* (rs2108622), target INR	[18]
2. Ragia et al. 2017	Caucasians	Age, weight, *CYP2C9* (*2 *3), *VKORC1* (rs9923231)	[19]
3. Kumar et al. 2015	Indian	Age, BMI, *CYP2C9* (*2 *3), *VKORC1* (rs9923231, rs7294), *CYP4F2* (rs2108622), *GGCX* (rs11676382)	[16]
4. Kumar et al. 2014	Indian	Age, weight, clinical conditions, *CYP2C9* (*2 *3), *VKORC1* (rs9923231, rs9934438, rs7294, rs2359612), *CYP4F2* (rs2108622), *GGCX* (rs11676382)	[17]
5. Wolkanin-Bartnik et al. 2013	Caucasian	Age, weight, vitamin K intake, *CYP2C9* (*2 *3), *VKORC1* (rs9923231), creatinine clearance	[20]
6. Pop et al. 2013	Caucasian	Age, BMI, *CYP2C9* (*2 *3), *VKORC1* (rs9923231)	[21]
7. van Schie et al. 2012	Caucasian	Age, sex, height, weight, amiodarone use, *CYP2C9* (*2 *3), *VKORC1* (rs9923231)	[22]
8. Rathore et al. 2012	Indian	Age, weight, height, smoking status, BSA, indications, *CYP2C9* (*2 *3), *VKORC1* (rs9923231), *CYP4F2* (rs2108622), *GGCX* (rs11676382)	[23]
9. Markatos et al. 2008	Caucasian	Age, *CYP2C9* (*2 *3), *VKORC1* (rs9923231)	[24]

BMI, body mass index; BSA, body surface area.

Results

A total of 63 Russian patients participated in this study. The clinical information on the subjects is summarized in Table 1 and genetic information in Table 3. Forty-one males (65%) and 22 females (35%) were included in this study. The mean age was 60 ± 8 years, ranging from 40 to 73 years. The mean maintenance dose of acenocoumarol was 2.83 ± 1.04 mg/day, ranging from 1.0 to 6.0 mg/day.

Table 3: Genotype frequencies for *CYP2C9*, *VKORC1*, *CYP2F4*, and *GGCX*.

CYP2C9 genotype[a]	
*1/*1	34 (54)
*1/*2	11 (18)
*1/*3	12 (19)
*2/*2	2 (3)
*2/*3	2 (3)
*3/*3	2 (3)
VKORC1 genotype[a]	
AA	12 (19)
AG	24 (38)
TT	27 (43)
CYP2F4 genotype[a]	
CC	40 (63)
CG	20 (32)
GG	3 (5)
GGCX genotype[a]	
CC	57 (90)
CT	6 (10)
TT	0 (0)

[a]Presented are numbers of patients (%). *CYP2C9*, gene encoding cytochrome P450 2C9; *VKORC1*, gene encoding vitamin K epoxide reductase complex, subunit 1; *CYP4F2* is a vitamin K cycle related enzyme that metabolizes vitamin K1 to hydroxyvitamin K1; *GGCX* (γ-glutamyl carboxylase) is a protein-coding gene.

The results are summarized in Table 4. The lowest MAEs were from the van Schie algorithm [22] with MAE of 0.81 ± 0.64 mg/day, Wolkanin-Bartnik et al. with the MAE of 0.82 ± 0.61 mg/day and Pop et al. [21] with MAE of 0.86 ± 0.67 mg/day. The worst and highest three MAEs were from Kumar et al. [16] (1.38 ± 1.05 mg/day), Kumar et al. [17] (1.31 ± 1.42 mg/day), and Rathore et al. [23] (1.16 ± 0.94 mg/day).

The predictive power of each algorithm can be deduced from the percentage of the difference between estimated and actual doses, as shown in Figure 1. Two of the algorithms, as suggested by Schie (43%) and Pop (44%), were able to calculate the dose classified as ideal (<20% variation from the actual maitenance dose) for more than 40% of the patients. Four of the algorithms [suggested by Kumar et al. [16], Kumar et al. [17], and Rathore and Markatos [24]] were more likely to overestimate the dose compared with the ideal one.

We also completed a separate analysis for patients taking amiodarone. For this group, the best MAE results (see Table 4) are shown by the van Schie et al. [22] and Tong et al. [18] algorithms with MAEs of 0.48 ± 0.42 mg/day and 0.56 ± 0.31 mg/day, respectively.

Discussion

The purpose of our study was to evaluate the effectiveness of the nine previously published acenocoumarol-dosing algorithms in Russian patients. The EU-PACT algorithm

Table 4: Correlation coefficient, coefficient of determination and MAE with statistical values in all patients and patients taking amiodarone.

Algorithm	r		MAE	
	All (n = 63)	p-Value	All[a] (n = 63)	Amiodarone use[a] (n = 5)
1. Tong et al. [18]	0.382	0.002	0.94 (±0.75)	0.56 (±0.31)
2. Ragia et al. [19]	0.358	0.004	0.96 (±0.75)	0.6 (±0.49)
3. Kumar et al. [16]	0.274	0.030	1.38 (±1.05)	1.6 (±1.22)
4. Kumar et al. [17]	0.287	0.023	1.31 (±1.42)	2.2 (±0.52)
5. Wolkanin-Bartnik et al. [20]	0.397	0.001	0.82 (±0.61)	0.98 (±0.74)
6. Pop et al. [21]	0.376	0.002	0.86 (±0.67)	0.62 (±0.59)
7. van Schie et al. [22]	0.394	0.001	0.81 (±0.64)	0.48 (±0.42)
8. Rathore et al. [23]	0.331	0.008	1.16 (±0.94)	1.44 (±0.94)
9. Markatos et al. [24]	0.345	0.006	0.98 (±0.65)	1.28 (±0.61)

r, correlation coefficient; MAE, mean absolute error. [a]MAE is reported ± the standard deviation.

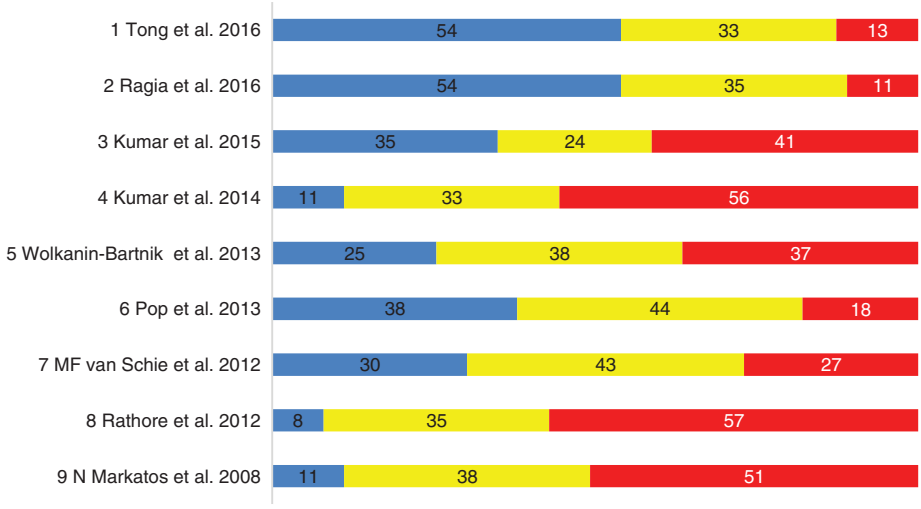

Figure 1: Percentages of patients with underestimated (blue), ideal (yellow), and overestimated (red) calculated doses of acenocoumarol.

[22] and Wolkanin-Bartnik algorithm [20] demonstrated the best correlation values (r = 0.394, MAE 0.81 ± 0.64 and r = 0.397, MAE 0.82 ± 0.64, respectively). EU-PACT also managed to give an estimate within the ideal range in 43% of the cases. We hypothesize that such results might stem from a number of factors starting from the genetic similarities between the populations to lifestyle similarities like dietary habits. The least accurate results were received from the three algorithms based on Indian patients: Kumar et al. [16] (r = 0.274, MAE 1.38 ± 1.05), Kumar et al. [17] (r = 0.287, MAE 1.31 ± 1.42), and Rathore et al. [23] (r = 0.331, MAE 1.16 ± 0.94). This finding may be attributed to ethnic differences.

As far as we know, no studies evaluating the influence of ethnicity on acenocoumarol dosing have been published so far. However, for another widely used VKA, warfarin, Limdi et al. have shown that the ethnic origin of the patient can influence the value of the optimal warfarin dose no less than genetic or clinical factors do [25]. They argued that "recommend that warfarin dosing algorithms should be stratified by race rather than adjusted for race" [25]. Yang et al. have reached a similar conclusion for Korean patients. Their research on warfarin-dosing algorithms definitively shows that strategies "based on data from Korean or Japanese patients exhibited better performance than those from other ethnic groups" [11]. Chinese researchers have also noticed a similar trend: algorithms based on certain ethnic groups work better than the unified International Warfarin Pharmacogenetics Consortium (IWPC) algorithm. They thus suggest building separate algorithms for each ethnic group to replace the IWPC one that does not factor in ethnic differences [25]. Given that this is the first extensive and intensive study to evaluate, compare, and validate the performance of the nine previously published dosing algorithms in the Russian population, it is difficult to argue whether ethnic

variations are the reasons behind such distribution of the results. We do believe, though, that this a factor worth considering in further research.

Among the rest, the algorithms by van Schie et al. [22] and Tong et al. [18] proved to be the most effective among patients receiving amiodarone. Only these two out of nine algorithms counted amiodarone intake as a factor. As a result, other algorithms showed higher MAEs. In their 1984 study, Arbox et al. have shown that patients on amiodarone require a lower acenocoumarol dose than their amiodarone-free counterparts. Acenocoumarol plasma concentrations, however, did not vary between the two groups of patients. This finding suggests a pharmacokinetic interaction in which pharmacodynamics mechanisms do not play a significant role [26]. In 1985, Richard et al. proposed that amiodarone serves as inhibitor of acenocoumarol metabolism [27]. It has been proven that amiodarone inhibits cytochrome CYP2C9 responsible for (R)-acenocoumarol metabolism [28]. This finding suggests that amiodarone intake is a factor that absolutely must be considered when determining acenocoumarol dose. Nowadays, the number of people with comorbidities and multiple simultaneous medication intake is steadily increasing, and this trend can lead to increased risks involving undesirable drug interactions [29].

Our study certainly had limitations, including its retrospective nature and limited information on some of the genetic factors. *VKORC1* (rs7294) and *VKORC1* (rs2359612) were not available for our validation cohort, which could have influenced estimated doses of the Kumar et al. [16] and Kumar et al. [17] algorithms using these particular polymorphisms. The number of patients in the study is also relatively low, but it does, however, pave the road to new research that could significantly improve our understanding of genetic-guided dosing algorithms for one of the most widely used anticoagulant medications in the world. Unfortunately, the number of patients in our study was not enough to draw conclusions that would allow us to build our own dosing algorithm. This will be the logical next step once the patient data we keep collecting become sufficient.

Conclusions

While all the existing algorithms used in the study have failed to predict the ideal acenocoumarol dose in at least 50% of the cases in Russian patients, we can draw important conclusions from the distribution of resulting doses. The best-performing algorithm was based on the European population and the two least accurate results were yielded by the Indian population-based algorithms, from which we can infer that patient ethnicity is a factor that must be considered in building future algorithms. There is also reason to believe that amiodarone intake has significant influence on the needed dose and is also a factor to be considered. As for the algorithms needed to make accurate estimations of maintenance doses of acenocoumarol in Russian patients, further research is required to find the perfect dosing formula.

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