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CYP2C9 Polymorphism and Unstable Anticoagulation with Warfarin in Patients Within the First 3 Months Following Heart Valve Replacement*

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article; G – other

Abstract

Background. Warfarin dose requirements are partly determined by common single nucleotide polymorphisms in VKORC1 and CYP2C9 genes.

Objectives. The aim of this study was to investigate how the presence of allelic variants in CYP2C9 affects the stability of anticoagulation in patients within the first 3 months following elective heart valve replacement.

Material and Methods. In a case-control study we compared 18 consecutive carriers of CYP2C9*2 and/or *3 and 25 well-matched patients with the wild type CYP2C9*1/*1 genotype. The former group was randomly assigned to use coagulometers or monitor international normalized ratio (INR) in local outpatient clinics. Subjects receiving drugs potently interfering with warfarin were ineligible. Anticoagulation with the baseline warfarin regimens based on pharmacogenetic algorithm was assessed by time in the therapeutic INR range (TTR) within the first 3 months following implantation.

Results. Carriers of the CYP2C9*2 and/or *3 genotypes were characterized by lower estimated warfarin dose (median, 21 [interquartile range, 21–35] vs. 35 [28–42] mg/week, p = 0.02) and actual (27.8 ± 13.2 vs. 46.3 ± 13.9 mg/week, p < 0.001), together with lower TTR values (56 [38.6–74.9] vs. 75.4 [58.1–83.6] %, p = 0.03) and longer time above the therapeutic range (13.8 [4.9–34.5] vs. 4.5 [0–15.3] %, p = 0.047) than patients with the CYP2C9*1/*1 genotype. There were no differences in the estimated and actual warfarin doses, TTR values and adverse events between the self-testing and standard-care subgroups.

Conclusions. The presence of CYP2C9*2 and/or *3 genotypes is associated with unstable warfarin treatment in patients after heart valve replacement, regardless of the type of INR testing (Adv Clin Exp Med 2015, 24, 607–614).

Key words: warfarin, TTR, pharmacogenetics, heart valve replacement.

Despite increasing clinical use of direct thrombin and factor (F) Xa inhibitors, mainly in non-valvular atrial fibrillation (AF), 4-hydroxycoumarin derivatives – vitamin K antagonists (VKAs) – are used in the prevention of valve thrombosis and arterial thromboembolism in patients with artificial heart valves [1–3]. The most commonly used VKA worldwide, warfarin, exhibits its anticoagulant effect by inhibiting the recycling of oxidized vitamin K to the reduced form (KH₂) by vitamin K epoxide reductase complex subunit 1 (VKORC1) in the liver. Vitamin KH₂ serves as a cofactor in carboxylation of glutamate residues (Gla) on the N-terminal regions of vitamin K-dependent blood coagulation factors (F), i.e. FI, FVII, FIX, and FX [4]. Treatment with warfarin

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results in the hepatic production of partially carboxylated and decarboxylated proteins with reduced coagulant activity.

However, VKA therapy is challenging because of its narrow therapeutic index combined with the wide inter-individual dosing variation. The efficacy and safety of warfarin treatment are highly dependent on the time in which the international normalized ratio (INR) is in the therapeutic range (TTR) [5]. A maintenance dose of VKA depends on several factors, predominantly diet and medications, or individual features such as age and body weight as well as genetics factors [6]. VKORC1 and cytochrome P450 (CYP) 2C9 genetic variants contribute largely to inter-individual variations in warfarin dose requirements affecting its pharmacodynamics and pharmacokinetics, respectively [7, 8]. The CYP2C9 gene is located on chromosome 10q24 and encodes the cytochrome P450 enzyme that metabolizes the S-warfarin isof orm, which is 2.7 to 3.8 times more potent than the R enantiomer [6].

The major CYP2C9 polymorphisms, CYP2C9*2 in exon 3 (p.Arg144Cys, c.430C > T, rs1799853) and CYP2C9*3 in exon 7 (p.Ile359Leu, c.1075A > C, rs1057910) are associated with reduced enzyme activity [2, 6]. In vitro study has shown that intrinsic clearance of S-warfarin was 5.5-fold and 27-fold lower when the reaction was catalyzed by enzymes encoded by CYP2C9*2 and CYP2C9*3 allelic variants, respectively, compared with the wild type genotype CYP2C9*1/*1 [9]. Patients with the VKORC1 wild type and the CYP2C9*1/*2 genotypes require approximately the same dose of warfarin [10]. In the presence of any of the genotypes – CYP2C9*2/*2, CYP2C9*2/*3 or CYP2C9*1/*3 together with the VKORC1 wild type variant, a warfarin dose is decreased approximately 1.7-fold compared to the CYP2C9*1/*1 variant. Subjects with the CYP2C9*3/*3 variant require approximately from 3.5 to 10-fold lower dose of warfarin to achieve therapeutic INR compared to the CYP2C9*1/*1 variant [10].

The carriers of the CYP2C9*2 and/or CYP2C9*3 allele, who represent 10% and 6% of the European population, respectively, have an increased risk of bleeding complications, especially at the beginning of anticoagulation therapy and need a longer time to stabilize the VKAs dose [2, 11, 12]. The risk of bleeding complications during warfarin treatment has been increased by 90% for CYP2C9*2 and by 80% for CYP2C9*3 allele variants [2]. However, this data was derived mostly from studies in patients for whom the most frequent indication for warfarin treatment was AF (up to 60%), and then venous thromboembolism (VTE) (up to 40%). Patients after heart valve replacement have constituted less than 10% of all participants in the large published studies regarding the role of genetic polymorphisms in the optimization of VKA therapy [13–15].

Patients following mitral or aortic valve implantation have a relatively high risk of bleeding complications and exhibit a slightly different profile of bleeding and thromboembolic risk as compared to those with AF. It has been reported that total bleeding incidence is higher in patients after mitral valve replacement (32.3%) than in those after aortic valve replacement (21.8%), whereas the incidence of clinically relevant moderate or severe bleeding is not significantly different among the groups during 13 months of follow-up [16]. Similarly, Schapkaiz et al. have reported that there was no significant difference in overall bleeding incidence between the mechanical valve replacement subgroups and the control group over a 4-month follow-up [17]. However, patients with double (aortic and mitral) valve replacements had a higher proportion of combined bleeding and thromboembolic complications (30.61%) than patients with single aortic or mitral valve replacements (14.29% vs. 18.05%, respectively) and patients in the control group (12.87%) [17].

To the best of our knowledge, most of the studies concerning the genetic associations with quality of anticoagulation and adverse events have been performed on AF and VTE patients and the subjects after heart valve replacement have not been analyzed separately. Therefore, we sought to evaluate the relationship between CYP2C9 polymorphisms and TTR in this subset of anticoagulated patients in whom INR was monitored using 2 different approaches, i.e. self-testing and standard care.

Aim of the Study

The aim of study was to investigate how allelic variants in CYP2C9 affect the stability of anticoagulation with warfarin in patients within the first 3 months following elective heart valve replacement.

Material and Methods

Between March and October 2013, 18 consecutive carriers of CYP2C9*2 and/or *3 and 25 patients with wild type CYP2C9 *1/*1 were enrolled. The inclusion criteria were: age of at least 18 years, elective aortic and/or mitral valve replacement and need to use warfarin for at least 3 months. The exclusion criteria were: acute infective endocarditis, renal failure (creatinine > 200 umol/L), acute
vascular incident within 3 months prior to enrollment, psychiatric diseases, alcoholism, the use of thienopyridines, oral corticosteroids or immuno-suppressive agents. Subjects receiving drugs interfering with warfarin, including amiodarone, rifampicin, carbamazepine, antifungal azole agents, ritonavir and barbiturates, were ineligible.

Demographic and clinical characteristics of the patients were recorded prior to surgery. Arterial hypertension was diagnosed based on blood pressure > 140/90 mm Hg or preadmission of antihypertensive treatment. Smoking was defined as the daily use of 1 or more cigarettes. Patients receiving insulin or oral hypoglycemic drugs, or having at least 2 random fasting glucose levels of > 7 mmol/L were classified as having diabetes mellitus. The left ventricular ejection fraction was measured by Doppler echocardiography using the modified Bernoulli equation. All patients gave written informed consent and the study was approved by the University Bioethics Committee.

Carriers of mutations in CYP2C9 were randomly assigned to 2 groups: (1) using coagulometers at home to measure INR (Alere INRatio®, INR Monitoring Systems, ALERE™, San Diego, CA, USA) and (2) monitoring INR values in a standard manner at the primary care physician’s or local cardiologist’s discretion. The former group was instructed to use the point-of-care INR devices weekly to self-test at home. The self-testing group received INR testing instruction, including data interpretation and coping with typical issues of the measurements. Training was initiated as soon after valve replacement as the patient’s clinical state allowed and was completed before discharge. The first INR measurement was performed by a physician and thereafter by the patients. If there were any doubts in the measurement procedure, the patient was excluded from the self-testing group. In some cases, the patient’s family member was also trained. When INR was out of the therapeutic range, the patient was required to consult with the physician.

The latter group and patients with the wild type CYP2C9*1/*1 genotype measured INRs in local outpatient clinics at least once every 3–4 weeks. The estimated warfarin dose was obtained from the online algorithm (http://www.warfarindosing.org) for each patient within 72 h after the surgery. The first warfarin dose was administered after removal of the epicardial electrode (5–10 days after surgery). Further doses of warfarin were modified based on the INR measurements. Within the first 2 weeks, measurements were performed every 2–3 days and then every 7–9 days, until the maintenance dose was established. To reliably calculate TTR, we defined a sufficient number of available INRs within the first 3 months since surgery study as 3.

The target INR range was 2.5–3.5 for mitral and 2.0–3.0 for aortic heart valve in accordance with the European Society of Cardiology (ESC) guidelines. The quality of warfarin dosing was assessed by the percentage of TTR, as described by Rosendaal et al. [5]. The last INRs were determined at a follow-up outpatient visit in the hospital laboratory after 3 months (90 ± 13 days) since surgery. At that visit we recorded adverse events, including death, minor (nose bleeds, subconjunctival hemorrhage, bruises and skin hematomas) and severe bleeds (hemorrhagic stroke, gastrointestinal bleeding) as well as thromboembolic events (valve thrombosis, transient ischemic attack, stroke, myocardial infarction, venous thromboembolism or other thrombotic episode), that were documented in medical records and/or self-reported.

DNA was isolated from whole blood collected in EDTA using the QIAamp® DNA Blood Mini Kit (QIAGEN, Valencia, CA) and stored at −80°C until analysis according to the manufacturer’s protocol. Genotyping of VKORC1 (c.-1639G > A; rs9923231), CYP2C9*2 (p.Arg144Cys, c.430C > T; rs1799853) and CYP2C9*3 (p.Ile359Leu, c.1075A > C; rs1057910) SNPs was determined by the allelic discrimination test using TaqMan Genotyping assays and the ABI PRISM 7900HT Fast Real-Time PCR System (Life Technologies Co., Carlsbad, CA, USA; assays IDs: C_30403261_20, C_25625805_10 and C_27104892_10, respectively). The genotype determination was confirmed by positive and negative controls.

Statistical Analysis

The normality of data distribution was tested using the Shapiro-Wilk test. Data was shown as mean ± standard deviation or median (interquartile range), as appropriate. Differences between 2 independent groups were compared with a Student’s t-test or Mann-Whitney U test. Differences between the estimated and actual warfarin doses were assessed with Wilcoxon test. Qualitative data was compared by the Fisher exact test. Distribution of genotypes was evaluated by the χ² test. A p-value < 0.05 was considered statistically significant. Analysis was performed with STATISTICA v. 9.0 (StatSoft Inc., Tulsa, Oklahoma, USA).

Results

Patient characteristics are presented in Table 1. The prevalence of the CYP2C9*2 and *3 allele (for a total of 43 patients) was: 0.17: CC-30
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Non-carriers of CYP2C9*2/3 (n = 25)</th>
<th>Carriers of CYP2C9*2/3 (n = 18)</th>
<th>P-value</th>
<th>Self-testing (n = 8)</th>
<th>Clinical-testing (n = 10)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Age (year)</td>
<td>63.7 ± 9.5</td>
<td>65.2 ± 7.3</td>
<td>0.38</td>
<td>63.0 ± 2.4</td>
<td>66.9 ± 9.4</td>
<td>0.27</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>17 (68)</td>
<td>11 (61.1)</td>
<td>0.44</td>
<td>4 (50)</td>
<td>7 (70)</td>
<td>0.35</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>29.0 ± 4.2</td>
<td>28.3 ± 3.7</td>
<td>0.35</td>
<td>28.6 ± 4.4</td>
<td>28.1 ± 3.2</td>
<td>0.82</td>
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**Comorbidities**

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<tr>
<td>Arterial hypertension, n (%)</td>
<td>22 (88)</td>
<td>14 (77.8)</td>
<td>0.31</td>
<td>5 (62.5)</td>
<td>9 (90)</td>
<td>0.21</td>
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<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>23(92)</td>
<td>14 (77.8)</td>
<td>0.19</td>
<td>6 (75)</td>
<td>8 (80)</td>
<td>0.62</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>7 (28)</td>
<td>3 (16.7)</td>
<td>0.31</td>
<td>1 (12.5)</td>
<td>2 (20)</td>
<td>0.59</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>11 (44)</td>
<td>6 (33.3)</td>
<td>0.35</td>
<td>1 (12.5)</td>
<td>5 (50)</td>
<td>0.12</td>
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<tr>
<td>Atrial fibrillation, n (%)</td>
<td>9 (36)</td>
<td>7 (38.9)</td>
<td>0.55</td>
<td>3 (37.5)</td>
<td>4 (40)</td>
<td>0.65</td>
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<tr>
<td>LVEF (%)</td>
<td>55.0 (47.0–60.0)</td>
<td>59.5 (50.0–67.0)</td>
<td>0.30</td>
<td>52.0 (42.5–67.5)</td>
<td>62.0 (55.0–67.0)</td>
<td>0.45</td>
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<tr>
<td>Symptomatic HF, n (%)</td>
<td>0</td>
<td>2 (11.1)</td>
<td>0.17</td>
<td>1 (12.5)</td>
<td>1 (10)</td>
<td>0.71</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>2 (8)</td>
<td>0</td>
<td>0.33</td>
<td>0</td>
<td>0</td>
<td>n.a.</td>
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**Medications**

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<tr>
<td>Beta-blockers, n (%)</td>
<td>23 (92)</td>
<td>15 (83.3)</td>
<td>0.34</td>
<td>5 (62.5)</td>
<td>10 (100)</td>
<td>0.07</td>
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<tr>
<td>Aspirin, n (%)</td>
<td>11 (44)</td>
<td>11 (61.1)</td>
<td>0.21</td>
<td>5 (62.5)</td>
<td>6 (60)</td>
<td>0.65</td>
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<tr>
<td>VKA, n (%)</td>
<td>9 (36)</td>
<td>6 (33.3)</td>
<td>0.56</td>
<td>2 (25)</td>
<td>4 (40)</td>
<td>0.44</td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>20 (80)</td>
<td>12 (66.7)</td>
<td>0.26</td>
<td>6 (75)</td>
<td>6 (60)</td>
<td>0.44</td>
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<tr>
<td>ACEI, n (%)</td>
<td>15 (60)</td>
<td>10 (55.6)</td>
<td>0.51</td>
<td>5 (62.5)</td>
<td>5 (50)</td>
<td>0.48</td>
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**Surgery and its complications**

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<tr>
<td>Aortic valve replacement, n (%)</td>
<td>20 (80)</td>
<td>14 (77.8)</td>
<td>0.58</td>
<td>5 (62.5)</td>
<td>9 (90)</td>
<td>0.21</td>
</tr>
<tr>
<td>Mitral valve replacement, n (%)</td>
<td>3 (12)</td>
<td>2 (11.1)</td>
<td>0.66</td>
<td>1 (12.5)</td>
<td>1 (10)</td>
<td>0.71</td>
</tr>
<tr>
<td>Both valves replacement, n (%)</td>
<td>2 (8)</td>
<td>2 (11.1)</td>
<td>0.56</td>
<td>2 (25)</td>
<td>0</td>
<td>0.18</td>
</tr>
<tr>
<td>Major thrombotic complications, n (%)</td>
<td>1 (4)</td>
<td>1 (5.5)</td>
<td>0.67</td>
<td>0</td>
<td>1 (10)</td>
<td>0.56</td>
</tr>
<tr>
<td>Minor bleeding complications, n (%)</td>
<td>5 (20)</td>
<td>4 (22.2)</td>
<td>0.58</td>
<td>2 (25)</td>
<td>2 (20)</td>
<td>0.62</td>
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**Anticoagulant therapy**

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<tbody>
<tr>
<td>TTR (%)</td>
<td>75.4 (58.1–83.6)</td>
<td>56.0 (38.6–74.9)</td>
<td>0.03</td>
<td>42.5 (36.0–55.7)</td>
<td>62.4 (54.5–79.6)</td>
<td>0.08</td>
</tr>
<tr>
<td>Above TTR (%)</td>
<td>4.5 (0.0–15.3)</td>
<td>13.8 (4.9–34.5)</td>
<td>0.05</td>
<td>10.2 (2.5–32.6)</td>
<td>16.0 (8.1–34.5)</td>
<td>0.63</td>
</tr>
<tr>
<td>Below TTR (%)</td>
<td>16.7 (8.2–32.1)</td>
<td>6.7 (0.0–58.2)</td>
<td>0.56</td>
<td>45.1 (2.0–59.5)</td>
<td>1.2 (0.0–27.1)</td>
<td>0.25</td>
</tr>
<tr>
<td>Number of INR measurements</td>
<td>7.9 ± 2.5</td>
<td>9.0 ± 2.9</td>
<td>0.2</td>
<td>10.1 ± 3.2</td>
<td>8.1 ± 2.3</td>
<td>0.14</td>
</tr>
<tr>
<td>Warfarin estimated dose (mg/week)</td>
<td>35.0 (28.0–42.0)</td>
<td>21.0 (21.0–35.0)</td>
<td>0.02</td>
<td>21.0 (21.0–31.5)</td>
<td>21.0 (21.0–35.0)</td>
<td>0.69</td>
</tr>
</tbody>
</table>
CYP2C9 Polymorphism and Anticoagulation

(69.8%), CT-11 (25.6%) and TT-2 (4.6%) and 0.07:
AA-37 (86%), AC-6 (14%) and CC-0 (0%), re-
spectively. The distribution of CYP2C9 *2 and
CYP2C9 *3 genotypes was in accordance with the
Hardy-Weinberg equilibrium (p = 0.54 and 0.24,
respectively).

The patients with CYP2C9 *2 and/or *3 al-
lele and the control subjects with the
CYP2C9 *1/*1 genotype did not differ with regard to de-
mographic data, clinical factors, the prevalence of
VKORC1 -1639G > A polymorphism and number
of INRs measurements (Table 1).

In the group with CYP2C9 *2 or *3 allele, there were 14 (77.8%) patients following aortic,
2 (11.1%) following mitral and 2 (11.1%) with both
aortic and mitral valve replacement. The CYP-
2C9*2 allelic variant was observed in 12 (66.7%)
patients, while the CYP2C9*3 allelic variant was
found in 5 (27.8%) patients. There was one (5.5%)
patient with the both variants. The VKORC1 -1639G > A polymorphism, i.e. the GA or AA genotypes,
was detected in 12 (66.7%) patients with the
CYP-2C9 *2 or *3 allele.

During the first 3 postoperative months, no
death or hemorrhagic or ischemic strokes were
noted in either group. Transient ischemic at-
tack occurred in 1 (4%) patient with the CYP-
2C9*1*1 variant and in 1 (5.5%) patient with a
CYP2C9*1*3 mutation. Gastrointestinal bleeding
was observed in 2 (8%) patients without mu-
tation in the CYP2C9 gene. Subconjunctival
hemorrhage was observed in 2 (11%) patients with
CYP2C9*1*3 and CYP2C9*2*3 mutations. Nose-
bleed was recorded in 1 patient with the CYP-
2C9*2 variant. Bruises and skin hematomas were
reported by one (5.6%) patient with the
CYP2C9*2 allele. There were no differences between
the wild type and CYP2C9*1*1 genotype. In contrast to the wild-type carriers, no differences between the esti-
mated and actual warfarin doses in patients having
CYP2C9*2 and/or *3 variants were observed (Ta-
ble 1).

The carriers of mutations in CYP2C9 were
characterized by lower TTR (56.0 [38.6–74.9] %, p = 0.03) and spent a lon-
ger time in which the INR was above the ther-
apeutic range (13.8 [4.9–34.5] % vs. 4.5 [0–15.3] %,
p = 0.047) than the wild type patients.

There were no significant differences between
the self-testing (n = 8, 44%) and standard-care
(n = 10, 56%) groups with regard to demograph-
ic and clinical characteristics (Table 1). There were
also no differences in the frequency of the studied
allelic variants. However, in the self-testing group,
the CYP2C9*3 variant was less frequent than in the
standard-care group (1 carrier, 12.5% vs. 4 carriers,

### Table 1. Patient characteristics (cn.)

<table>
<thead>
<tr>
<th></th>
<th>Non-carriers of CYP2C9*2/3 (n = 25)</th>
<th>Carriers of CYP2C9*2/3 (n = 18)</th>
<th>P-value</th>
<th>Self-testing (n = 8)</th>
<th>Clinical-testing (n = 10)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin actual mean dose (mg/week)</td>
<td>46.3 ± 13.9</td>
<td>27.8 ± 13.2</td>
<td>&lt; 0.001</td>
<td>30.1 ± 16.3</td>
<td>27.1 ± 11</td>
<td>0.78</td>
</tr>
<tr>
<td>Differences between the estimated and actual warfarin dose (mg/week)</td>
<td>9.0 (6.5–22.0) p = 0.001*</td>
<td>4.5 (3.0–10.5); p = 0.39*</td>
<td>0.03</td>
<td>8.8 (5.0–14.0); p = 0.32*</td>
<td>9.0 (4.0–21.0); p = 0.84*</td>
<td>0.17</td>
</tr>
<tr>
<td>Genotyping</td>
<td>CYP2C9*2, n (%)</td>
<td>0</td>
<td>12 (66.7)</td>
<td>&lt; 0.001</td>
<td>6 (75)</td>
<td>6 (60)</td>
</tr>
<tr>
<td></td>
<td>CYP2C9*3, n (%)</td>
<td>0</td>
<td>5 (27.8)</td>
<td>0.009</td>
<td>1 (12.5)</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Both allelic variants of CYP2C9, n (%)</td>
<td>0</td>
<td>1 (5.5)</td>
<td>0.42</td>
<td>1 (12.5)</td>
<td>0</td>
<td>0.44</td>
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<tr>
<td>VKORC1 -1639G &gt; A, n (%)</td>
<td>19 (76)</td>
<td>12 (66.7)</td>
<td>0.37</td>
<td>4 (50)</td>
<td>8 (80)</td>
<td>0.20</td>
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Data is given as mean ± SD, median (interquartile range) or number (percentage). ACEI – angiotensin-converting enzyme inhibitor; BMI – body mass index; CAD – coronary artery disease; CYP2C9 – cytochrome P450 2C9; HF – heart failure; LVEF – left ventricular ejection fraction; TTR – time within therapeutic range; VKA – Vitamin-K antagonist; VKORC1 – – vitamin K epoxide reductase complex subunit 1.

* – association between the estimated and actual warfarin doses within a group.
40%, respectively), with one patient (12.5%) with both mutated CYP2C9 allelic variants. No differences in the estimated and actual warfarin doses, TTR values and adverse events between the self-testing and standard-care subgroups were observed.

Discussion

The current study demonstrated that in patients following elective heart valve replacement the common allelic CYP2C9*2 and/or *3 variants are associated with lower warfarin dosing and lower TTR in comparison to the CYP2C9*1/*1 genotype evaluated within the first 3 months of anticoagulation. This finding is consistent with previous reports published mainly for patients with AF and/or VTE [13–15, 18]. Importantly, our study shows a similar impact of the two CYP2C9 mutations on the quality of anticoagulation in heart valve recipients with several comorbidities, e.g. heart failure, which might be perceived as factors that contribute to large variations in TTR and INR values.

The TTR value of the most common patient group, i.e. subjects with the CYP2C9*1/*1 genotype, was 75.4% and was even higher or similar to those reported previously, mostly for AF patients [13, 19, 20]. This highlights the good quality of warfarin therapy in Polish patients after valve implantation, which indicates a large improvement in TTR values in everyday practice nowadays, although compared to countries with the best quality of anticoagulation, e.g. Sweden, Poland, without anticoagulation clinics, still has an overall suboptimal quality of long-term VKA treatment.

In the current study, patients possessing mutated allelic variants of the CYP2C9 gene had lower both estimated and actual warfarin doses than patients with the CYP2C9*1/*1 genotype. This is in line with the previous reports concerning Turkish and Lithuanian patients after heart valve replacement where carriers of CYP2C9*2 and/or CYP2C9*3 genotypes required a lower maintenance dose of warfarin than patients with the CYP2C9*1/*1 wild-type genotype [21, 22]. Furthermore, in our study, no differences between the estimated and actual warfarin doses and no significant bleeding complications in carriers of CYP2C9*2 and/or *3 were observed. On the contrary, in the CYP2C9*1/*1 group, differences between the estimated and actual warfarin doses were observed. It may be speculated that in our study group the pharmacogenetics algorithm is less helpful for patients without mutations in CYP2C9 requiring the intermediate warfarin dosing, as has been found previously [23]. The International Warfarin Pharmacogenetics Consortium has reported that a pharmacogenetics algorithm was more accurate for patients requiring lower (≤ 21 mg per week) or higher doses (≥ 49 mg per week) of warfarin than a clinical algorithm. For patients requiring ≤ 21 mg per week, the pharmacogenetic algorithm has given 50% of patients a well-predicted dose of warfarin, while the clinical algorithm has given only 33% [23]. In our study, we confirmed that the pharmacogenetic algorithm may be a useful for the estimation of appropriate anticoagulation with warfarin in patients who require the lower warfarin doses. However, in this group of patients, the strong influence of CYP2C9 variants was demonstrated in a less stable anticoagulation reflected by shorter TTR and a longer period where the INR was above the therapeutic range. These results might suggest that careful warfarin dosing and more frequent INR testing in the group with CYP2C9*2 or *3 variants are necessary.

INR testing can be done in outpatient clinics or by patients themselves at home. Self-testing of INRs has become more and more popular in Europe. In the current study, no differences were found in TTR or adverse event occurrence between the self-testing and standard-care groups. Similarly, previous studies in a large cohort of patients mostly with AF and after mechanical heart valve implantation have shown no differences in frequency of the first stroke, major bleeding complications and death between the self-testing and standard-care group [24]. However, better TTR has been achieved in the self-testing group than the standard care group [19, 24]. We did not find these associations probably due to the limited size of our study group. Similarly, bleeding episodes were not associated with the presence of the mutated variants of CYP2C9, probably due to the small number of patients. However, in a recently reported case-control study where patients after heart valve replacement constituted 20 and 10%, respectively, the CYP2C9*1/*3 and VKORC1 variants showed only a non-significant trend toward increased major bleeding risk in the initial 6 months of warfarin use [25]. It might be concluded that self-testing in everyday practice among mostly elderly patients is not superior to the standard care if the INR measurements are performed regularly, the patients are instructed on the risk and benefits from the therapy and modification of warfarin dosage is promptly recommended. Self-testing should be limited to anticoagulated patients who have objective obstacles to measure INR in outpatient clinics, e.g. logistical problems to reach them at least every 3–4 weeks.

Limitations

First, the major limitation of the current study is the small size of the patient groups. However, the impact of the 3 genetic polymorphisms evaluated
in the context of TTR was potent enough to be observed. Second, follow up in our study was restricted to the first three postoperative months, and a longer follow-up might provide additional data, including the postoperative long-term clinical outcome, especially bleedings associated with the various genotypes. Finally, the current observations cannot possibly be extrapolated on patients receiving other VKAs, in particular acenocoumarol, which is still the most commonly used VKA in Poland. There are some differences in the role of the polymorphisms studied in the stability of anticoagulation with acenocoumarol versus warfarin [9].

The authors concluded that CYP2C9*2 and/or *3 variants increase the risk of unstable anticoagulation with warfarin in patients within the first 3 months following heart valve replacement. INR-self testing does not deteriorate the anticoagulation control in patients with CYP2C9 variants in comparison to patients who monitor the INR in local outpatient clinics. Genotyping of CYP2C9*2 and/or *3 variants might improve outcome in patients after heart valve replacement.

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References


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