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Original Article

The influence of VKORC1 and CYP2C9 mutations on warfarin response after total hip and knee arthroplasty

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ABSTRACT

Aims: This study characterizes the influence of genotype at two loci on warfarin response after arthroplasty.

Methods: 121 postarthroplasty patients given warfarin thromboprophylaxis were reviewed for international normalized ratio (INR) values on the first three days postoperatively. Significant differences among genotypes in INR values on each of the first three postoperative days were assessed.

Results: Wild-type patients at both loci (~23% of patients) had yet to reach therapeutic INR (1.5–2.0) by postoperative day three more frequently than those with a mutation conferring hyper-responsiveness (61% vs. 30%; $P \leq .01$).

Conclusions: Wild-type patients are not anticoagulated in a sufficiently prompt manner after arthroplasty.

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1. Introduction

Optimal warfarin dosing varies greatly among patients, as there are multiple factors that influence its anticoagulant effect. One major factor is the individual's genetic makeup.¹ Debate has emerged as to whether genetic testing is indicated

prior to initiation of warfarin therapy, as persistently subtherapeutic anticoagulation may lead to fatal thromboembolic events, while supratherapeutic anticoagulation can lead to bleeding. A recent prospective randomized trial of a clinical vs. genotype-guided warfarin-dosing algorithm has been reported in patients anticoagulated for atrial fibrillation or venous thromboembolic disease, revealing that genetic-based

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dosing leads to greater time spent in, and shorter time to reach therapeutic international normalized ratio (INR) range.² For patients taking the drug, warfarin genotyping is becoming the standard-of-care at select medical centers internationally, with a cardiology setting as the most common point of testing.

Warfarin metabolism is primarily governed by variants of the CYP2C9 and VKORC1 genes. CYP2C9 is a cytochrome P450 enzyme found primarily in the liver that is largely responsible for the degradative metabolism of warfarin. Its most common variant, wild-type *1, has two loss-of-function variants termed *2 (430C>T) and *3 (1075A>C) that prolong the drug's half-life and potentiate its anticoagulant effect.^{3,4} Estimated variant frequencies for *1, *2, and *3 are 81%, 11%, and 8%, respectively.^{5,6} The gene encoding vitamin K epoxide reductase, VKORC1, has an associated 1639G>A polymorphism leading to the possible genotypes GG (wild-type normal), GA (heterozygous), and AA (homozygous), with respective estimated frequencies of 49%, 40%, and 11%.⁷ These polymorphisms lead to decreased expression of the enzyme and increased warfarin sensitivity.³ The majority of patients have at least one *2, *3, or A allele and are deemed "hyper-responders", while wild-type G/G *1/*1 patients are considered "normal responders". Collectively, it is estimated that these two genes account for as high as 40% of the variance in warfarin-dosing requirements.⁸

Most data assessing the benefit of genetic-based warfarin dosing have only considered patients requiring anticoagulation for a medical indication.¹ However, the postoperative patient represents a perturbed metabolic system due to whole-body inflammation, in which the genetic influence on warfarin response may vary considerably, and consequences of subtherapeutic or supratherapeutic dosing could be magnified. The total joint replacement represents a commonly performed operation after which patients generally receive thromboprophylaxis for as long as a month. The recommended target INR window is between 1.5 and 2.0.^{9,10} Moreover, warfarin genetic testing is not routinely recommended. However, efficient anticoagulation to the desired levels is critical due to the high rate of venous thrombosis in these patients. In 2008, Lenzini and colleagues used CYP2C9 genotype to derive a genetically based dosing algorithm for warfarin initiation. Patients postoperatively dosed with this algorithm spent significantly more time within the therapeutic window, relative to those dosed with a standard clinical algorithm.¹¹ A 2009 pilot study in thirty patients found that postarthroplasty patients were more likely to be warfarin hyper-responders with the AA genotype than with the GG or GA genotype of the VKORC1 gene.¹² Our institution has genotyped over 14,000 patients for both CYP2C9 and VKORC1 alleles, many of whom had once received warfarin thromboprophylaxis after a total hip or knee replacement. The purpose of this study was to retrospectively investigate the influence of both CYP2C9 and VKORC1 genotypes on warfarin responsiveness in the critical first three postoperative days after total joint replacement.

2. Materials and methods

This was a single-institution retrospective study, and all information was obtained from the Synthetic Derivative, a

de-identified database that mirrors the Vanderbilt electronic medical record. Approval was obtained from the Institutional Review Board and informed consent was waived. The initial search algorithm for patients included specification of a CPT code indicative of hip or knee arthroplasty (27447, 27130, or 27132), presence of a known genotype for either VKORC1 or CYP2C9 genes, as well as mention of the use of "warfarin," "Coumadin," or "warfarin sodium." The initial search yielded 343 patients, which were individually reviewed.

Of the 343 patients identified, 222 were excluded. Patients were excluded if they did not have a full genotype known for both genes, or if the date on which the genotyping was done was unavailable. All patients who had been genotyped prior to surgery were excluded as well, as it is unclear if the known genotype biased postoperative warfarin dosing. Patients without INR values documented on the first three postoperative days were excluded, as were patients who had used chronic warfarin therapy within two years prior to surgery.⁴ Other exclusion criteria included a history of deep venous thrombosis or pulmonary embolism, as well as any of the following: blood transfusion ≤ 2 weeks of the day of surgery (including intraoperatively), chronic liver disease, active cancer, irritable bowel syndrome, irritable bowel disease, myeloproliferative disorders, bleeding or hypercoagulability disorders, and congestive heart failure.^{4,12} Patients of Asian ethnicity,¹² or those with procedures prior to 2003, were also excluded. Finally, patients with charts that were incomplete, questionable, or had obviously spurious data were excluded. Derivation of the study cohort is shown in Fig. 1. Ultimately, 121 patients were included in the study, and 94 had genotypes with sufficient prevalence for comparative analysis (minimum 10 patients).

Patients who undergo total knee arthroplasty (TKA) or total hip arthroplasty (THA) require short-term anticoagulation for deep venous thrombosis (DVT) prophylaxis. Institutionally, patients generally receive 5 mg of warfarin on the night of surgery and the subsequent two days before dose adjustments. The target therapeutic range was 1.5–2.0, with duration of treatment between 3 and 4 weeks.

Inequalities in potential confounders of warfarin response among genotypic groups, including age, gender, preoperative smoking status, body-mass index (BMI), operation (TKA or THA), preoperative CYP2C9 inducer medications,¹³ and preoperative CYP2C9 enzyme inhibitor medications,¹³ were assessed by the Kruskal-Wallis test with Dunn's post hoc analysis of multiple comparisons. As groups were otherwise evenly matched, no adjustments to INR values were made. INR values on the first three postoperative days were similarly compared among genotypic groups, as was the percent of patients with subtherapeutic INR on postoperative day three. Additionally, linear regression of the INR values on the first three postoperative days was performed among genotypes, with pairwise analyses used to detect differences in rates of rise of INR (slopes). Statistical analysis was performed using GraphPad Prism (La Jolla, CA) and JMP statistical software (Cary, NC). Continuous variables were expressed as median (interquartile range [IQR]), while categorical variables were expressed as percentages. $P \leq .05$ was used to denote statistical significance.

Fig. 1 – Derivation of the study cohort.

3. Results

Demographics and patient characteristics were obtained for the 121 patient study cohort. Median age at surgery was 64.6 (59.9–71.8) years. 48% of the cohort was male, and 9% were active tobacco users. Median BMI was 32.6 (28.2–38.2) kg/m². Median number of preoperative CYP450 inhibitor and inducer medications were 1 (0–2; mean of 1.2 per patient) and 0 (0–1; mean of .5 per patient), respectively. Seventy-six percent of the patients received total knee arthroplasty, while 24% received total hip arthroplasty. Full patient characteristics, with a breakdown of genotype prevalence, are reported in Table 1. Genotypes meeting criteria for analysis were G/G *1/*1 (wild-type; $n = 28$), G/G *1/*2 ($n = 11$), A/G *1/*1 ($n = 32$), A/G *1/*2 ($n = 13$), and A/A *1/*1 ($n = 10$).

A comparison of potential confounders of postoperative warfarin response is reported in Table 2. No specific factor, including age, gender, BMI, tobacco use, type of operation, or medication regimen, was disproportionally represented in any genotypic group, preventing the need to adjust INR values.

Comparison of INR values on each of the first three postoperative days revealed no significant differences among genotypic groups on postoperative days one ($P = .35$, Kruskal-Wallis statistic [KWS] = 4.4) and two ($P = .14$, KWS = 7.0). Differences in INR values among genotypes were detectable by postoperative day three ($P = .02$, KWS = 11.8). On post hoc analysis, postoperative day three INR values were decreased in normal responders (G/G *1/*1) relative to patients of the genotype A/G *1/*1 (1.4 [1.3–1.6] vs. 1.6 [1.4–1.7]; $P \leq .05$). Normal responders were also more likely to be subtherapeutic by

postoperative day three, significantly more so relative to patients of the genotype A/G *1/*1 (61% vs. 25%; $P \leq .05$). These data are summarized in Table 3. Additionally, comparison of normal responders ($n = 28$) to the collective cohort of hyper-responders ($n = 66$) revealed that the former group had both a significantly lower INR (1.4 vs. 1.6; Mann-Whitney U statistic = 545, $P = .001$) and carried twice the relative risk (RR) of being subtherapeutic (61% vs. 30%, RR 2.0, 95% confidence interval 1.3–3.2, $\chi^2 = 7.6$, $P = .006$) on the third postoperative day.

Considering INR values on each of the first three postoperative days, linear regression analysis was performed on patients within each genotype, as well as for the collective hyper-responders. The regression lines are seen in Fig. 2. Pairwise comparisons revealed that, relative to normal responders (G/G *1/*1), patients with genotypes G/G *1/*2 ($P = .006$), A/G *1/*1 ($P = .04$), and A/G *1/*2 ($P = .02$) all had a significantly increased slope (rate of rise of INR). Ostensibly due to sample size, differences between G/G *1/*1 and A/A *1/*1 were not detected ($P = .12$). Additionally, slopes between normal responders and the collective hyper-responders were significantly different ($P = .02$).

4. Discussion

TKA and THA procedures are extremely common, with almost 800,000 operations performed annually in the United States.¹⁴ Moreover, orthopedic operations have the highest rate of venous thromboembolism among all surgical specialties.¹⁵ In THA/TKA patients without thromboprophylaxis, rates of DVT

Table 1 – Baseline demographics and characteristics of the study cohort.

Patient characteristics (n = 121)	Median (IQR), or percent (number)
Age at surgery (years)	64.6 (59.9–71.8)
Male gender	48% (58/121)
Current tobacco users	9% (9/101)
Body mass index (kg/m ²)	32.6 (28.2–38.2)
# Preop CYP450 inhibitor meds.	1 (0–2; n = 89)
# Preop CYP450 inducer meds.	0 (0–1; n = 89)
Surgery type	
Total knee arthroplasty	76% (92/121)
Total hip arthroplasty	24% (29/175)
VKORC1/CYP2C9 genotype	
G/G *1/*1	23% (28/121)
G/G *1/*2	9% (11/121)
G/G *1/*3	6% (7/121)
G/G *2/*2	.8% (1/121)
G/G *2/*3	0% (0/121)
G/G *3/*3	0% (0/175)
A/G *1/*1	26% (32/121)
A/G *1/*2	11% (13/121)
A/G *1/*3	7% (8/121)
A/G *2/*2	2% (2/121)
A/G *2/*3	0% (0/121)
A/G *3/*3	.8% (1/121)
A/A *1/*1	8% (10/121)
A/A *1/*2	7% (8/121)
A/A *1/*3	0% (0/121)
A/A *2/*2	0% (0/121)
A/A *2/*3	0% (0/121)
A/A *3/*3	0% (0/121)
CYP, Cytochrome P450 family.	
Bold indicates genotype included in analysis (n ≥ 10).	

or pulmonary embolism are between 41% and 85%. While most of these venous thromboembolisms remain asymptomatic, postoperative anticoagulation reduces the rate of symptomatic pulmonary embolism, the most feared sequela of DVT, from >3% to <1%.^{16–19} Furthermore, venous thromboembolism represents the most common indication for postoperative readmission and is the third leading cause of vascular death.^{15,20} Therefore, it is critical to ensure prompt and adequate anticoagulation to the therapeutic goal after TKA/THA.

Multiple thromboprophylactic regimens for these patients are approved; for example, aspirin as a more cost-efficient alternative is replacing warfarin for thromboprophylaxis in some centers, while mobile compression devices may represent a potential monotherapy as well.^{19,21} Nonetheless, as many practitioners remain comfortable with its use, warfarin remains the most widely used pharmacologic agent for post-THA/TKA thromboprophylaxis in the United States.^{14,15,22,23} Warfarin has a very narrow therapeutic index and can be difficult to dose.¹⁰ Excess postoperative anticoagulation must be avoided as it increases the risk for spontaneous or traumatic bleed. These complications may be pronounced in the postarthroplasty population, as this cohort is prone to falls.²³ Recent guidelines by the American Academy of Orthopedic Surgeons recommend a goal INR in the range of 1.5–2.0.^{16,24} This reflects the legitimate concern that excess anticoagulation can lead to bleeding events, and that the postoperative patient must be anticoagulated with greater caution than those receiving warfarin for another indication.²³

Pharmacogenomic profiles are being used to provide personalized medicine initiatives nationwide. Clopidogrel, statin compounds, tacrolimus, thiopurines, and warfarin represent a group of drugs with known loci whose mutations

Table 2 – Potential confounders of warfarin responsiveness, stratified by genotype.

Patient variable	G/G *1/*1 (n = 28)	G/G *1/*2 (n = 11)	A/G *1/*1 (n = 32)	A/G *1/*2 (n = 13)	A/A *1/*1 (n = 10)	P (KWS)
Age	66.1 (60.6–72.6)	62.0 (59.3–71.7)	64.5 (58.4–72.4)	64.6 (61.2–73.1)	63.2 (54.5–66.8)	.77 (1.8)
Male gender	44% (13/28)	31% (4/11)	59% (19/32)	46% (6/13)	60% (6/10)	.65 (2.5)
BMI (kg/m ²)	31.1 (28.8–37.2)	34.2 (25.5–38.2)	31.8 (26.4–41.8)	34.2 (31.2–36.8)	32.1 (26.2–39.7)	.96 (0.6)
Tobacco user	9% (2/22)	0% (0/9)	8% (2/24)	15% (2/13)	29% (2/7)	.42 (3.9)
Percent TKA	79% (22/28)	73% (8/11)	72% (23/32)	77% (10/13)	90% (9/10)	.82 (1.5)
# Preop CYP450 inhibitor meds.	1 (0–2) (n = 21)	1 (0–2) (n = 7)	1 (0–2) (n = 22)	0 (0–1) (n = 11)	.5 (0–3) (n = 6)	.52 (3.2)
# Preop CYP450 inducer meds.	0 (0–1) (n = 21)	0 (0–1) (n = 7)	0 (0–1) (n = 22)	0 (0–1) (n = 11)	1 (0–2) (n = 6)	.47 (3.5)
Continuous variables reported as median (interquartile range), categorical variables reported as percent (number of patients). The Kruskal-Wallis test was used to assess differences among genotypes.						
BMI, body-mass index; TKA, total knee arthroplasty; CYP, Cytochrome P450 family; KWS, Kruskal-Wallis statistic.						

Table 3 – Postoperative INR values, stratified by genotype.

Outcome measure	G/G *1/*1 (n = 28)	G/G *1/*2 (n = 11)	A/G *1/*1 (n = 32)	A/G *1/*2 (n = 13)	A/A *1/*1 (n = 10)	P (KWS)
INR, POD1	1.2 (1.1–1.2)	1.2 (1.1–1.3)	1.1 (1.1–1.3)	1.1 (1.1–1.2)	1.1 (1.2–1.4)	.35 (4.4)
INR, POD2	1.3 (1.2–1.5)	1.4 (1.3–2.0)	1.4 (1.3–1.6)	1.4 (1.3–1.6)	1.4 (1.3–1.8)	.14 (7.0)
INR, POD3	1.4 (1.3–1.6)	1.7 (1.4–2.3)	1.6* (1.4–1.7)	1.5 (1.3–2.0)	1.6 (1.4–1.9)	.02 (11.8)
% patients with INR < 1.5, POD3	61% (17/28)	27% (3/11)	25%* (8/32)	46% (6/13)	30% (3/10)	.05 (9.3)

INR, international normalized ratio; POD, postoperative day.

INR is represented by median (interquartile range), while % of patients with INR <1.5 is represented by percent (number). The Kruskal-Wallis test with Dunn's post hoc analysis of multiple comparisons was used to assess differences among genotypes.

* P ≤ .05 relative to wild-type G/G *1/*1.

Fig. 2 – Linear regression of INR profiles on the first three days postoperatively, stratified by genotype. Pairwise comparisons used to compare slopes. Gray area represents therapeutic INR (1.5–2.0), * $P \leq .05$, ** $P \leq .01$. Dotted line represents the combined four hyper-responder genotypes. Pearson r^2 values were .36 (G/G *1/*1, $n = 28$), .35 (G/G *1/*2, $n = 11$), .16 (A/G *1/*1, $n = 32$), .24 (A/G *1/*2, $n = 13$), .27 (A/A *1/*1, $n = 10$), and .19 (all hyper-responders, $n = 66$).

significantly impact drug efficacy.^{1,25–27} The PREDICT project, which was launched institutionally in 2010, provides patients with a pharmacogenomic profile of possible sensitivities to these specific medications.²⁵ There were over 14,000 genotyped patients within the PREDICT database, panels which included genotypes of both VKORC1 and CYP2C9. For warfarin and other drugs, this information has greatly assisted practitioners manage medications in the inpatient and clinical settings. However, anticipation of the need for warfarin thromboprophylaxis after TKA or THA does not currently constitute an indication for preoperative genotyping.

In the report by Gonzalez Della Valle et al., AA homozygosity of the VKORC1 gene was associated with postarthroplasty warfarin hyper-responsiveness.¹² The *2 and *3 variants of the CYP2C9 genotype were associated with postarthroplasty hyper-responsiveness as well, as reported by Lenzini et al.¹¹ Our study examined the postoperative INR profiles in patients stratified by the five most frequent genotypes derived from both of these two genes. These patients were not dosed using a clinical nomogram, rather, they were simply dosed as per the institutional protocol. Data from our cohort demonstrated significant variation in postoperative warfarin responsiveness among various genotypes at the CYP2C9 and VKORC1 loci. Notably, patients with the wild-type G/G *1/*1 genotype were twice as likely to be inadequately anticoagulated on the third postoperative day relative to hyper-responders when dosed as per institutional protocol. This represents an increased risk for thromboembolic complications, exacerbated by the lack of concomitant use of heparin or a direct thrombin inhibitor during the initiation phase of warfarin, in which the patient may be paradoxically hypercoagulable. Our study did not have the power, however, to detect differences among the multiple nonwild-type genotypes or determine relative contributions from the A, *2, and *3 alleles.

After discharge, these patients had warfarin dose adjustments made postoperatively at anticoagulation clinics; however, in the critical first three days postoperatively, the dramatic differences in postoperative INR values among genotypes represent a disparity in patient management potentially rectified with preoperative genetic testing. At a high-volume center such as ours, the PREDICT blood test is of reasonable cost to the institution and incurs the patient a \$420 fee, covered by many providers. The additional costs of a postarthroplasty symptomatic DVT and pulmonary embolism are approximately \$25,000 and \$35,000, respectively, while postoperative hemorrhages at or away from the surgical site cost, on average, approximately \$7000 and \$5000, respectively; all events are further associated with a concomitant decrement in quality-adjusted life years.¹⁹ However, whether it is successful at preventing thromboembolic and bleeding complications and, similarly, whether testing solely for planned postoperative warfarin use is cost-effective are two questions requiring further study in larger, prospective cohorts.

This study had several limitations. First, the data were retrospectively gathered from a prospectively maintained database at a single institution, leading both to introduction of bias inherent in this mode of data collection and the need for external validation. Data collection was constrained to only the information available in the medical record, and thus, for some patients, all desired variables were not available, while others had to be excluded due to a prohibitively incomplete or questionable medical record. Second, while the association with protocolled warfarin dosing and inadequate anticoagulation of normal responders is shown in this study, the sample size represents a major limitation, albeit commensurate with similar studies.^{4,7,12} As only 121 patients were included, this study was not sufficiently powered to correlate genotype to thromboembolic complications, such as deep venous

thrombosis or pulmonary embolism. Furthermore, the limited sample size, compounded by the rarity of specific alleles and genotypes, made the discernment of warfarin response among various genotypes difficult to detect. Third, our results are partially predicated on the assumptions that INR values increase in a linear fashion during the first three days postoperatively, and that these warfarin-naïve patients had a baseline INR of 1.0 at the time of surgery, though those values were not available. Finally, the INR values obtained were subject to inconsistencies, as they necessarily reflected clinical variables that could not have been considered. Among these potential variables were rare changes in warfarin dose or frequency, inconsistent timing of medication administration and blood draws, as well as inpatient diets or undocumented medications that may have influenced the values. Furthermore, these INR values may have been affected by preoperative factors that were not considered in this analysis. Nonetheless, within the institutional cohort, our findings convincingly show a genotypic influence on warfarin response in the postoperative period.

5. Conclusions

Efficient anticoagulation after arthroplasty is necessary to prevent thromboembolic complications in the postoperative period. A simple standard warfarin-dosing regimen is frequently employed in orthopedic centers, allowing dosing regimens to be established in the outpatient setting. The majority of those patients who are inadequately anticoagulated in the first three postoperative days possess the G/G *1/*1 genotype at the VKORC1 and CYP2C9 loci, respectively. Our data suggest preoperative genotyping of these patients may make the clinician suitably aware of the possible need for an altered initiation and maintenance dose of warfarin during the postoperative inpatient stay, leading to more appropriately guided and effective anticoagulation. Alternatively, if an increase in thrombotic complications is ultimately shown among normal responders, this would further support use of alternative regimens that may not require preoperative genotyping for optimal efficacy.

Conflicts of interest

The authors have none to declare.

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