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INVITED REVIEW

Warfarin pharmacogenomics: current best evidence

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Summary. The utility of using genetic information to guide warfarin dosing has remained unclear based on prior observational studies and small clinical trials. Two larger trials of warfarin and one of the acenocoumarol and phenprocoumon have recently been published. The COAG trial addressed the incremental benefit of adding genetic information to clinical information and demonstrated no benefit from the pharmacogenetic-based dosing strategy on the primary outcome. The EU-PACT UK trial compared an algorithm approach using genetic and clinical information to one that used a relatively fixed starting dose. The pharmacogenetic-based algorithms improved the primary outcome. The study of acenocoumarol and phenprocoumon compared a pharmacogenetic with a clinical algorithm and demonstrated no benefit on the primary outcome. The evidence to date does not support an incremental benefit of adding genetic information to clinical information on anticoagulation control. However, compared with fixed dosing, a pharmacogenetic algorithm can improve anticoagulation control.

Keywords: drug therapy; genetics; pharmacogenetics; randomized controlled trials as topic; warfarin.

Introduction

Whether or not to use genetic information to guide and/or alter therapy remains a controversial issue in many fields [1–4]. The utility of using genetic information to guide warfarin dosing is one of the more debated. A large body of literature has documented the association between genetic polymorphisms and warfarin maintenance dose requirements, but such data do not answer the question: If one uses genetic information to select the initial dosing of warfarin, will outcomes improve? This review will discuss an approach to evaluating scientific data on genetic-based prescribing, highlight the importance and distinction between clinical validity and clinical utility, review the most recent evidence for clinical utility of warfarin pharmacogenetics, and consider possible approaches to using genetic information in warfarin-treated patients.

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Evaluating genetic-based medication dosing: when is it ready for clinical use?

There are several pieces of evidence that are important to consider before using genetic information for medication dosing. These can be categorized as: Analytic Validity; Clinical Validity; Clinical Utility; and Ethical, Legal, and Social Issues (ELSI) [5,6].

Analytic Validity is how accurately and reliably the test measures the genotype of interest; that is, does the assay provide accurate information about the genetic variants being used?

Clinical Validity refers to how consistently and strongly the genetic variants relate to the outcome of interest. Typically this is determined from non-randomized studies examining the association between genetic variants and outcomes.

Clinical Utility refers to how likely the test is to significantly improve patient outcomes; that is, if one were to use genetic information to guide medication dosing, does it make a difference?

ELSI are any of these important issues that can arise from the use of genetic information in practice.

Using warfarin as an example, analytic validity would measure how accurately and reliably one can measure the variants of interest in the laboratory in actual practice. If the genotyping error rate is large, then the assay does not have analytic validity and, of course, should not be used. Clinical validity would be demonstrated by high-quality, replicated studies demonstrating that patients with different genotypes require different warfarin doses to reach a therapeutic and stable level of anticoagulation. However, even if analytic and clinical validity are demonstrated, it may still not be clear whether using genetic information at warfarin initiation will actually improve outcomes. ELSI may include whether patients are properly informed of their genotype and how it may affect not only their war-

farin therapy but other therapies as well, whether the risk-benefit of genotype is adequately disclosed to patients, etc.

Warfarin pharmacogenetics current evidence

Using the approach outlined above, one can assess the current evidence for warfarin and thus make an informed decision about whether genetic testing should be performed for patients treated with the drug.

There are several genotyping assays for warfarin that have demonstrated outstanding accuracy for the variants of interest (in particular, variants in the cytochrome P-450 family 2 subfamily C polypeptide 9 enzyme (CYP2C9) gene and the vitamin K epoxide reductase complex 1 (VKORC1)) and that have been FDA approved for clinical use. (CYP2C9 is the major metabolizing enzyme for the S-enantiomer of warfarin, the more active form of the drug, and VKORC1 encodes the enzyme that is directly inhibited by warfarin.) Thus, analytic validity has been clearly met for warfarin pharmacogenetics.

There is also a very large body of scientific data that demonstrate a consistent and strong relationship between certain genetic variants and warfarin dose requirements [7]. Variants in CYP2C9 and VKORC1 have been the best studied and demonstrate consistent relationships with warfarin dose requirements. There are, however, some differences among racial groups. In particular, CYP2C9*2 and CYP2C9*3 are not as useful in African Americans, most likely because of the low prevalence of these variants. Other variants in CYP2C9 that are more common in African Americans appear to be more useful in predicting warfarin dosing requirements [8], but to date there are no FDA-approved assays for clinical use of these variants.

It is important to note that the studies that have established a relationship between genetic variants and warfarin dose requirements have almost all been done by relating patients' stable maintenance dose to their genetic variants. The analyses assess the relationship between the genetic variants and the maintenance dose. These studies are limited in that only patients reaching a stable dose are included; those that may be most affected by altered pharmacokinetics or pharmacodynamics of warfarin – those that fail to achieve a stable dose – are typically excluded. In addition, just because a genetic variant is associated with the ultimate warfarin maintenance dose, it does not mean that starting patients at their genetically predicted dose from the start of therapy will improve their anticoagulation control, time to reach a stable maintenance dose, or risk of adverse events. In addition, there are many other patient and environmental factors that can influence warfarin response, including age, body size, interacting medications, comorbidities, and medication adherence. Further, clinicians can titrate the dose of warfarin based on the INR response to the drug and thus correct for doses that may not be appropriate for an individual patient. These other considerations highlight the importance of testing the clinical utility of using genetics to guide warfarin dosing.

There is no one way to demonstrate clinical utility of warfarin pharmacogenetics. However, it is clear that the randomized controlled trial (RCT) remains the gold standard for comparing genetic-based strategies with other approaches. Thus, although observational studies have suggested potential utility from genetic-based warfarin dosing [9,10], these studies are subjected to uncontrolled confounding and epidemiological biases.

RCTs can also be designed to test different hypotheses about warfarin pharmacogenetics. As there are many non-genetic factors that can alter warfarin response that are commonly considered in practice, one might want to test whether the use of genetic information is useful above and beyond the clinical information readily available prior to starting warfarin (e.g., age, body size, interacting medications). Such a study would be designed so that the two study arms differ from each other only in the use of genetic information, with one arm using this information and the other not using this information (but both arms using clinical information). Another approach would be to compare the use of both clinical and genetic information to guide warfarin dosing vs. using neither. Such a study would test whether a pharmacogenetic algorithm (i.e., on that includes both genetic and non-genetic information) is superior to an approach that used neither clinical nor genetic information (sometimes referred to as 'fixed-dose' strategies).

RCTs can also test efficacy or effectiveness. An efficacy trial would test whether the use of genetic information improves outcomes when used under carefully controlled clinical care. For example, an efficacy trial would try to ensure that the dose titration of warfarin after the initial dosing period (the period in which genetics is used to select the dose) was uniform between study arms. It might also blind both patients and clinicians to both the patients' genotype and their warfarin dose to prevent differences in care between the two arms that are related to knowing which arm a patient was in. In contrast, effectiveness trials would test whether the use of genetic information improves outcomes under usual clinical practice settings. Such a trial could allow for differences in dose titration between study arms and allow patients and clinicians to know their warfarin dose. As a more extreme example, an effectiveness trial could simply randomize patients and physicians to knowing or not knowing a patient's genotype and allow the clinicians to use the information in any way they see fit. It can be argued that without efficacy there can be no effectiveness, but this may not always be the case for pharmacogenetics. For example, providing genetic information to clinicians and patients prior to warfarin therapy could alter both patient

and physician behavior (e.g., monitoring frequency, patient adherence) in way that has positive or negative effects on outcomes.

Prior to 2013, there were several small RCTs of warfarin pharmacogenetics [11–14]. One trial of 206 patients compared a pharmacogenetic algorithm that included both genetic and clinical information with standard ('fixed') dosing [11]. This study did not demonstrate a benefit on the primary outcome of percent out-of-range INRs, although it did suggest that those with either zero or more than one variants in the two genes studied (CYP2C9 and VKORC1) might benefit from the pharmacogenetic algorithm. Another trial of 230 patients compared a pharmacogenetic algorithm that included both genetic and clinical information with a clinical-only algorithm that used clinical information to inform the starting dose [13]. This study also did not demonstrate a benefit on time in therapeutic range with pharmacogenetic dosing. Of note, both of the latter studies showed that the pharmacogenetic algorithms clearly predicted maintenance dose better than the comparison arms. Two other studies used only genetic information to determine dose and compared it with a starting dose that did not include either genetic or clinical information [12,14]. In one of the studies, among 101 patients, the genetic-based dosing arm had a shorter time to achieving warfarin maintenance dose [14]. The other study of 191 patients demonstrated better anticoagulation control in the genetic-guided arm and less minor bleeding, but suffered from high dropout rates [12]. Taken together, these studies did not provide definitive evidence for a benefit of pharmacogenetic-based warfarin dosing.

In 2013, three independent clinical trials were published simultaneously in the New England Journal of Medicine [15–17]. These studies were larger than prior studies. They also had different designs that addressed different questions. Several characteristics of these studies are illustrated in the Table 1. All studies used the same three single nucleotide polymorphisms (SNPs): CYP2C9*2, CYP2C9*3, and a single VKORC1 SNP (rs9923231).

Table 1 Comparison of recent RCTs*

	COAG	EU-PACT UK	EU-PACT N/G
Drug	Warfarin	Warfarin	Acenocoumarol/ Phenprocoumon
PGx arm	Algorithm	Algorithm (w/loading)	Algorithm
Comparison arm	Clinical algorithm	Fixed dose (By Age)	Clinical algorithm
Blinding	Double	Single	Single
African Americans	27%	1.1%	0%
Primary outcome	PTTR at 4 weeks	PTTR at 12 weeks	PTTR at 12 weeks
Primary results	Negative	Positive	Negative

*N/G, Netherlands/Greece; PGx, pharmacogenetic; PTTR, percent time in therapeutic range.

Clarification of optimal anticoagulation through genetics

The Clarification of Optimal Anticoagulation through Genetics (COAG) trial was the largest trial to date, randomizing 1015 patients and making it larger than the other two trials combined [15]. The trial used a pharmacogenetic dosing algorithm that included clinical and genetic factors. The study did not use a loading dose strategy although the first dose was calculated without considering the effects of CYP2C9 because CYP2C9 variants are known to have little influence on INR response early in therapy and because of the concern that decreasing the first dose in slow metabolizers would delay the time until the INR is therapeutic. The comparison group was a clinical algorithm that used all of the same clinical factors as in the pharmacogenetic arm but did not use genetic information. The study included dosing algorithms for the first 3 days of therapy and dose-revision algorithms on days 4 and 5 for both study arms. The COAG trial therefore tested whether genetics provides incremental benefit, above and beyond what can be determined from clinical information alone. The trial also performed dose titration after the initial dosing phase (the intervention phase) using a computer-based algorithm that was applied equally across both arms and across all sites.

The study was unique in that it was the only trial that blinded patients and clinicians to the dose of warfarin during the primary outcome period. As noted in the study protocol (see supplement in [15]): 'The primary outcome of the study (PTTR) could therefore be affected not only by warfarin dose or warfarin dose adjustments, but by other, post-randomization factors that could differ if study arms and drug dose are not blinded. These include differential dropout, protocol deviations, cross-overs (e.g., genotyping those in the non-genotype-guided arm), differences in adherence, and differences in patient care. These would be particularly problematic if the occurrence of these post-randomization factors both differed by study arm and were also related to anticoagulation control, as might be expected. For example, patients who know or suspect that they are in the clinical arm who are having difficulty with anticoagulation early in therapy (those who might contribute the most to any differences by study arm) may be more likely to withdraw from the protocol than those in the genotyping arm because clinicians (or the participants themselves) would want to know their genotype or manage their dosing themselves. Another potential bias is that patients on very low doses, who would be known or presumed to carry genetic variants that make them sensitive to warfarin, may be managed more carefully: they may be counselled more aggressively about dietary adherence and they may be more

meticulous about avoiding interacting medications, be asked to come for more frequent INR monitoring beyond that required by protocol, and/or seek such extra monitoring. As another example, physicians could be more likely to withdraw a patient from the study if they felt that one of the algorithm-based approaches was not working and wanted to dose patients themselves (e.g., in a patient taking too long to reach adequate levels of anticoagulation, thus delaying hospital discharge). Patients may also be scheduled for extra study visits and be more likely to be adherent with these visits (e.g., less missed visits) if they know they are 'more sensitive' to warfarin. All of these scenarios could bias the results in manners that are difficult if not impossible to measure and control.'

The COAG trial also included 27% African Americans. Prior to COAG, the total number of African Americans in similar warfarin pharmacogenetic trials was 3. The trial's *a priori* hypothesis was that there would be differences between African Americans and other racial groups because it was known that dosing algorithms performed less well in African Americans even though the algorithms included a variable to specify race [18]. As such, the trial stratified the randomization by race.

The study demonstrated no benefit of pharmacogenetic-based dosing vs. clinical-based dosing on the primary outcome of percent time in therapeutic range (PTTR) of the INR at 4 weeks: PTTR of 45.2% vs. 45.4%, respectively. There was also no significant benefit of pharmacogenetic-based dosing in the pre-specified subset of patients in whom the two algorithms predicted at least a 1 mg day^{-1} dose difference for warfarin. However, there was a statistically significant difference between African Americans and non-African Americans. African Americans fared worse with the pharmacogenetic algorithm than with the clinical algorithms (PTTR 35.2% vs. 43.5%, respectively; adjusted mean difference, −8.3%; $P = 0.01$), while there was no statistically significant benefit of pharmacogenetic vs. clinical dosing in non-African Americans (PTTR 48.8% vs. 46.1%, respectively; adjusted mean difference, 2.8%; $P = 0.15$). There was no difference in the principal secondary outcome of INR of 4 or more, major bleeding, or thromboembolism.

European pharmacogenetics of anticoagulant therapy UK

The European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) UK study took a different approach from the COAG trial [17]. EU-PACT UK compared a pharmacogenetic-based dosing strategy to a relatively fixed-dose strategy. The pharmacogenetic arm used clinical and genetic data (using the same genetic variants as COAG but different clinical factors and a different dosing equation) and also loaded patients up-front by giving a higher proportion of the first 3 days of warfarin on day 1 than on day 2 and a higher proportion on day 2 than day 3. The pharmacogenetic algorithm also used a pharmacogenetic-based dose-revision algorithm on days 4 and 5; this was the same algorithm as used in COAG. The comparison arm dosed all patients 75 years of age and under the same dose (20 mg over the first 3 days) and patients greater than 75 years of age the same dose (15 mg over the first 3 days). There was no dose-revision algorithm in this arm. The trial thus compared a strategy using clinical and genetic information in a formal dosing algorithm with a strategy that used neither (except for reducing the dose by 5 mg on the first day of therapy in those over 75 years of age). After the initial 5 days of therapy, dose titration was performed as per local practice at each site, although each site did use a formal dose titration method.

The EU-PACT UK trial tested a different hypothesis than the COAG trial. EU-PACT UK tested whether an approach that uses a formal dosing algorithm that incorporates both genetic and clinical information to determine dose over the first 5 days of therapy was superior to an approach that used neither (except for age in the first 3 days).

The EU-PACT UK study also did not blind patients or clinicians to the dosing strategy. Although patients and clinicians did not know their genotype, they could easily discern which study arm they were in because the dosing regimens were different and because only the genotype arm had genotyping done at the start of the trial. The EU-PACT UK trial included only 1.1% African Americans and thus could not determine the effects of their pharmacogenetic strategy in this group of patients.

The study enrolled a total of 455 patients and the primary outcome was PTTR at 3 months. The mean PTTR was better in the pharmacogenetic group (67.4%) than in the control group (60.3%; adjusted difference, 7.0 percentage points; $P < 0.001$). Patients in the pharmacogenetic arm also were less likely to have an elevated INR (4.0 or higher) and had a shorter time to the first therapeutic INR than patients in the control arm. There were no major bleeds in the trial.

EU-PACT Netherlands/Greece (N/G)

The third trial did not use warfarin but rather the coumarin anticoagulants acenocoumarol and phenprocoumon [16]. Originally designed as two separate trials of the two different drugs, the data from the two trials were combined for analyses because of low enrollment. Similar to the COAG trial, the EU-PACT N/G trial compared a formal pharmacogenetic algorithm that included clinical and genetic factors with a clinical algorithm that used the same clinical factors as the pharmacogenetic but did not use genetic information. Similar to the EU-PACT UK trial, the study did not blind patients and clinicians to the dosing strategies. Also, management of dose titration was not required to be standardized between the study arms although each site used its own standardized dose titration algorithms. The trial had the same primary endpoint

as the EU-PACT UK trial (PTTR at 3 months) and enrolled no African Americans.

The primary results of the trial demonstrated no benefit to the pharmacogenetic approach. The PTTR was 61.6% in the pharmacogenetic arm and 60.2% in the clinical arm ($P = 0.52$). There also were no significant differences between the two groups for multiple secondary outcomes, including INRs ≥ 4.0, time to reach therapeutic INR, and patients with stable dose within 12 weeks of starting therapy. There were no differences as well in bleeding or thromboembolic outcomes. In an analysis of PTTR at different time points in the study, there was a significant difference in PTTR at 4 weeks between the pharmacogenetic arm (PTTR 52.5%) and the clinical arm (PTTR 47.5%, $P = 0.02$).

Conclusions

In summary, the current evidence does not support an incremental benefit on anticoagulation control of using CYP2C9*2, CYP2C9*3, and VKORC1 rs9923231 to determine the initial warfarin dosing above and beyond what is available from clinical information. The EU-PACT UK study demonstrated that a pharmacogenetic algorithm was superior to an approach that did not use a formal clinical algorithm and only incorporated age. The COAG study demonstrated worse anticoagulation control in African Americans with the use of a pharmacogenetic algorithm compared with a clinical algorithm. Although, taken together, the trials suggest that a clinical-only algorithm might be the preferable approach to dosing warfarin, no study to date has directly compared a clinical-only algorithm with a fixed-dose approach. None of the studies were powered to examine major bleeding or thromboembolic events. In addition, these studies were carried out in carefully managed protocols for dose titration with frequent follow-up and do not necessarily reflect the effects of pharmacogenetic-based dosing in different practice settings. Pragmatic effectiveness trials would be needed to address the effects of pharmacogenetic-based dosing in broad-based practice and with less control over dose titration methods.

It should be noted that all of the recent trials demonstrated clear superiority from the pharmacogenetic algorithms in predicting the final warfarin maintenance dose. The disconnect between predicting maintenance dose and improving anticoagulation control in many studies illustrates the important distinction between clinical validity (strong relationship between genetic variants and dose requirements) and clinical utility (the use of genetics to alter dose in practice).

An additional study, the Genetics informatics trial (GIFT) is underway to examine the effects of pharmacogenetic dosing on outcomes in patients undergoing orthopedic surgery [19]. Although meta-analyses are also being published of the existing trials, the differences in study design among the trials make combining data problematic and the most valid results are those that come for each individual trial.

Disclosure of Conflict of Interests

The author reports personal fees from Pfizer, outside the submitted work.

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