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Warfarin pharmacogenetic trials: is there a future for pharmacogenetic-guided dosing?

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Abstract

“In clinical practice, it is common for warfarin to be initiated at a fixed dose for the first several doses.”

Keywords

clinical utility; *CYP2C9*; pharmacogenetics; pharmacogenomics; randomized controlled clinical trial; *VKORC1*; warfarin

A major obstacle impeding the adoption of pharmacogenetic-guided warfarin dosing in clinical practice has been the lack of randomized controlled trial evidence supporting a clinical benefit over conventional dosing. In an attempt to address this knowledge gap, several clinical trials have been performed, with the largest among them only very recently reported [1,2]. These recent high-profile studies will undoubtedly have an impact on the future landscape of warfarin pharmacogenomics; however, before overarching conclusions are made, a careful assessment of common warfarin dosing practice and the reported clinical trial designs and results is warranted.

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Warfarin & current clinical practice

A prominent characteristic of warfarin is its narrow therapeutic window bound by ineffective anticoagulation at sub-therapeutic doses and increased bleeding risk at supratherapeutic doses. Preventing both under- and over-dosing of warfarin during initiation requires monitoring of the international normalized ratio (INR) through periodic blood testing. In clinical practice, it is common for warfarin to be initiated at a fixed dose for the first several doses [3]. INR levels, and hence warfarin dose requirements, are dynamic and influenced by both modifiable (e.g., *patients initiated on warfarin*. compliance, dietary vitamin K intake, weight, drug interactions and therapeutic level surveillance) and non-modifiable (e.g., age, sex and genetic variation) factors [4]. Although only incorporated into dosing algorithms in the past 10 years, the importance of *CYP2C9* and *VKORC1* variants in therapeutic warfarin dose requirements has been established by 20 years of basic and applied research, including prospective observational studies and comparative effectiveness trials [5–13].

Interventional warfarin pharmacogenetic studies

Despite positive research findings and US FDA warfarin label revisions, the Centers for Medicare and Medicaid Services (CMS) have not routinely covered clinical *CYP2C9* and *VKORC1* genotyping, again citing the need for additional evidence. As such, CMS, other insurers and the pharmacogenomics research community at large have all eagerly awaited the results from the recently reported randomized warfarin pharmacogenetic trials. These and other notable trials are detailed below.

CoumaGen

One of the first interventional trials testing a dosing algorithm with *CYP2C9* and *VKORC1* was CoumaGen (n = 206), which randomized patients to pharmacogenetic-guided or standard dosing with a primary end point of percentage of out-of-range INRs [14]. Although pharmacogenetic-guided dosing was more accurate and efficient than standard dosing, a reduction in out-of-range INRs was not achieved.

Marshfield Clinic Research Foundation

Reported in 2011, the Marshfield trial (n = 230) randomized patients to pharmacogenetic-guided dosing or clinical algorithm dosing with primary outcomes of absolute prediction error relative to therapeutic dose and percentage of time in therapeutic range (PTTR) [15]. Although enrollment only reached 89% of the pre-trial goal, the pharmacogenetic algorithm more accurately predicted the therapeutic dose; however, this did not translate to greater PTTR.

CoumaGen-II

The relatively small sample size and limited power of previous trials was addressed, in part, by CoumaGen-II [16], which included a clinical effectiveness comparison between pharmacogenetic-guided patients (n = 504) and a standard dosing control group (n = 1866). Reported in 2012, primary outcomes were percentage of out-of-range INRs and PTTR.

Notably, the pharmacogenetic cohort had significantly lower percentage of out-of-range INRs, higher PTTR, fewer INRs >4 and <1.5, and fewer serious adverse events. Despite the use of a large control population treated in a standard real-world fashion, this effectiveness study was not randomized, limiting definitive conclusions.

European Pharmacogenetics of Anticoagulant Therapy (EU-PACT)

The multicenter, single-blinded European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) trial (n = 455) randomized patients to pharmacogenetic-guided dosing or a fixed dosing regimen with a primary outcome of PTTR during the first 12 weeks of therapy [1]. Pharmacogenetic-guided dosing was for the first 5 days and subsequently based on local practice, whereas the control group received one of two fixed loading dosing regimens based on age for the first 3 days, with subsequent dosing based on local practice. Similar to CoumaGen-II, pharmacogenetic-guided dosing resulted in significantly greater PTTR (67 vs 60%), fewer patients with INR >4, and less time to achieve therapeutic INR levels; however, bleeding event rates did not differ and thromboembolic events were too infrequent to compare.

The EU-PACT trial demonstrates that pharmacogenetic-guided dosing is superior to a fixed-dosing regimen for achieving therapeutic INRs in Caucasian patients initiated on warfarin. Furthermore, pharmacogenetic-guided dosing was associated with a lower proportion of individuals who experienced excessive anticoagulation. However, these benefits did not translate into reductions in bleeding or thromboembolic events, although the trial was not powered for these end points.

Clarification of Optimal Anticoagulation Through Genetics (COAG)

The multicenter, double-blinded Clarification of Optimal Anticoagulation Through Genetics (COAG) trial (n = 1015) randomized patients to pharmacogenetic-guided dosing or clinical algorithm dosing for the initial 5 days with a primary outcome of PTTR during the first month of therapy [2]. In contrast to EU-PACT, no significant differences were detected in PTTR (~45% in both groups), nor were there differences in percentage of time above or below therapeutic range, in time to first therapeutic INR, or in adverse event rates. However, one of the most potentially instructive findings was the significant interaction detected between dosing strategy and race. Black patients (27% of enrolled subjects) had a lower PTTR, more INRs above therapeutic range and increased time to therapeutic INR in the pharmacogenetic-guided group compared with the clinical algorithm group. Despite both dosing algorithms accounting for race, these data indicate that inclusion of *CYP2C9**2, *3 and *VKORC1* c.-1639G>A actually reduces the effectiveness of a multivariable clinical dosing algorithm among black patients.

Although COAG ultimately does not support inclusion of genetic information into clinical dosing algorithms for warfarin initiation, the trial did not compare pharmacogenetic-guided dosing to usual care or a fixed-dose regimen, nor was it powered to assess bleeding or thrombotic event rates. Given the multi-ethnic composition of COAG, an important issue to acknowledge is the allele frequencies of the variants included in the pharmacogenetic algorithm. *CYP2C9**2, *3 and *VKORC1* c.-1639G>A are common among Caucasians, but

much less prevalent among individuals of African descent, which was reflected in the very different percentages of COAG patients carrying at least one of these variants (75% non-black versus 24% black). Since COAG was initiated, other variants implicated in warfarin dosing have been identified among African-Americans [17], which likely contributed to the ineffectiveness of the tested pharmacogenetic algorithm for the self-reported black patients.

Genetics Informatics Trial (GIFT) of warfarin to prevent deep venous thrombosis

The Genetics Informatics Trial (GIFT) is an ongoing randomized controlled trial (n = 1600) assessing the safety and effectiveness of pharmacogenetic-guided warfarin dosing for the reduction of deep venous thrombosis compared with clinical algorithm dosing following total hip or knee repair [18]. In contrast to previous trials, the dosing algorithms will guide therapy for the first 11 days of treatment and the primary end point is a composite of venous thromboembolism, major hemorrhage, INR ≥ 4 or death.

Outcomes & future directions for warfarin pharmacogenomics

The question permeating the field now is how to interpret these clinical trial data and what are the consequences, if any, to managing anticoagulation in practice? Despite some of the evidence favoring pharmacogenetic-guided warfarin dosing, one could conclude from COAG and the smaller trials that *CYP2C9* and *VKORC1* genotyping is unwarranted. However, before doing so, it is important to consider the possible reasons why COAG and the smaller trials, unlike EU-PACT, failed to achieve their primary outcomes.

Comparison arms

The control arms differed across trials. The results of COAG underscore the fact that considering both modifiable and non-modifiable factors, other than genetic variation, may significantly influence warfarin dose requirements. The incremental effect of incorporating three *CYP2C9* and *VKORC1* variants into clinical algorithms for a short time period may be minimal when other factors influencing warfarin dose requirements are optimized.

Allele frequencies

Disparate Caucasian and African-American *CYP2C9* and *VKORC1* allele frequencies resulted in fewer COAG patients carrying variants included in the pharmacogenetic algorithm.

Day 1 dose

Only 45% of COAG patients had genotype information available for their day 1 dose, compared with 100% of patients in EU-PACT.

INR monitoring & anticoagulation setting

All trials had high frequencies of INR monitoring in specialized anticoagulation clinics, which may mask any effect of an algorithm-guided dosing intervention. Additionally, this setting likely does not reflect anticoagulation practice in other community clinics with fewer INR measurements [19].

Future directions

Taken together, these trials indicate that pharmacogenetic-guided warfarin dosing is more accurate than standard fixed, but not clinical algorithm-guided, dosing. Thus, the added benefit of genetic information over clinical information alone, if implemented in practice, is not supported. Efforts to implement clinical algorithm guided recommendations for warfarin initiation are warranted. Furthermore, it is clear that further research is needed to identify relevant variants in populations other than Europeans, and to develop and test more refined ethnic-specific warfarin dosing algorithms, particularly for individuals of African descent. As clinical outcomes have yet to be adequately assessed by pharmacogenetic trials, it is unlikely that CMS will support warfarin pharmacogenetic testing in the near future. Similarly, it is also unlikely that there will be any increased use of *CYP2C9* and *VKORC1* genotyping in most anticoagulation clinics. However, for those medical centers independently supporting pre-emptive pharmacogenetic genotyping programs [Rasmussen-Torvik LJ, Stallings SC, Gordon AS *et al.* Design and anticipated outcomes of the eMERGE-PGx project: a multi-center pilot for pre-emptive pharmacogenomics in electronic health record systems (2014), Submitted], the totality of evidence from the reported warfarin pharmacogenetic trials largely supports more accurate dosing using a pharmacogenetic algorithm compared with standard fixed dosing in Caucasian patients. The ongoing debate over clinical outcome benefit will hopefully be addressed following completion of the GIFT trial.

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