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Pharmacogenetic implementation lessons from the “real world”

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Introduction

The manuscript "Anticoagulation Endpoints with Clinical Implementation of Warfarin Pharmacogenetic Dosing in a Real- World Setting - A Proposal for a New Pharmacogenetic Dosing Approach" describes process outcomes in an institutional program to use pharmacogenetic testing to optimize warfarin dose in a cohort of 257 patients of diverse ancestries. The strengths and weaknesses of the approach and program are discussed, along with the current and potential future status of warfarin as a model for pharmacogenetic testing.

It has been 20 years since the first report that *CYP2C9* variant alleles contribute to the clinically well-recognized variability in warfarin steady state dosage requirement.¹ Given that variability, the ease of measuring warfarin effect (by INR), and the real risks of over- and under-anticoagulation, warfarin became an early “poster child” for the idea that using pharmacogenetic information to refine dosage could improve outcomes. A fascinating historical footnote for the field is that FDA staff began in 2003 planning a study to evaluate the effects of *CYP2C9**2 (a reduction of function allele) and *CYP2C9**3 (a near loss-of-function allele) on outcomes during warfarin therapy. However, those efforts were shelved when variation in the *VKORC1* promoter was identified as a second, probably more important, contributor to variable warfarin dosages.^{2,3} The stories get more complicated with identification of variants in other genes such as *CYP4F2* and *CALU* that appear to contribute; other variants in *CYP2C9* (such as *6, *8, and *11) and at other loci,⁴ prevalent in non-European populations; and the discovery of non-synonymous variation in *VKORC1* (such as D36Y, prevalent in Ashkenazi populations). As result, we now recognize that, at the very least, pharmacogenetically-based predictive algorithms should either be tailored for specific ancestries or genotyping should include all known variants across ancestries, thereby reducing a need to stratify.

In the present issue of *Clinical Pharmacology and Therapeutics*,⁵ Arwood and colleagues describe their experience with a warfarin pharmacogenetic consultation service at the University of Illinois at Chicago, serving an ethnically-diverse population. The results are presented stratified by 0, 1, or 2 loss-of-function variants in *VKORC1* and *CYP2C9*. Rapid turnaround pharmacogenetic testing results were available before the second warfarin dose in the vast majority (88%) of subjects, a tribute to system efficiency. Management guidelines

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based on existing algorithms and the genetic test results were then made available to practitioners, 84% of whom followed the recommendations. The whole idea of this approach is to rapidly, and without regard to genotype, achieve and maintain therapeutic anticoagulation. It was a surprise, and a bit of disappointment, therefore, that subjects with 2 loss-of-function variants achieved therapeutic INR values earlier, and ran a significantly greater risk of achieving INR values >3 , compared to the other groups. The conclusion is that existing algorithms need to be further tweaked to both accelerate the pace at which anticoagulation can be achieved in subjects with 0 or 1 variant, and to avoid risks of over anticoagulation in subjects with 2 variants. The authors propose a new improved algorithm, and present data that the outcome would likely be better with this approach than with predictions based on the FDA label.

This study has some important strengths. One is an ability to engage disciplines with multiple strengths including pharmacy, pharmacogenetics, laboratory services, and information science. Further, an important lesson for pharmacogenetic implementation in general is that programs such as this cannot be realistically contemplated in the absence of a strong institutional commitment and that was in place here. A second strength is the fact that this is an ethnically diverse population and that variants beyond CYP2C9*2 and *3 were studied. Unfortunately, one of the major loss-of-function alleles in African American subjects is CYP2C9*8 (minor allele frequency, around 6%) and this was not genotyped. CYP4F2 V433M was genotyped, but its contribution to overall variability in warfarin steady state dosage was thought to be small and therefore it was not included in the final algorithms used.

There are also weaknesses, some of which reflect the general state of the art in this field. The total number of subjects evaluated was small ($n=257$). The statistical analysis was still performed stratified by ancestry, and one goal of studies such as this should be to ultimately eliminate the need for such stratification. The fact that the new algorithm “beats” the FDA label is a rather low bar since the FDA label was developed empirically and based exclusively on a European population. The new algorithm is proposed, but a superior trial design would be to evaluate it in a prospective fashion.

One big issue in this field is the right endpoint to study. One of the reasons warfarin has been as attractive as a target for pharmacogenetics implementation is the availability of the INR measurement makes metrics such as time in therapeutic range or time to achieve therapeutic anticoagulation readily tractable. To the extent that any of these indices are markers of risk for recurrent thrombosis and/or bleeding, they should make sense. However, as this field is now well aware, large prospective trials comparing pharmacogenetically-guided therapy to other forms of therapy have had mixed outcomes. The European EU-PACT study⁶ compared fixed dose warfarin to an algorithm that included genetic data, and showed improved in the primary endpoint of time in therapeutic range in the first 84 days of treatment. The US COAG study,⁷ by contrast, compared algorithmically defined warfarin dosing (taking into account factors such as age, gender, interacting drugs, etc.) to algorithms that also included genetic data. In COAG, there was no difference in the primary endpoint of time in therapeutic range from day 4 to day 28. Further, a subgroup analysis showed that the algorithms that included genetic information performed worse than those that did not in the

27% of the study group that were African American; notably, both COAG and EU-PACT (which was >98% European ancestry) studied a key *VKORC1* promoter polymorphism and CYP2C9*2 and *3. One obvious conclusion is that using algorithms that include only variants common in European populations is inappropriate for other populations. The present paper addresses these issues as well, and as with COAG and EU-PACT focuses on process outcomes – that is, what happens to indices of warfarin action when a pharmacogenetic program is implemented? However, neither RCT nor the present paper have much to say (given their short durations) about actual healthcare outcomes like risk of recurrent thrombosis or of bleeding. Other studies, using retrospective analyses of electronic health records or of registries, have reported an influence of CY4F2 V433M⁸ or of CY2C9*3⁹ on risk of bleeding.

The title of the present manuscript includes the term “real world”, and this highlights one of the biggest difficulties with this study and the field in general. Only 67% of subjects ever achieved a therapeutic INR within 28 days of starting warfarin therapy, and in 39% there was no outpatient follow up data available after hospital discharge. This truly reflects “real world” medicine in cost-constrained environment, but how to interpret even short term outcomes (let alone outcomes looking at bleeding or thrombosis risk over months or years) given these kinds of constraints on efficacy and follow up is vexing at best.

The first sentence of the present manuscript highlights an important question the whole field of pharmacogenetic implementation needs to face: how much energy to devote to warfarin given the emergence of the “direct oral anticoagulants” (DOACs). In randomized clinical trials, fixed dose DOACs prove equivalent or superior to INR-adjusted warfarin. Arguments have been made that DOACs perform well in these trials because the success of warfarin therapy was lower than might have been achievable, or the devices used to monitor INR were inaccurate, or covariates like renal function influenced outcome. One of the drivers to developing DOACs has been the idea that monitoring should be unnecessary and a fixed dose highly desirable. These are imperatives driven by a powerful marketing apparatus, and to me make little medical sense: anticoagulants have narrow margins between doses required for therapy and doses that will result in increased bleeding risk and any measure that one can mobilize to reduce that variability ought to reduce those risks. Given that premise, it is all the more remarkable that the DOACs “beat” warfarin even without a need for monitoring; as a result, warfarin uptake is slowing and in the future its use will likely be limited to specific populations such as those in whom DOACs are ineffective or contraindicated. This includes economically disadvantaged sectors and more data are needed on non-European variants and on hard outcomes like bleeding. One of the lessons I take away from the “real-world” aspect of the present paper is the high rate of nonadherence and lack of follow up: this has to result in increased risk for inefficacy and bleeding with both warfarin and newer drugs, and genetics won’t fix any of that.

Finally, I cannot resist an editorial comment, a stone in my shoe for the last several decades. The introduction to this manuscript says “Warfarin will likely remain an important option for... those who fail treatment...” I wish we would get away from the idea that “patients fail treatment”: treatments fail patients or the healthcare system fails patients, but patients don’t “fail” treatment.

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