

ALTERNATIVE VIEWPOINTS

Will Genetic Testing for Warfarin Dosing Ever be Ready for Prime Time?

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We read with interest the editorial by Dr. Bussey and colleagues entitled, “Genetic Testing for Warfarin Dosing? Not Yet Ready for Prime Time.”¹ We wholeheartedly agree with the authors’ recommendations that more research is needed in this area and “a clear benefit of such testing should be required before such testing is recommended on a routine basis,”¹ but believe that we may never see a significant impact on patients’ long-term well-being, despite the best study design. An example in point is a landmark study² that apparently was published after Dr. Bussey’s editorial went to press. This study² conducted the first randomized controlled trial of its kind comparing pharmacogenetic-guided to standard empirical dosing in patients starting warfarin therapy. Although they found a pharmacogenetics approach to improve accuracy and efficiency of warfarin dose initiation, the study failed to achieve its primary end point of a reduction in out-of-range INR values in the pharmacogenetic-guided group compared with the standard warfarin dosing group. We are writing to suggest that this negative finding could have been predicted in advance and how warfarin maintenance is more “high touch” than “high tech”.

In 2006, Alexander Roy and his co-driver completed the Cannonball Run (of cinema fame) from New York City to Santa Monica in a record 31 hours, crossing the country in a 2000 BMW M5, a powerful car able to accelerate the drivers to cruising speed very quickly. In effect, the pharmacogenetics approach in the Anderson et al study² was the engine that got warfarin dosing up to speed, the same way that a powerful V-8 did for Roy’s BMW M5. However, maintaining patients in a therapeutic INR range is not the result of having a powerful engine. Sure, a few seconds may be saved with an M5 rather than a Smart Car; yet, the ability to stay at a safe but efficient speed in crossing the country was determined largely by the drivers’ planning and strategy rather than the power of the engine. Similarly, with warfarin dosing, speed or efficiency in attaining INRs within the therapeutic range is not the most critical factor. Just as Roy had to stop for gas, patients miss warfarin doses and thereby introduce variation into the targeted cruising speed. The drivers minimized number of gas stops by adding a second gas tank and were efficient when they had to stop. For patients on warfarin, missed doses are best avoided. When they do occur, it is important that clinicians managing the warfarin therapy do not overreact to any changes in INR as a consequence of the missed dose; this merely requires knowledge that the dose was missed rather than a highly technical pharmacogenetics approach. Similarly, the Cannonball Run record beaters, in planning their trip, were careful to avoid toll roads, construction, stoplights, and potential police entanglements which would have disrupted their record-breaking trip. When we manage patients on warfarin, we also need to

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anticipate and avoid or manage potential disruptors (e.g., drug interactions, variations in diet, other sources of interference, etc.) to warfarin's primary end point.

In summary, we believe that the ability to maintain patients in the therapeutic range is more based on a good understanding of the potential sources of variation and a careful and planned approach to therapy that avoids or manages these sources of variation. This strategy requires a personal communication with the patient, a clear medication history, and an understanding of potentially interfering factors. While we believe that genotype-guided warfarin dosing has merit in initiating therapy, these improvements are unlikely to show a significant impact on patients' long-term wellbeing and our ability to keep them in the therapeutic range, regardless of study design.

References

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Authors' Reply

I am pleased that Drs. Ensom and Ensom found our commentary to be of interest and apparently stimulating enough for them to develop the “Cannonball Run” analogy between long-term warfarin dosing and a cost-to-coast road race. In almost any analogy, one can over-interpret the meaning and/or find a flaw. In their “Cannonball Run” analogy, they appear to suggest that the BMW M5 (genetic testing) may be better than an under-powered Smart Car at “getting up to speed” (achieving an initial therapeutic INR) quicker; but that the power of the BMW M5 has little relevance over the “long haul” of chronic warfarin dosing which can be affected by so many factors than the power of the vehicle. In other words, they seem to concede that genetic testing may be useful for the initial dosing of warfarin (perhaps based on the study they referenced by Anderson and colleagues¹), but may have little value during chronic therapy. In the “race” reported by Anderson and colleagues it may appear that the BMW M5 (genetic testing) got off to a faster start than the Smart Car (another dosing approach). I would

argue, however, that the results of that “race” simply show that the particular BMW M5 beat that particular “Smart Car” in getting off the line based on how the “Smart Car” was driven. Perhaps the Smart Car would have performed better with a different driver – one who had been allowed to rely more on his/her own judgment and skill, had faster reflexes, or remembered that the Smart Car had a turbo-charger. In other words, maybe the difference is not in the methods employed but rather how the methods are employed and by whom. Let me give a couple of examples.

First Example (2C9 polymorphisms)

At a presentation some months ago the speaker presented an example of how genetic testing was used to adjust (or rather *not* adjust) the warfarin dose in a particular patient. After several days of genomic-directed warfarin dosing the patient's INR was still sub-therapeutic. The clinician, however, did not increase the warfarin dose because the genomic information indicated that the patient was a slow metabolizer who was going to continue to accumulate additional warfarin and would move into the therapeutic INR range within a few more days. An alternative view (mine) would be that frequent testing of the INR would also indicate that the patient was a slow metabolizer who was continuing to accumulate warfarin before reaching a therapeutic INR. In such a situation, one could give the patient a partial loading dose and get to that target range a day or two quicker and then reduce the dose to avoid drug accumulation and INR over-shoot. In other words, the “driver” could activate his turbo-charger to get up to speed and then cut back so as not to over-shoot the end of the track or lose control due to excessive speed.

Second Example (VKORC1 polymorphisms)

I recently over-shot the target INR range when dosing a non-Asian patient who happened to have the AA (sensitive) VKORC1 genotype. However, let's look at how that “accident” happened. This episode occurred in a study protocol that required that patients be started on a given dose of a vitamin K antagonist (VKA) and that the INR not be checked until about 3 days later. Genetic test results were received later and the INR was not checked for several days. In our car race analogy, that is like pushing the gas pedal to the floor, activating the turbo-charger,

and keeping your eyes closed for the next 20 minute and then being *surprised* that you are not where you wanted to be. Had we checked the INR at approximately 24 hours after the first dose, that INR result would have told us that the patient was unusually sensitive to the VKA and we could have “backed off” on the dose (turned off the turbo-charger and eased up on the gas). Then the rate of rise in the INR over time would have told us whether the patient was also a slow metabolizer.

So, in summary, it seems that the genetic testing may provide little value in routine warfarin dosing beyond the information obtained by careful and close monitoring of the INR. Perhaps some day such information may prove useful in predicting the characteristics of a drug interaction in a specific patient; but I know of no current data in that area. I also absolutely agree with Drs. Ensom and Ensom in their analogy that the patient and clinician (“driver”) need to stay in communication about bridges being out, the need to make a pit stop, being hit by another racer (flu, pneumonia, heart failure, etc.) so that appropriate adjustments can be made. In fact, I believe that the “essential triad” of almost 60 years ago is as true today as it was then when Askey and Cherry said (paraphrased):

“The successful use of anticoagulation depends on an essential triad of a vigilant clinician, a cooperative patient, and a readily available and reliable laboratory. If these factors are present, continuous use is practical, practicable, and effective. If not, the use of the drug is dangerous.”²

Additionally, a hematologist friend of mine was being questioned recently about genetic testing and warfarin dosing by several physicians within his network. I found his brief response rather profound (paraphrased): “In warfarin dosing, genetic testing will not make a less proficient physician an expert.”

References

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