# Warfarin Pharmacogenetics: A Rising Tide for its Clinical Value

**Running title:** *Johnson, Clinical utility of warfarin pharmacogenetics*

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Warfarin has been in clinical use for nearly 60 years, and in 2010 there were over 25 million prescriptions for warfarin in the U.S. While warfarin is highly efficacious, it has a narrow therapeutic window to achieve desired anticoagulation without excess risk of bleeding. Anticoagulation status is monitored with the International Normalized Ratio (INR), where the most common target INR is 2 to 3. Not only does warfarin exhibit a narrow therapeutic index, but there can be 10 to 20-fold differences in the warfarin dose required to achieve target INR. Thus the early period after warfarin therapy initiation requires frequent INR monitoring to determine the proper dose for the patient, is often associated with multiple dose adjustments, and many patients experience prolonged periods of over- or under-anticoagulation while the appropriate dose is identified. These challenges lead warfarin to be a leading cause of emergency room visits and hospitalizations for an adverse drug reaction, and lead to significant underuse of the drug in patients for whom it is strongly indicated, particularly those with atrial fibrillation.[1]

The difficulties associated with warfarin use led to great enthusiasm for the new oral anticoagulants. Dabigatran and rivaroxaban were approved in the last 18 months, yet they have made only a small dent in the market share for oral anticoagulants, with warfarin remaining the predominant anticoagulant used clinically. For example, in the first year of use in the US, approximately 1.1 million dabigratran prescriptions were dispensed, in contrast to the 25 million per year for warfarin.[2] Reasons for the lack of uptake may include recent concerns about excess bleeding risk with dabigatran,[2] lack of reversibility of the anticoagulation, twice daily dosing, challenges with dosing in renally impaired patients, bothersome adverse effects (particularly gastrointestinal adverse effects with dabigatran), cost, among others. Overall, these new agents have not been widely embraced in the manner anticipated, suggesting that warfarin will remain

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the mainstay of oral anticoagulant therapy for the foreseeable future.  Thus there remains a need

to identify ways to more safely and effectively utilize warfarin.

That genetic polymorphisms might influence the variability in warfarin dose

requirements was first recognized in 1999, and since then there has been a vast body of literature

documenting the effects on warfarin dose of genetic variation in cytochrome P450 2C9

(*CYP2C9)*, the major drug metabolizing enzyme of S-warfarin, and vitamin K epoxide reductase

(*VKORC1*), the protein target of warfarin.[3]  Numerous studies have shown that polymorphisms

in these genes explain up to 35% of the variability in warfarin dose requirements, and through

consideration of additional clinical factors (e.g. body size, age, interacting drugs) over 50% of

inter-patient dose variability can be explained.[3-6]

That a better approach to identification of the therapeutic dose for a given patient is

needed is highlighted by data from numerous studies suggesting that bleeding risk during the

first one to three months of therapy is up to 10-fold higher than subsequent monthly risk.[1]

Utilization of genetic and clinical information to guide initial dose selection holds promise as

such an approach.  Indeed numerous warfarin pharmacogenetic algorithms have been developed

that incorporate both genetic and clinical factors, and the best validated among these come from

the International Warfarin Pharmacogenetics Consortium (IWPC)[5] and Gage and colleagues[4].

And in 2010, the FDA revised the warfarin product label to include dose recommendations based

on *CYP2C9* and *VKORC1* genotype.[7]  The study by the IWPC in over 5,000 patients from four

continents clearly documented that its pharmacogenetic algorithm was superior to a clinical

algorithm, or the usual 5 mg daily starting dose in estimating the stable warfarin dose.[5]  A later

analysis by Finkelman and colleagues confirmed this, and documented that algorithm-based

dosing was also superior to the FDA dosing table.[8]  Based on these and numerous other studies,

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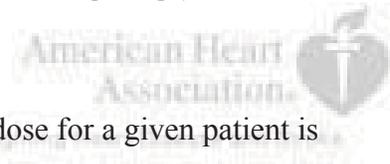
the Clinical Pharmacogenetics Implementation Consortium recently recommended use of the IWPC or Gage algorithms as the preferred approach for genetic-guided initial warfarin dose selection.[3]

While there is little debate that genetic information allows for more precise initial dose selection, questions have remained about whether this leads to any real therapeutic advantage, such as fewer out of range INRs, greater time within the therapeutic range, or reduced incidence of adverse events, particularly thromboembolic events and bleeds. Several small studies have attempted to address these issues, but none have been adequately powered, and thus there has continued to be a lack of clarity regarding the potential clinical benefits of pharmacogenetic-guided warfarin dosing. It is in this context that the paper by Anderson and colleagues[9] represents an important advance.

CoumaGen-II was a well-powered two-part study of genotype-guided warfarin dosing.[9] Part one was a randomized controlled trial testing a 1-step, modified version of the IWPC warfarin pharmacogenetic algorithm versus a 3-step algorithm. In the 1-step algorithm, genetic information was incorporated no later than the second dose, but 84% had the genetic information incorporated for determination of the first dose. The 3-step algorithm incorporated *VKORC1* but not *CYP2C9* genotype for the first dose, with *CYP2C9* genotype incorporated starting with dose 2 (step 2), with further incorporation of genetic information through a dose-revision algorithm based on the day 4/5 INR (step 3). Both patients and clinicians managing the warfarin therapy were blinded to the dosing algorithm utilized, and events were evaluated by a blinded events adjudication committee.

The second component was a comparative effectiveness research study of genotype-guided dosing of patients from part one compared against a parallel standard dosing cohort of

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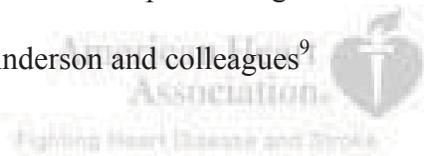
patients treated with warfarin in the same hospitals, in the same time-frame, and managed by the same clinicians or anticoagulation service teams.

The comparison of the two dosing algorithm approaches found the 3-step algorithm approach was non-inferior, but not superior to the 1-step algorithm, suggesting there is little reason to utilize the more complex 3-step approach. Based on similarity of the data from the two dosing algorithms, these data were combined to compare against the parallel standard care cohort.

The findings from the pharmacogenetic versus standard care analysis were most impressive and suggest there is clinical benefit associated with utilizing genetic information to guide warfarin dosing. Nearly all the endpoints tested showed significant benefits with the pharmacogenetic guided dosing, including out of range (OOR) INRs, percent of time in the therapeutic range (PTTR), and serious adverse events. Specifically, the pharmacogenetic cohort had a 10.3% absolute (and 25% relative) reduction in the OOR INRs at one month, with similar differences at 3 months. This was primarily due to significantly fewer INR values < 1.5, which coincided with a significant 66% lower rate of deep vein thrombosis (DVT). The reduced number of OOR INRs led to a greater PTTR in the pharmacogenetic cohort, with 69% and 71% PTTR at 1 and 3 months, versus 58% and 59% PTTR, respectively in the parallel control group. Thus, the absolute improvements in PTTR were 10.5% and 12.6% at 1 and 3 months respectively. This compares favorably with the estimated 5 to 10% absolute improvements in PTTR associated with management of patients in a specialty anticoagulation clinic, and exceeds the 5.5% absolute improvement in PTTR for which the NIH Clarification of Optimal Anticoagulation through Genetics (COAG) trial is powered.[10] Importantly, these benefits in the pharmacogenetic cohort accrued in a setting where warfarin-treated patients were typically

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managed by standard protocol by an anticoagulation service/clinic.

Additionally, while not powered to show differences in serious adverse events, such differences were noted. Incident serious adverse events at 90 days were 4.5% in the pharmacogenetic cohort and 9.4% in the parallel controls, for a 54% lower rate in the pharmacogenetic cohort. This was primarily due to significantly lower rates of death and DVT and borderline significant lower rates of moderate/serious hemorrhage. Globally, these are impressive differences in clinically important endpoints that point to the value of pharmacogenetic-guided dosing of warfarin.

The benefits from the pharmacogenetic dosing (compared to an assumed 5 mg daily initial dose) are presumed to derive from the more accurate initial dose prediction. Whether analyzed as the mean change or mean absolute change in warfarin dose from initial to stable dose, changes were significantly lower in the pharmacogenetics cohort for those with no or more than one *CYP2C9* or *VKORC1* variant alleles (where 3 is the number possible). For example, those with standard dosing with no variant in either gene required average 10.5 mg/week increases, and those with > 1 variant required 11 mg/week decreases, assuming a 35 mg/week (5 mg/day) initial dose. In contrast, the mean dose changes in the pharmacogenetics cohort in the zero and > 1 variant groups were 0.31 and 0.25 mg/week, respectively. Those with one variant allele have their dose similarly predicted by a standard 5 mg dose or by pharmacogenetic guidance.

Some will argue that the parallel control group is not an appropriate comparator since there might have been differences in the management of these patients, or specifically that the pharmacogenetic cohort was more aggressively managed because the clinicians knew those patients were in the pharmacogenetic study. While it is not possible to rule this out, the fact that

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the average number of INRs measured was essentially identical between the two groups would not support differential management of the patients. Additionally, the standard care group spent 59% of time in therapeutic range, which is consistent with two recent analyses suggesting that the average PTTR in the US ranges from 55-58%.[11] This suggests the parallel standard care arm patients were similarly to the standard of care in the US. There were also demographic differences in the two groups that might have contributed to differences in clinical outcomes, the most significant being the indication for warfarin therapy, where the pharmacogenetic cohort had a higher percentage of orthopedic surgery patients. However, stratified analyses of orthopedic and non-orthopedic patients found significant and nearly identical benefits of pharmacogenetic dosing in both groups for OOR INRs and PTTR.

There are at least four large, randomized controlled trials ongoing to test the benefits of pharmacogenetic-guidance of warfarin dosing, two in the U.S., one in Europe and one in Asia.[3, 8] These trials will provide important additional insights into the efficacy of pharmacogenetic dosing in a tightly controlled clinical trial setting. These trials will test hypotheses regarding warfarin pharmacogenetic dosing in a more robust manner than this comparative effectiveness study, and will answer some questions that were not addressed by the current study. However, the current study by Anderson and colleagues provides us with excellent insight into the effectiveness of utilizing pharmacogenetics in a real-world setting. In fact, if this study approximates the potential benefit of pharmacogenetic dosing in patients managed in an anticoagulation clinic, one can imagine the benefits might be even greater for the vast majority of warfarin-treated patients who do not have access (geographically or otherwise) to an anticoagulation clinic, and therefore have their INR monitored less frequently, with poorer anticoagulation control.

One limitation of the current study is that the participants were nearly all individuals of European ancestry, the group for whom the warfarin pharmacogenetic dosing algorithms are most predictive.[5, 6] It is therefore possible the benefits in African Americans or Asians would be less than observed in the present study. The ongoing clinical trials have broader ethnic representation and therefore will provide insights for those ethnic groups.

This study represents a landmark in the very large warfarin pharmacogenetics literature. For the first time we have a vision of the potential clinical benefits associated with use of genetic information to guide warfarin dosing. It suggests that clinicians should more seriously consider adoption of warfarin pharmacogenetics into clinical practice, and validates the recommendations from the Clinical Pharmacogenetics Implementation Consortium on warfarin pharmacogenetics.[3] And as we move toward a time when more and more patients will have their genetic information available, the current study data suggest clinicians will be hard pressed to justify ignoring genetic information in selection of an initial warfarin dose, if the necessary genetic information is available. Anderson and colleagues should be congratulated for this excellent contribution to the field.

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