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Are evidence standards different for genomic- vs. clinical-based precision medicine? - A quantitative analysis of individualized warfarin therapy

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Abstract

Evidence requirements for implementation of precision medicine (PM), whether informed by genomic or clinical data, are not well defined. Evidence requirements are driven by uncertainty and its attendant consequences; these aspects can be quantified by a novel technique in health economics, value of information analysis (VOI). We utilized VOI analysis to compare the evidence levels over time for warfarin dosing based on pharmacogenomic- vs. amiodarone-warfarin drug-drug interaction information. The primary outcome was the expected value of perfect information (EVPI), which is an estimate of the upper limit of the societal value of conducting future research. Over the past decade, the EVPI for the pharmacogenomic strategy decreased from \$1550 to \$140 vs. \$1220 to \$280 per patient for the drug-interaction strategy. Evidence levels thus appear to be higher for pharmacogenomic-guided vs. drug interaction-guided warfarin dosing. Clinical guidelines and reimbursement policies for warfarin PM could be informed by these findings.

Keywords

pharmacogenomics; precision medicine; drug-drug interaction; decision model; value of information; clinical practice guidelines; evidence levels

INTRODUCTION

There is substantial enthusiasm for precision medicine (PM), an approach for disease diagnosis, prevention, and treatment based on individual patients' clinical factors, genes, environment, and lifestyle (1). Although progress has been made in PM-related translational research, implementation in clinical practice has been slow (2, 3) primarily because of

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

D.L.V., D.D., G.F.G., J.J.C., and A.B. wrote the manuscript; D.L.V., D.D., G.F.G., J.J.C., and A.B. designed the research; D.L.V., D.D., G.F.G., J.J.C., and A.B. performed the research; D.L.V., D.D., G.F.G., J.J.C., and A.B. analyzed the data.

concerns about clinical evidence sufficiency and costs (4–6). Evidence thresholds strongly influence the time required for a new technology to move from research to practice(7). Low evidence thresholds may allow unsubstantiated technology to enter clinical practice, whereas high thresholds may slow the integration of a promising technology (7). Some have argued against ‘genetic exceptionalism’ for PM evidence thresholds, (7–9) yet the evidence thresholds for clinically-driven precision medicine (clinical PM) and genomically-driven precision medicine (genomic PM) lack consistency in clinical guidelines.

A well studied example of PM is warfarin, a commonly prescribed anticoagulant drug in atrial fibrillation with a narrow therapeutic window. The dose of warfarin can be individualized based on the presence of genetic variants in the two genes (*CYP2C9* and *VKORC1*), which are responsible for the metabolism and function of warfarin (10). Analogously, warfarin dose also can be individualized based on knowledge of an interacting drug, amiodarone, which exerts its effect through inhibition of the CYP2C9 enzyme (11). Notably, clinical guidelines recommended against the use of pharmacogenetics-based initial dosing of warfarin, (12, 13) yet recommended use of lower initiation dose (5 mg) for warfarin in patients taking amiodarone (13).

Is genomic PM held to a different standard than clinical PM? Measuring and comparing the evidence sufficiency for the two approaches of warfarin dose individualization may serve as a unique case study for PM. Commonly used methods for evaluating evidence levels are limited in their ability to address the sufficiency of evidence. For example, meta-analysis provides pooled estimates and associated uncertainty of clinical outcomes, but lacks a framework for weighing benefits vs. harms, as well as the consequences of uncertainty within the overall decision framework. A quantitative approach to assessing clinical decision uncertainty and current evidence levels may be helpful in addressing this policy conundrum.

Value of information (VOI) analysis is an increasingly utilized approach for quantifying current evidence levels and prioritizing future research. VOI is a measure of the benefit of reducing uncertainty surrounding a treatment. For example, each completed clinical trial generates safety and efficacy evidence pertaining to the treatment decision and as more evidence accumulates with each trial, the probability of making an optimal treatment decision improves (14). Importantly, VOI analysis not only evaluates current evidence, but does so within a clinical decision context, and thus can estimate the opportunity cost of making a non-optimal decision.

Expected value of perfect information (EVPI) is a VOI metric that estimates the monetary value a decision maker is willing to pay for removing all uncertainty (perfect information) surrounding the treatment decision. EVPI is a hypothetical concept and is the upper limit on the value of reducing treatment decision uncertainty by conducting more research; it can be used as a proxy for sufficiency of current evidence levels (15). The EVPI estimates the expected cost of uncertainty based on current evidence by taking into consideration the probability of making a wrong decision and the consequences of the wrong decision. The EVPI metric has been frequently used in research prioritization (16, 17). Recent VOI analyses were employed to prioritize future research, to estimate the potential return on investment of a specific clinical trial, to inform clinical trial funding decisions, and to extend

the results of a meta-analysis (18–20). EVPI is a measure of the value of conducting additional research, but not healthcare costs.

The objective of our study was to quantitatively compare the evidence levels over time for genomic- and clinical- PM for warfarin dosing in chronic atrial fibrillation (AF) patients using meta-analytic and VOI techniques. The findings of this study may provide an improved understanding of the evidence levels for warfarin PM and a general framework for considering precision medicine evidence requirements.

RESULTS

Meta-analysis of genomic PM of warfarin

Our systematic search strategy identified 657 publications including duplicates. After applying inclusion and exclusion criteria (Appendix Table 2a), we identified 9 randomized clinical trials comparing genotype-guided dosing of warfarin to clinical algorithm-based dosing to be included in the meta-analysis (21–29). Most (6 out of 9) of the included randomized clinical trials utilized *CYP2C9* and *VKORC1* testing, one trial utilized *CYP2C9*, *VKORC1*, and *CYP4F2* testing, and 2 randomized clinical trials utilized *CYP2C9* testing only for pharmacogenomics dosing algorithm arm (intervention) (Table 1). The clinical dosing arm (standard care arm of our analysis) consisted of either standard clinical practice (Hillman et al, Anderson et al, Burmester et al, and Pirmohamed et al study) or a variant of a clinical dosing algorithm to titrate the warfarin dose. The common indications for use of anticoagulation were AF, pulmonary embolism, and deep-vein thrombosis. More than 80% of patients were Caucasians, and approximately 50% were females. The follow-up period ranged from 28 days to more than 90 days. All but one RCT included patients who were warfarin naïve with an indication for anticoagulation at the time of enrollment. The studies included a total of 2697 patients for the major hemorrhage outcome (21–28, 30). For the thromboembolic (TE) events outcome, we only included 8 of the 9 randomized clinical trials, accumulating a total of 2671 patients because one of the randomized clinical trials did not report the TE as an outcome (26). Of note, not all of the RCTs included were statistically powered to detect the clinically relevant outcomes of major bleeding or TEs. Therefore, the results of meta-analysis of such clinical events should be interpreted with some caution. The uncertainty of the results in our cumulative meta-analysis reflects this limitation, and this uncertainty is fully factored into our VOI models' results.

The pooled relative risk for major hemorrhage for the first trial (23) was 2.22 (95% CI: 0.22, 22.49); with addition of each study by publication date, the pooled estimate decreased in magnitude and uncertainty to 1.17 (95% CI: 0.58, 2.38) by 2012 (Fig 1A). In 2013, three large studies (21, 22, 25) reported their results, which resulted in an overall pooled relative risk estimate of 0.67 (95% CI: 0.40, 1.13; p-value=0.60) with low levels of heterogeneity (I-squared=0%). Although the results were not statistically significant, the overall pooled estimate suggested lower risk of major hemorrhage in the pharmacogenomic intervention arm. While the statistical heterogeneity (I-squared) was low for the RCTs, the trials were different in terms of dosing algorithms, patient population included, trial design, indication for warfarin use, and follow-up times.

The risk of TE events in 2005 was lower with pharmacogenomic-guided dosing 0.22 (95% CI: 0.01, 4.32) and by 2011 as more evidence accumulated, the pooled risk estimate was close to null (1.11 (95% CI: 0.25, 4.98)). Sequential addition of randomized clinical trials for the relative risk estimate of TE events with the pharmacogenomic-based warfarin dose initiation resulted in the overall pooled relative risk of 0.98 (95% CI: 0.47, 2.06; p-value=0.96) with low levels of heterogeneity (I-squared=0%) in 2014 (Fig 1B).

Meta-analysis of clinical PM for warfarin

Our systematic search strategy retrieved 114 observational studies and no randomized controlled trials for the warfarin-amiodarone drug-drug interaction (See Appendix Table 1b and 2b for search strategy and inclusion/exclusion criteria). We identified three large population-based retrospective cohort studies based on our inclusion criteria (Table 2). A total of 35,735 patients were included for the major hemorrhage event related outcome; 8422 patients in the intervention arm (concomitant use of warfarin and amiodarone) and 27,313 patients in the control arm (on warfarin only) (31–33). The relative risk of major hemorrhage was 1.05 (95% CI: 0.35, 3.12) in 2006, and with the sequential addition of each study in 2011 and 2013, the pooled relative risk for major hemorrhage was 1.79 (95% CI: 0.89, 3.58; p-value=0.098) (Fig 1C). The heterogeneity in the clinical PM studies was very high (I-squared=85.8%). We performed the sensitivity analysis of excluding one study at a time and observed that the I-squared=0 when we excluded Zhang *et al* study. The high levels of heterogeneity may be due to the inclusion of minor and major hemorrhagic events in the study performed by Zhang *et al*. Thus, we did not pool the estimates from Zhang *et al* study in our final analysis. We did not perform the meta-analysis of TE events for clinical PM as none of the studies reported TE events as outcomes.

Value of information (VOI) analysis

The EVPI for both genomic and clinical approaches to warfarin PM decreased over time. The EVPI was \$1551 and \$1228 for the genomic PM (in 2005) and warfarin-amiodarone based clinical PM (in 2006), respectively (Figure 2C). As the uncertainty in both approaches to individualization decreased over time (Figure 2A & 2B), so did the EVPI (Figure 2C). Specifically, for the genomic PM, the per patient EVPI decreased to \$898 in 2011 and subsequently dropped to \$140 in 2014. Similarly, for clinical PM, the per patient EVPI decreased to \$502 in 2011 and subsequently dropped to \$279 in 2013. The trends were similar for WTP of \$25,000 and \$50,000 (see Appendix Fig 2). The EVPPI was non-zero only for the relative risk of major hemorrhage and relative risk of TE events in both decision models (Figure 3). Based on the current information, the per patient EVPPI for the relative risk of major hemorrhage was \$41 and \$104 for genomic PM and clinical PM of warfarin. The per patient EVPPI for the relative risk of TE events was \$72 and \$126 for pharmacogenomics-based and drug-drug interaction-based individualization, respectively. The EVPPI does not sum to EVPI due to interactions between the model structures (34).

The effect of pharmacogenomic test cost on per patient EVPI for the genomic PM is shown in Figure 4. The patient level EVPI decreased as the pharmacogenomic test cost decreased. Specifically, for a \$500, test, the per patient EVPI was \$233 and for a \$0 test, the per patient EVPI was \$109. At the current estimated test cost of \$175, the per patient EVPI of genomic

PM is \$140. The value of doing future research decreased by approximately 40% and 22% as the test cost changed from \$500 to \$175 (current test cost) and from \$175 to \$0, respectively.

Sensitivity Analysis

The exclusion of Verhoeff et al from our genomic PM analysis did not significantly change the estimates for either the cumulative meta-analysis or the EVPI. Specifically, the pooled estimates excluding Verhoeff et al for major hemorrhage and TE events were 0.67 (95% CI: 0.41, 1.16) and 0.87 (95% CI: 0.36, 2.14), respectively. The EVPI for genomic PM after excluding the Verhoeff et al study in 2015 was \$120 compared to \$140 with all RCTs included.

The trends observed for a decrease in EVPI over time for both the genomic and clinical PM were similar for all the WTP tested, i.e. \$25,000, \$50,000, and \$100,000 (see Appendix Fig 2). Specifically, for both genomic and clinical PM the EVPI was highest in 2006 and lowest in 2015, and the EVPI was lower for genomic PM strategy compared to the clinical PM strategy at \$25,000 and \$50,000 WTP thresholds.

The estimates for EVPI for genomic PM of warfarin dose did not change significantly, when the baseline probabilities for major hemorrhage and TEs were varied based on results from other major trials reporting the event rates for warfarin treated patients (Appendix Fig. 3).

DISCUSSION

We performed cumulative meta-analysis followed by value of information (VOI) analysis to quantify and compare the evidence levels for clinical- and genomic-guided warfarin dose individualization. We observed in both scenarios that as evidence accumulated over time, evidence uncertainty decreased and thus the EVPI decreased. The decision uncertainty was higher for dose modifications based on an amiodarone-warfarin drug interaction than for pharmacogenomic-guided dosing. We also observed that with decreasing genomic test cost the value of future research decreased, indicating evidence sufficiency increased.

The EVPI is an estimate of the upper bound of the value of future research that captures decision uncertainty and opportunity costs, and can be viewed as a proxy for evidence level for a decision problem. Our results suggest the evidence levels, and perhaps clinical guidelines, for the two approaches to warfarin PM should therefore be similar. However, clinical guidelines by American College of Chest Physicians (ACCP) recommend a dose reduction of warfarin in case of drug interaction with amiodarone, and recommend against the use of pharmacogenomics testing of warfarin (13).

Furthermore, most payers including Centers for Medicare & Medicaid Services (CMS) do not cover pharmacogenomic testing of warfarin but usually reimburse additional international normalized ratio (INR) testing and other costs consequent to warfarin-amiodarone drug interaction. Our analysis indicates in the case of warfarin genomic PM, as the test cost decreases the importance of clinical uncertainty decreases. Although this

finding will not hold for all cases, policies should explicitly consider the role of test cost in establishing evidence thresholds.

The results of our cumulative meta-analysis for pharmacogenomics-based individualization are generally similar to those published by Stergiopoulos *et al* (35) and Shi *et al* (36), who used a similar pool of studies. Stergiopoulos *et al* estimated relative risks for major hemorrhage and TE events to be 0.60 (95% CI: 0.29, 1.22) and 0.97 (95% CI: 0.46, 2.05) respectively for pharmacogenomic-guided vs clinical dosing of warfarin. Shi *et al* performed a meta-analysis followed by a subgroup analysis based on whether warfarin dose in the control groups was fixed dose or variable dose. Shi *et al* concluded that the pooled relative risk for major hemorrhage (RR = 0.36; 95% CI: 0.15 to 0.89, P = 0.03) and TE events (RR = 0.86; 95% CI: 0.75, 0.99; P = 0.03) favored the pharmacogenomic guided warfarin dosing. However, either of the two studies by Stergiopoulos *et al* and Shi *et al* did not perform VOI analyses.

Claxton *et al* demonstrated a similar methodological approach of extending meta-analysis to quantify the expected societal benefits of implementing an intervention based on current research findings versus performing additional research prior to implementation (37). The authors evaluated streptokinase to treat myocardial infarction and found that the value of conducting additional research declines as evidence from new studies accumulates. In contrast to their work, we included healthcare costs and quality of life impacts in addition to clinical events and life expectancy.

Although, we have addressed the issue of evidence quantification and comparison for genomic and clinical PM in context of warfarin personalization, additional barriers to adoption of pharmacogenetics testing in clinical guidelines still exist. These additional barriers for adoption include; time taken for genetic testing, efforts required for interpreting and documenting test results, liability issues for keeping track and acting clinically based on genetic information, and ethical issues (such as reporting incidental finding)(6). Our study has several limitations. First, the results of our study are specific to elderly (>65 years old) AF patients similar to those enrolled in the clinical studies included in our analyses. The value of conducting research in other patient populations may be higher given the paucity of data in such populations. Second, the evidence for clinical individualization of warfarin dosing was derived from observational studies, which may have more bias than randomized controlled trials. However, this bias would tend to underestimate the value of conducting additional research for warfarin-amiodarone drug interaction clinical outcomes. Third, the evidence for major hemorrhages for the clinical PM approach was estimated using warfarin dose reduction from a real-world vs a clinical trial setting, and may underestimate the treatment effect of the dose reduction following concomitant warfarin amiodarone use. We accommodated the lack of high quality data for all estimates by evaluating each estimate over a range of values and quantifying the value of better understanding these estimates. Fourth, although the RCTs included for meta-analysis of genomic PM demonstrated low levels of heterogeneity (I-squared=0), the trials differed with respect to the dosing algorithm, patient population included, design, indication for warfarin use and follow-up times. To accommodate for the apparent and inherent heterogeneity for both (genomic and clinical PM), we used random effects models. In conclusion, we quantitatively compared the

evidence levels for two approaches to individualizing warfarin dose using random effect meta-analysis and VOI analysis. We found that the evidence level for clinical individualization was weaker than the evidence level for genomic individualization of warfarin dosing. The results of our study highlight inconsistencies among clinical guidelines and reimbursement decisions for warfarin dose individualization, and suggest that evidence quantification frameworks for PM may be helpful in decision-making by clinicians, payers, and guideline development committees.

METHODS

Overall approach

To understand the impact of evidence accumulation over time on the value of research, we utilized a mixed methods approach that combined meta-analysis with VOI analysis techniques. First, we conducted cumulative meta-analyses for two warfarin dose individualization approaches to synthesize the accumulation of evidence over time. The primary outcomes of the evidence synthesis were the relative risks of major bleeding and thromboembolism for both the genomic PM and clinical PM of warfarin. Second, we developed two analogous decision models for the two PM approaches among AF patients (Figure 5). The only differences in the two models were the intervention-specific parameters. The primary outcome of each model was the EVPI. Third, we estimated the EVPI at different time points (from 2005 to 2015) for each warfarin PM approach based on the cumulative meta-analysis results.

Evidence Synthesis

We performed a systematic search on PubMed and EMBASE to identify published randomized clinical trials and observational studies for each warfarin PM approach (see appendix Table 1A and 1B for the two search strategies). For the genomic PM, we included randomized clinical trials that compared genotype-guided and clinical-algorithm-based dose initiation, were published in English, and were published between 2000 and 2015 (see appendix Table 2A for complete list of inclusion and exclusion criteria). For the clinical PM, we included both randomized clinical trials and observational studies in our search strategy, as we assumed that randomized clinical trials for the drug-drug interaction between warfarin and amiodarone might be scarce due to ethical reasons. We included studies published in English that reported bleeding risk or bleeding related hospitalization as one of the outcomes. We included studies published between 1983 to 2015 (see appendix Table 2B for inclusion and exclusion criteria), as amiodarone was first approved to be marketed in the US in 1985.

Based on the selected published evidence, we then conducted cumulative meta-analyses, wherein the studies were sequentially added by their publication date and the relative risk estimate for clinical events reflected the evidence up to that time point. Relative risks and odds ratios were pooled from the included studies using random-effect models. We assumed odds ratio to approximate the relative risk, as both the outcomes were rare events. For both meta-analyses, we calculated the I-squared statistics, which describes the percentage of variability in effect estimates as a result of heterogeneity (38).

Decision models

The two analogous decision models for warfarin PM were programmed in Microsoft Excel (Redmond, WA) (Figure 5). The models were analogous in that both required warfarin dose individualization and involve similar mechanistic requirements of dose adjustments. The only differences between the two models of warfarin dose individualization were the mechanism of individualization.

For the genomic PM model, the strategies were pharmacogenomic-based vs. clinical algorithm-based warfarin dosing among atrial fibrillation (AF) patients at the time of warfarin initiation. For the clinical PM model, the intervention was dose reduction of warfarin when concomitantly administered with amiodarone among AF patients. We modeled the long-term outcomes of AF patients over a 35 years using a Markov model that included four health states; well state, major hemorrhage events, TE events, sequelae, and death. We modified our Markov model of warfarin pharmacogenomic testing previously published by Meckley *et al* (39).

Population

The patient population modeled for genomic PM scenario was 65 year old atrial fibrillation patients who were candidates for warfarin dose initiation. The patient population modeled for clinical PM scenario was 65 year old atrial fibrillation patients who were already on warfarin for more than 6 months and were candidates for concomitant amiodarone initiation. The modeled populations were similar to patients enrolled in the identified clinical studies.

Clinical parameters

The baseline risk estimates for the genomic PM model, for major hemorrhage and TEs were obtained from patients on warfarin only in the Apixaban for reduction in stroke and other ThromboemboLic events in atrial fibrillation (ARISTOTLE) study (40). We multiplied the baseline risks by the relative risks of major hemorrhage and TE events from our meta-analysis of randomized clinical trials (Appendix Table 3) to derive the risk estimate for intervention arm.

The risk estimates for major hemorrhage and TEs for clinical PM model intervention arm (dose reduction of warfarin) were obtained from the subgroup of patients who were concomitantly on warfarin and amiodarone published as a re-analysis of ARISTOTLE study (41). The risk estimate for the standard care arm was derived from results of our meta-analysis of retrospective cohort studies of the concomitant use of warfarin and amiodarone. We assumed that the dose reduction among the retrospective cohort study patients following concomitant warfarin and amiodarone use was not perfect (dose reduction was assumed to be perfect in clinical trial settings) as the patients came from a variety of regions and clinical settings. We also assumed the risk of TE was identical for both arms of clinical PM model because the concomitant use of amiodarone and warfarin maintains INR levels ≤ 3.0 (based on pharmacokinetics data) leading to reduced risk of TE.

Health state utility and costs

Health state utility (quality of life) estimates were derived from US population-based EQ-5D scores(42). For the 'well' state we applied a disutility of 0.013 for AF patients taking warfarin(43, 44). Utilities for all the other health states were calculated by applying the disutility for having the condition (39). Medical costs for anticoagulation clinic, INR tests, direct medical costs, inpatient costs were based on the study published by Meckley *et al*, who estimated the total costs based on the Intermountain and University of Washington Medical Center Anticoagulation Clinic data (39). The costs of bleeds and TEs were derived from the Healthcare Cost and Utilization Project (HCUPnet) database(39). All costs were inflated to 2015 dollars

Value of information (VOI) analysis

The primary outcome for both decision models was expected value of perfect information (EVPI). EVPI was calculated utilizing net monetary benefit, which is calculated by multiplying the assumed society's willingness to pay (WTP) for each additional QALY saved for the treatment arm and subtracting the cost for that treatment arm ($WTP \times \text{total QALYs saved for the treatment arm} - \text{Total cost for the treatment arm}$). We calculated the average maximum net monetary benefit (NMB) for each arm for the two warfarin PM approaches by assigning the monetary value to the health outcomes for each model iteration. Costs and outcomes were discounted at an annual rate of 3%. We assumed the US payer perspective for which only direct healthcare costs typically incurred to the payers were included and indirect costs such as productivity loss or caregiver time were not included. We assumed a society's willingness to pay for each additional QALY to be \$100,000 in the US(45).

We estimated and compared the EVPI at different chronological time points for each warfarin PM approach, informed by our cumulative meta-analyses. In our models, the EVPI depended primarily on the uncertainty for the relative risk estimates (width of 95% confidence intervals). If the relative risk estimates are precise (high evidence levels) the EVPI would be low, whereas, if the risk estimates are less precise (low evidence levels) the EVPI would be high. Thus, higher the uncertainty in a decision, the higher the EVPI estimate and vice versa. The impact of pharmacogenomic test cost on the value of future research (evidence levels) of genomic PM was estimated by the estimating the EVPI at different assumed pharmacogenomic test costs. The test costs were varied from \$500 to \$0.

We performed VOI analysis using standard Monte Carlo simulation approach(46, 47). Specifically, we assigned the prior distributions to each input parameter and for each simulation we sampled from the assigned input distributions propagating the values through the model to calculate the outcomes (16, 46). We performed 5000 simulations and calculated the NMB for each simulation. The EVPI is the difference between the NMB with perfect information, which is calculated by averaging the maximum NMBs among treatment strategies for each simulation, and the NMB for the optimal treatment strategy.

Expected Value of Partial Perfect Information (EVPPI)

The EVPPI for a parameter is the difference between the expected value with perfect and current information about that parameter, and provides the upperbound to the parameter specific value of future research. We estimated the EVPPI for the relative risk of major hemorrhage (safety parameter) and the relative risk of TEs (efficacy parameter). We also estimated the EVPPI for the costs of treatments, the utility estimates, and transition probabilities between Markov states as groups of parameters rather than as individual parameters. The grouped parameters contain related individual parameters and in additional research efforts, it is efficient to generate information on multiple parameters within each group simultaneously. For the pharmacogenomic-based individualization, we also estimated EVPPI for the pharmacogenomic test cost.

Sensitivity Analysis

One of the included studies in evidence synthesis for genomic-PM model was for non-warfarin vitamin K antagonists (acenocoumarol and phenprocoumon). Therefore, we tested sensitivity of our results to exclusion of the non-warfarin vitamin K antagonist study (Verhoeff et al).

We performed the sensitivity of the results to varying levels of WTP of \$0, \$25,000, and \$50,000 per QALY. We also tested our results by varying the baseline probabilities for the genomic PM model based on the event rates for major hemorrhage and TEs from three other large recent RCTs; Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY Trial), Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation - Thrombolysis in Myocardial Infarction 48 (ENGAGE TIMI 48 Trial), and Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF Trial).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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STUDY HIGHLIGHTS

What is the current knowledge on the topic?

The clinical guidelines recommend against the use of pharmacogenetics-based initial dosing of warfarin but recommend the use of lower initiation dose for warfarin in patients taking amiodarone. Although, there are several clinical studies for pharmacogenetic-based dosing of warfarin and warfarin amiodarone drug-drug interaction, but evidence sufficiency is unclear. Commonly used methods for evaluating evidence levels are limited in their ability to address evidence sufficiency.

What question did this study address?

How did the evidence for warfarin dose individualization based on the two approaches of individualization (pharmacogenomic- and drug-drug interaction-based) change and compare over time?

What this study adds to our knowledge?

The evidence level for clinical individualization was weaker than the evidence level for genomic individualization of warfarin dosing. The results of this study highlight inconsistencies among clinical guidelines and reimbursement decisions for warfarin dose individualization.

How this might change clinical pharmacology or translational science?

The results of this study suggests that evidence quantification frameworks for personalized medicine may be helpful in decision-making by clinicians, payers, and guideline development committees.

Figure 1.

A) Cumulative meta-analysis of risk major hemorrhage following pharmacogenomic-based dose initiation of warfarin. Randomized clinical trial studies were added chronologically by publication date. The relative risk of major hemorrhage became less uncertain over time. **PGx**: pharmacogenomic, **Std**: standard care.

Figure 1. B) Cumulative meta-analysis of the risk of thromboembolic events following pharmacogenomics-based dose initiation of warfarin. Randomized clinical trial studies were added chronologically by publication date. The relative risk of thromboembolic(TE) events became less uncertain over time. **TE**: thromboembolic, **Std**: standard care.

Figure 1. C). Cumulative meta-analysis of risk major hemorrhage following concomitant use of warfarin and amiodarone. Population-based retrospective cohort

studies were added chronologically by publication date. The relative risk of major hemorrhage became less uncertain over time. **DDI:** warfarin-amiodarone drug-drug interaction, **Std:** standard care.

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Figure 2.

A). Evidence uncertainty for hemorrhage events over time for pharmacogenomic-based warfarin individualization. RR: relative risk, 95% CI-LL: 95% confidence interval lower limit, 95% CI-UL: 95% confidence interval upper limit.

Figure 2B). Evidence uncertainty for hemorrhage events over time drug-drug interaction-based warfarin individualization. EVPI: expected value of perfect information, PGx: pharmacogenomics, WTP; willingness to pay, W+A DDI: warfarin-amiodarone drug-drug interaction.

Figure 2C). Comparison of per patient level expected value of perfect information (EVPI) over time for the pharmacogenomic-based and drug-drug interaction-based

warfarin dose individualization. EVPI: expected value of perfect information, **PGx:** pharmacogenomics, **WTP:** willingness to pay.

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Figure 3. Expected value of partial perfect information (EVPPI) for key parameters for the pharmacogenomic-based and drug-drug interaction-based individualization of warfarin dose **RR:** relative risk, **EVPPI:** expected value of partial perfect information, **EVPI:** expected value of perfect information, **TE:** thromboembolic.

Figure 4. Effect of pharmacogenomic test cost on the expected value of information (EVPI)
EVPI: expected value of perfect information, PGx: pharmacogenomics, WTP: willingness to pay.

Figure 5. Decision models A) Model for genomic PM of warfarin dosing. B) Model for Clinical PM of warfarin dosing
PGx: pharmacogenomics, **DDI:** drug-drug interaction, **yo:** years old.

Table 1

Study Characteristics of Included Studies for Genomic PM Cumulative Meta-analysis

Studies Included for Genomic PM (Pharmacogenetic-guided Warfarin Dosing) Cumulative Meta-analysis							
Study (Country)	N	Male	Race (% White)	Indication	Genotype	Target INR	Follow-up Time
Hillman et al 2005(20) (US)	PG arm – 18 Control – 20	44% 45%	100% 100%	AF, prosthetic valve/join, DVT, PE	CYP2C9	N/A	4 weeks
Anderson et al 2007(44) (US)	PG arm – 101 Control – 99	50% 57%	94% 95%	AF, DVT, PE, pre-operative orthopedic	CYP2C9 VKORC1	2.0–3.0	12 weeks
Caraco et al 2008 (24) (Israel)	PG arm – 95 Control – 96	48% 44%	N/A	DVT, PE, AF	CYP2C9	2.0–3.0	Not specified. Followed up until the INR stabilized (two consecutive INR values, 7 days apart, within therapeutic range)
Burmester et al 2011 (25) (US)	PG arm – 95 Control – 96	57% 61%	100% 100%	AF, VTE, PV	CYP2C9 VKORC1 CYP4F2	2.0–3.5	60 days
Borgman et al 2012 (23) (US)	PG arm – 13 Control – 13	54% 54%	85% 100%	DVT, AF, Stroke	CYP2C9 VKORC1	1.8–3.4	12 weeks
Kimmel et al 2013 (19) (US)	PG arm – 514 Control – 501	53% 49%	67% 66%	DVT, PE, AF, others	CYP2C9 VKORC1	2.0–3.0	6 month
Jonas et al 2013 (18) (US)	PG arm – 53 Control – 53	44% 50%	80% 65%	AF, DVT, PE, other	CYP2C9 VKORC1	2.0–3.0 or 2.5–3.5	90 days
Pirmohamed et al 2013 (22) (UK and Sweden)	PG arm – 227 Control – 228	64% 58%	98% 99%	AF, VT	CYP2C9 VKORC1	2.0–3.0	3 months
Verhoef et al 2013 (21) (The Netherlands and Greece)	PG arm – 273 Control – 275	63% 56%	96% 98%	AF	CYP2C9 VKORC1	2.0–3.0	Intended 12 weeks but modified ITT of at least 10 weeks considered

PG: pharmacogenetic, **AF:** atrial fibrillation, **DVT:** deep vein thrombosis, **PE:** pulmonary embolism, **VT:** venous thromboembolism, **ITT:** intention to treat, **INR:** international normalized ratio.

Table 2

Study Characteristics of Included Retrospective Cohort Studies for the Clinical PM Cumulative Meta-analysis.

Studies included for the cumulative meta-analysis of warfarin-amiodarone DDI model			
Study	Population	Outcome	Results
Lam et al 2013 (28) (Retrospective cohort study, Canada)	Patients 65 years and older on 6 months or more on warfarin. (60,497 patients with warfarin usage)	Hospitalization for hemorrhage	aHR – 2.45 (95%CI:1.49–4.02)
Vitry et al 2011 (29) (Retrospective cohort study, Australia)	Patients 65 years and older (17,661 patients with warfarin usage)	Bleeding related hospitalization	aRR-3.33 (95%CI:1.38–8.00)
Zhang et al 2006 (30) (CVS Caremark retrospective cohort study, US)	Caremark enrolled members (17,895 patient used warfarin)	Minor or major hemorrhage	aOR- 0.98 (95%CI:0.83, 1.16)

aHR: adjusted Hazards Ratio, **aRR:** adjusted Relative Risk, **aOR:** adjusted Odds Ratio