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Review

Pharmacogenetic-guided algorithms to estimate personalized dose or individual responses to anti-thrombotic drugs

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ABSTRACT

Purpose: Genotyping seems to be regarded as less useful than expected for predicting the inter-individual variation in drug response. We aim to improve the predictive accuracy of genotyping by developing models that also incorporate certain non-genetic factors.
Study selection and results: The anti-coagulant warfarin is widely used to prevent venous thromboembolic events. Although frequent monitoring of the prothrombin time international normalized ratio (PT-INR) allows an appropriate maintenance dose to be obtained for most individuals, there are some individuals for whom it is difficult to achieve the target PT-INR even when warfarin dose is increased. The anti-platelet drug clopidogrel is typically used with aspirin to prevent cardiovascular events following percutaneous coronary intervention. However, the existence of clopidogrel resistance is a major concern in Asian populations owing to the high prevalence of deficient allele of the *CYP2C19* gene, which encodes a major enzyme that produces the active metabolite. Individual response to these anti-thrombotic drugs cannot be accurately predicted based on genetic factors alone. We have constructed two algorithms, one that predicts the maintenance dose of warfarin and one that estimates individual responses to clopidogrel in outpatients without a device-based platelet function test. We applied Akaike's Information Criterion to evaluate the validity of these algorithms.
Conclusions: In addition to genotyping data, inter-individual variation in non-genetic factors, such as clinical laboratory data, should be considered to predict drug response more accurately in each individual.

1. Introduction

Japan became a super-aged society in 2007, and by 2013, elderly people (65 years of age or older) accounted for 25% of the overall population. The percentage of elderly people is estimated to reach 30% in 2035 and 40% in 2075. Epidemiological data indicates that heart disease and cerebrovascular disease are, respectively, the second and third most common causes of death in people aged 50–79 years in Japan. Therefore, along with treatment of malignant neoplasms, suppressing the onset and recurrence of cardiovascular and cerebrovascular diseases will become increasingly important in the future. For this reason, it is necessary to investigate the optimal use of anti-thrombotic drugs in Japan.

Abbreviations: ACS, acute coronary syndromes; ADP, adenosine diphosphate; AIC, Akaike's Information Criterion; BSA, body surface area; CYP, cytochrome P450; DAPT, dual anti-platelet therapy; DL, dyslipidemia; DVT, deep vein thrombosis; GWAS, genome-wide association studies; Hct, hematocrit; HPR, high on-clopidogrel treatment platelet reactivity; IWPC, the International Warfarin Pharmacogenetics Consortium; LOF, loss of function; MACE, major adverse cardiovascular events; NOAC, novel oral anticoagulants; PCI, percutaneous coronary intervention; PON1, paraoxonase-1; PPI, proton pump inhibitor; PRU, P2Y12 reaction units; PT-INR, prothrombin time international normalized ratio; TTR, time in therapeutic INR range; VKORC1, vitamin K epoxide reductase complex, subunit 1; WBC, white blood-cell count.

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2. Difficulties encountered when predicting optimal maintenance doses of warfarin

Warfarin is widely used for the prevention and treatment of thromboembolism. Even though novel oral anticoagulants (NOAC) have been developed, the use of warfarin is most likely to continue owing to the ease by which its effects can be monitored, the existence of a neutralizing agent, and its low cost. There is a marked inter-individual difference in susceptibility to warfarin, which depends on various factors such as age, race, body size, diet, concomitantly used drugs, and genetic factors [1–3]. CYP2C9 is a major enzyme responsible for the metabolism of *S*-warfarin; its activity is thought to be determined mainly by genetic polymorphism and, in 2000, it was shown to be the most important factor related to warfarin sensitivity and associated effects—including risk of bleeding [4–6]. However, even in a group homozygous for wild-type (**1/*1*) CYP2C9 [7], the clearance of unbound *S*-warfarin varied dramatically, thus indicating that other factors must be involved in the pharmacokinetics of *S*-warfarin. On the other hand, the gene encoding vitamin K epoxide reductase (VKOR) in humans was identified [8], and a polymorphism in the *VKORC1* gene was shown to be associated with inter-individual variability in the effects of warfarin [9]. Some studies have shown that the genotype of *VKORC1* has more effect on inter-individual variability in warfarin response than *CYP2C9* [10–13]. Genome-wide association studies (GWAS) have shown that known polymorphisms in *VKORC1* and *CYP2C9* are the two major genetic determinants of warfarin response [14,15], although *CYP4F2* only has a minor effect on warfarin response in some races [16,17]. Importantly, GWAS demonstrated that there were no additional genes that were significantly associated with warfarin response. However, even after taking into account *VKORC1* and *CYP2C9*, it was still difficult to predict the optimal maintenance dose of warfarin required by each patient [18,19]. This strongly suggests that factors other than genotype are responsible for inter-individual differences in warfarin response. For this reason, researchers have begun to use algorithms that include clinical and demographic factors as well as genetic factors to predict the optimal warfarin dose needed by a patient [18,20].

2.1. Published pharmacogenetic-guided algorithms for estimation of warfarin maintenance dose and their evaluation

Many pharmacogenetic-guided warfarin dosing algorithms have been constructed and a representative selection is summarized in Table 1. The usefulness of those algorithms in a clinical setting has been assessed using several approaches. One approach is external validation of published algorithms [21–29]. Among the many dosing algorithms, several studies [23,25,27] have shown that the most effective algorithms are those proposed by Gage et al., (available at www.warfarindosing.org) [30], and by the International Warfarin Pharmacogenetics Consortium (IWPC) [31]. However, other studies have shown that, most algorithms have comparative performance [21,24]. Currently, no algorithm has been shown to have superior performance across all dosing ranges [23,25,26,28,29], for all ages of patients [32–34], and for all ethnicities [29,35,36].

An alternative approach involves a comparison of the performance of pharmacogenetic-guided dosing and traditional dosing methods (e.g. a simple nomogram with an empirical starting dose or a formal clinical algorithm based on a randomized controlled trial) [37–41]. Although most [37–40], but not all [41], studies have appeared to indicate that pharmacogenetic-guided dosing results in a better outcome than clinical dosing, with one exception [42], no meta-analyses of randomized trials have provided conclusive evidence [43–46] that pharmacogenetic-guided dosing algorithms can improve the safety and/or efficacy of initial warfarin therapy. Controversial results might be owing to differences in the segments of subject populations used, the pharmacogenetic-guided dosing algorithm used, the clinical algorithm adopted for the control arm, and the primary endpoint. With regard to the endpoint, one of the problems is that the primary endpoint of studies is either the percentage of out-of-range international normalized ratio (INR) values or the percentage of time in the therapeutic INR range (TTR). Without evaluating hard endpoints, such as the occurrence of bleeding or thrombosis, the usefulness of a pharmacogenetic-guided dosing algorithm in a clinical setting is limited.

2.2. Our approach to evaluating a warfarin dosing algorithm

We have previously attempted to construct an algorithm to help clinicians individualize warfarin maintenance therapy. In order to develop a better pharmacogenetic-guided dosing algorithm, we applied Akaike's Information Criterion (AIC) to evaluate the adequacy of a warfarin dosing algorithm constructed by multiple linear regression modeling [47]. In general, the decision coefficient (R^2) value is used to evaluate a model consisting of various explanatory variables. When the algorithm is derived from the first (derivation or model-building) cohort, there is a possibility that false-positive variables will be incorporated into the model, and this possibility is enhanced by small derivation cohorts. As a model is improved by the stepwise method, the number of variables increases and therefore the residual error between the predicted and actual doses decreases; this itself leads to an increased R^2 value. Increase in R^2 value by incorporating false-positive variables into the model causes over-fitting. As a result of over-fitting, a model derived from a cohort that is not ideal may contain false-positive variables. Therefore, the algorithm must be applied to a second unrelated (validation or replication) cohort to evaluate its validity. If the R^2 value obtained from the validation cohort is comparable to that obtained from the derivation cohort, the model is judged to be valid. However, it is sometimes difficult to prepare a second cohort of equal or larger size in a single medical institution. Additionally, although the R^2 value can be used to judge whether the algorithm can be applied to another cohort, it cannot detect false-positive variables. A model that can estimate the required dose more accurately with the smallest number of variables is more desirable because of its speed and low cost. To reduce the number of variables and appropriately select indeed-positive (relevant) factors when constructing an algorithm, AIC is a useful index, and the algorithm with the smallest AIC is considered to be the most desirable [48]. Elevation of the R^2 value due to over-fitting was actually observed following the addition of several factors that showed no significant association with warfarin dose [47] (Fig. 1A). Thus, it was not possible to judge whether the increase in R^2 value was due to over-fitting when R^2 was the only index used to evaluate the model. AIC gradually increases as false-positive (irrelevant) factors are added (Fig. 1B), and thus indicates that certain factors are irrelevant. The equation for the final algorithm that was found to be suitable for our patient cohort ($n = 97$) was as follows:

$$\begin{aligned}\text{Dose (mg/day)} = {} & 6.800 + 2.013 \times (\text{BSA}) - 0.04306 \times (\text{age}) \\ & - 2.870 \times (\textit{VKORC1}\text{*}2/\text{*}2) - 2.233 \\ & \times (\textit{VKORC1}\text{*}1/\text{*}2) - 0.912 \times (\textit{CYP2C9}\text{*}1/\text{*}3) \\ & - 0.171 \times (\text{WBC}) - 0.596 \times (\text{allopurinol}) \\ & + 0.674 \times (\textit{CYP4F2}\text{*}3/\text{*}3),\end{aligned}$$

where, BSA (body surface area) is in m^2, age is in years, genotype is coded as 1 if present or 0 if absent, white blood-cell count (WBC) is