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Commentary

Population diversity and the performance of warfarin dosing algorithms

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Warfarin combines several characteristics that make it a case study for personalized drug therapy, as follows: it is the most commonly prescribed oral anticoagulant worldwide, there is large interindividual variation in dose requirements, its therapeutic index is narrow, and a reliable biomarker, the international normalized ratio (INR), is available for quantifying the anticoagulant effect of warfarin. Several pharmacogenetic algorithms have been described for the prospective estimation of individual warfarin dose requirements in different populations. Most algorithms, whether derived from single or multi-ethnic cohorts, incorporate age, bodyweight or surface area, co-medication with CYP2C9 inhibitors (e.g. amiodarone) and inducers (e.g. carbamazepine) and polymorphisms in *VKORC1* (mainly 3673G>A, also designated −1639G>A, rs9923231) and *CYP2C9* (alleles *2 rs1799853 and *3 rs1057910) as covariates. Gender, 'race', co-morbidities (e.g. venous thromboembolism), drugs such as statins, additional *CYP2C9* alleles, *VKORC1* haplotypes and polymorphisms in other pharmacogenes (e.g. *CYP4F2* rs2108622) are included in some algorithms.

The performance of warfarin dosing algorithms, expressed by the correlation coefficient (R^2) between predicted and prescribed doses, varies considerably (<0.2–>0.6), but is consistently superior in Europeans compared with Asians or populations of African descent. This discrepancy is not corrected by inclusion of a 'race' term in some algorithms [1, 2]. This is not surprising, considering the complex interplay of genetic and nongenetic factors in modulating drug response, and the fluctuation of racial definitions according to social context, geographic location, historical period and personal experience [3].

Genome-wide studies identified *VKORC1*, *CYP2C9* and *CYP4F2* as the sole pharmacogenes associated with warfarin dose–response variability in Caucasians, but it is not known whether this prevails in other populations. For example, a polymorphism in the gene encoding the VKORC1 regulator calumenin (*CALU*, rs339097), which is rare in Caucasians but occurs in 14% of African-Americans, predicts higher warfarin dose requirements in the latter [4]. A related observation pertains to *CYP2C9*8* (rs7900194), the most frequent *CYP2C9* defective allele in populations of African descent, albeit rare or absent in Caucasians. Scott *et al*. [5] have shown that genotyping for *CYP2C9*8* alone could reclassify the predicted metabolic phenotypes of almost 10% of African-Americans, or when combined with *CYP2C9*5*, *6 and *11*, more than 15%. It is likely that incorporation of these alleles, in addition to *CYP2C9*2* and *3, into genotyping panels will improve the performance of warfarin dosing algorithms in patients of African descent. By contrast, incorporation of additional *VKORC1* single nucleotide polymorphisms or haplotypes does not further improve dose prediction by algorithms comprising rs9923231 in whites, Asians and blacks [6]. Indeed, the variable frequency of this single nucleotide polymorphism is a major determinant of the differences in the percentage variance in warfarin dose explained by *VKORC1* across populations [6].

Collectively, the above-mentioned observations may suggest that warfarin dosing algorithms are 'population specific'. In the present issue of BJCP, Botton *et al*. [7] explore this notion in the context of the Brazilian population. Brazilians are a highly heterogeneous people, as a result of centuries of admixture of Europeans, sub-Saharan Africans and Amerindians [8]. The pattern and extent of admixture differ considerably across the vast Brazilian territory, which allowed Botton *et al*. [7] to recruit a Southern Brazilian patient cohort of exclusively European ancestry. From this cohort, the authors derived two algorithms, including 12 and 18 pharmacogenetic, clinical, demographic and medication covariates, which explained, respectively, 58 and 63% of the interindividual variation in warfarin prescribed dose. These are among the highest coefficients of determination described in the literature, although other algorithms of similar predictive power and considerably fewer covariates have been previously published. These include algorithms that we derived for an admixed Brazilian cohort of self-identified white, brown

Table 1

Validation of warfarin dosing algorithms in an admixed Brazilian cohort*

Cohort	*n*	Algorithm 1† R^2	Algorithm 1† MAE‡	Algorithm 2† R^2	Algorithm 2† MAE‡
Overall	390	0.44	11.3	0.46	9.6
White‡	196	0.49	10.4	0.50	8.8
Brown + black§	194	0.34	12.2	0.40	10.4

*Cohort studied by Perini *et al*. [10]. †Algorithms 1 and 2 from Botton *et al*. [7]. ‡MAE, mean absolute error between predicted and observed warfarin doses. §Self-identity according to criteria and terminology adopted by the Brazilian Census.

('pardo', in Portuguese) and black patients [9, 10]. Botton *et al*. [7] observed that one of the latter algorithms had a comparatively inferior performance in their patients and ascribed this discrepancy to differences in biogeographical ancestry between the two study cohorts, exclusively European in their study *vs.* admixed European/African/Amerindian in ours. By the same token, the Botton algorithms did not reproduce their original performance when validated in our overall cohort (R^2 = 0.44–0.46; Table 1). However, the predictive power of the Botton algorithms was considerably higher in our self-reported white patients (R^2 = 0.49–0.50) compared with brown and black patients (R^2 = 0.37–0.40; Table 1).

Although these results seem consistent with the notion that warfarin dosing algorithms 'need to be population specific' [7], it is noteworthy that five algorithms derived from Caucasian patients performed poorly when tested in Brazilians of exclusively European ancestry (table 5 in ref. [7]). Of note, one of the tested algorithms [11], originally derived from British Caucasians, provided reliable estimates of warfarin dosing in a Swedish cohort [12]. Do these observations imply a 'cohort specificity' within European populations? Does this occur in other major ethnic/racial/continental categories commonly used in the pharmacogenetic literature, such as Asians, Africans, Hispanics, etc.? Assuming that the frequency distribution of pharmacogenetic polymorphisms within these categories is relatively constant, does the discord in performance of warfarin algorithms reflect a greater than acknowledged contribution of nongenetic factors, such as diet, concomitant medication, concurrent diseases, compliance with warfarin prescription, etc.? These are open questions at the present time, which deserve further investigation.

A personalized strategy for initiation of warfarin therapy, allowing for improved safety and cost-effectiveness worldwide, must take into account inter- and intra-ethnic/racial diversity. Accounting for this diversity in algorithms that are clinically useful across populations and 'friendly' enough to be adopted by practising physicians around the globe is a challenge to clinical pharmacologists and pharmacogeneticists. A successful response to this challenge requires information from trials gathered at different population levels, but demands also a critical appraisal of racial/ethnic labels that are commonly used in the clinical pharmacology literature but do not accurately reflect genetic ancestry and population diversity.

Competing Interests

There are no competing interests to declare.

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