The influence of VKORC1 3730 G > A polymorphism on warfarin dose: reply

Michela Cini · Cristina Legnani · Benilde Cosmi ·
Giuliana Guazzaloca · Lelia Valdrè · Mirella Frascaro ·
Gualtiero Palareti

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Dear Sirs,

Skov et al. object that the effect of the variant allele rs7294 which is associated with higher warfarin requirements is not relevant in our dosing algorithm, its effect being significant at the univariate but not at the multivariate analysis.

Skov et al. also show that there is not a complete linkage disequilibrium but a significant correlation between rs 7294 and the variant allele rs 9934438 which is associated with warfarin sensitivity, based on the data of their study [1]. The frequency of the variant allele rs 7294 was 9.6% in their study vs 7.3% in our derivation group and 10% in the validation group. The partial linkage disequilibrium between the rs 7294 and the rs 9934438 is also consistent with data previously published by Wadelius et al [2].

In the algorithm recently elaborated by Pavani et al. [3], various parameters were included in the multiple linear regression model, and they concluded that the incorporation of VKORC1*3 (rs 7294) and VKORC1*4 (6009 C/T) could help in a precise prediction of therapeutic warfarin dose.

Moreover, in a recent meta-analysis [4], Jorgensen et al. showed that for the Caucasian ethnic group, the pooled effect estimate of the VKORC SNP rs 7294 on warfarin dosing was nonsignificant for heterozygotes versus wild-types, but was statistically significant for mutant-types versus wild-types.

In our study [5], we chose to employ a simultaneous multivariate regression as our analysis was exploratory and hypothesis generating. The loss of significance of the effect

of rs 7294 at the multivariate analysis could be due to our limited sample size, as acknowledged in our discussion, and larger studies are required to confirm our algorithm.

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M. Cini (✉) · C. Legnani · B. Cosmi · G. Guazzaloca ·
L. Valdrè · M. Frascaro · G. Palareti
Department of Angiology and Blood Coagulation “Marino Golinelli”,
University Hospital S. Orsola-Malpighi,
Via Albertoni, 15,
40138 Bologna, Italy
e-mail: michela.cini@aosp.bo.it