

Incorporating assessment of fibrinogen gene polymorphisms and bleeding risk in patients treated with direct oral anticoagulants

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Direct oral anticoagulants (DOACs) have become entrenched as the dominant anticoagulant over the last decade for patients with venous thrombosis and atrial fibrillation.¹ Compared to warfarin, bleeding risk is similar or lower for patients on DOACs but clinically relevant bleeding is still a risk, especially for patients with impaired organ function.² Furthermore, current bleeding risk assessment tools, such as the Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalised ratio, Elderly, Drugs/alcohol concomitantly (HAS-BLED) score, were designed for patients on warfarin. As such, tools for the prediction of bleeding risk in patients taking DOACs are clearly wanting.

Various studies have been performed to determine if genetic polymorphisms could predict bleeding risk for patients on antithrombotic agents, including DOACs.³ These existing works have been predominantly focused on the pharmacodynamic and pharmacokinetic aspects of drug metabolism and how these pharmacogenetic factors are associated with clinical outcomes.^{4,5} In this issue of the *Annals*, Choi et al. adopted a novel genetic polymorphism approach to study bleeding in patients taking DOACs.⁶ The group of Korean investigators examined polymorphisms in genes encoding fibrinogen and 2 targeted representative variants of prothrombin and FX genes. Fibrinogen, prothrombin and FX are crucial clotting factors in the generation of fibrin clots. It is theoretically plausible that polymorphisms in these genes, especially fibrinogen genes, could contribute to differences in bleeding risk in this patient population.

In this study, patients treated with DOACs demonstrated a significant association between genetic polymorphisms in fibrinogen genes and bleeding. The study included 468 patients on DOACs, of which 50 had bleeding episodes (14 of which were major). Single nucleotide polymorphisms (SNPs) in the prothrombin (*F2* rs5896) and fibrinogen gamma chain (*FGG* rs1800792) genes were significantly associated with bleeding risk. While rs1800792 was not the strongest overall predictor in the model, it is the strongest

predictor among all fibrinogen gene SNPs. Applied to a scoring system, a significant and almost linear association with bleeding risk was found. Allelic and genotypic frequencies as well as Hardy-Weinberg Equilibrium estimates were provided for each single nucleotide polymorphism to justify how the authors arrived at their conclusions.

The association between bleeding risk and the genetic polymorphisms in prothrombin and fibrinogen genes refers to all DOACs in the study. One may argue the clinical usefulness of detecting these non-modifiable factors. However, if these findings are validated, the presence of these SNPs can help identify patients with higher bleeding risk to physicians for early review and closer follow-up. It would be interesting to compare the performance of this novel approach to the more established risk assessment models.

Another key function of applying a bleeding risk assessment score is to highlight to the prescribers of anticoagulants any potential modifiable factors amenable to intervention. This study identified 2 modifiable factors, namely, anaemia and overdosing of DOACs, both of which were strongly associated with bleeding. Overdosing of DOACs as a factor was given the highest weightage in the proposed risk score model and is probably most amenable to intervention. Inappropriate dosing and overdosing of DOACs have been well-reported to be associated with adverse outcomes in patients taking DOACs.⁷ Different types of DOACs are currently available and each DOAC has its own specific variations in dosing according to indications, creatinine function, age and concomitant drugs, to name a few. This has understandably created potential dosing problems and may put patients at risk of bleeding and/or thrombosis. Continuous education of prescribers as well as checks and prompts on the electronic prescribing system can mitigate the problem.

While it is logical that patients with coagulation factor deficiencies taking antithrombotic agents would be at higher bleeding risk, the mechanism of how carrying SNPs in fibrinogen and prothrombin genes contribute to

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heightened bleeding risk is less apparent. No functional assays or biological data have been reported on how the 2 SNPs detected in this study contribute to increased bleeding. Further mechanistic studies are needed to investigate the effects of these SNPs. Only Asian populations living in Korea were included in this study, thus reducing the generalisability of the results. As genetic variation and its effects could vary across race and ethnic groups, it should be applied with caution. Also, genetic polymorphism testing is not a routinely available test and there are many other confounders that are not considered in the risk scoring system.

Confirming the study findings in a broader population with other ethnic groups could lead to significant findings and methodologies that could be applied to stratify dosing for patients on DOACs. As we eagerly await more advancements in genetic polymorphism testing in the use of antithrombotic agents, and further confirmatory and validation of the findings in this study, let us not forget about getting the basics right—knowing DOACs and our patients well to minimise bleeding risk for our patients.

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