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Dabigatran enhances platelet reactivity and platelet thrombin receptor expression in patients with atrial fibrillation : comment

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We read with interest the article by Achilles et al. [1] in a recent issue of the Journal of Thrombosis and Haemostasis, in which the authors raised a concern regarding the safety of the oral direct thrombin inhibitor (ODTI) dabigatran. The authors aimed to investigate a potential mechanism involved in the increased risk of myocardial infarction (MI) observed in several trials of patients treated with dabigatran when they were compared head-to-head with patients treated with indirectly acting therapeutic anticoagulants. In this study, platelet reactivity and thrombin receptor expression were measured in 13 patients before and after planned initiation of dabigatran medication. In 'treatment-naive' patients, a first intake of dabigatran was found to increase thrombin receptor-activating peptide (TRAP)-induced platelet aggregation by enhancing thrombin receptor density on platelets, probably contributing to the increased risk of MI in this population. It is important to underline the fact that, although the association between dabigatran treatment and a higher risk of MI was controversial in the literature, and is considered to be slight, it is well documented today. In fact, a large meta-analysis of seven randomized controlled trials, including 30 514 patients, in which dabigatran was compared either with indirectly acting anticoagulants (warfarin or low molecular weight heparin) or with placebo showed a 33% relative increase in acute coronary events with dabigatran, corresponding to an absolute increase of 0.27% during a follow-up of up to 2 years [2]. These results were further confirmed by another meta-analysis of 11 randomized controlled trials comparing ODTIs with warfarin, in which data from 39 357 patients demonstrated that ODTIs were associated with a 41% relative increased risk of MI, corresponding to an absolute increase of 0.53% (odds ratio 1.35; 95% confidence interval 1.10–1.66; P = 0.005) [3].

However, the mechanisms involved in this association remain poorly understood. It has been speculated that the combination of tissue factor and contact activation-generated thrombin might overwhelm the local concentrations of dabigatran in some cases [4]. Furthermore, platelet reactivity as a contributor to platelet-mediated events in patients treated with dabigatran was previously investigated, with conflicting results. Some groups found that dabigatran was able to inhibit thrombin-induced platelet aggregation [5,6], with no inhibitory effect on other platelet-stimulating agents [6,7]. In contrast, our group, which aimed to explore differential effects of oral anticoagulants on platelet aggregation in patients treated with oral anticoagulants for atrial fibrillation, documented that patients treated with dabigatran exilate 150 mg twice daily for at least 1 month in the absence of concomitant antiplatelet agents showed significantly higher levels of platelet reactivity induced by TRAP than healthy volunteers [8], suggesting that this high platelet reactivity may contribute to an increased risk of platelet-mediated events, as thrombin is known to be the major pathway for platelet activation in vivo. Consistent with the results of Achilles et al. [1] and of our group [8], an interesting in vitro study characterized the thrombin-bound

dabigatran effect on protease activated receptor-1 (PAR-1) expression and signaling, and showed that catalytically inactive thrombin was able to modulate PAR-1 function by increasing PAR-1 surface expression [9]. It is of note that this effect was only observed for dabigatran concentrations 20-fold higher than therapeutic concentrations [9].

Last, but not least, a recent and important study by Petzold et al. [10] shed light on this topic by providing a clear demonstration that ODTIs modulate platelet adhesion and thrombus formation via a glycoprotein (GP) Ib α -mediated mechanism. In this study, the platelet function of 95 patients receiving either dabigatran or dose-adapted vitamin K antagonists were analyzed by the use of whole blood aggregometry. Ristocetin induced aggregation was increased in patients treated with dabigatran, whereas aggregation induced by other agonists was only marginally affected [10]. Under flow conditions, platelet adhesion to collagen and aggregate formation on von Willebrand factor were consistently increased in dabigatran-treated blood [10]. These results were confirmed in a carotid and wire injury model of mice. Finally, inhibition of GPIb α -thrombin interactions abrogated the effects of ODTIs on thrombus formation, demonstrating the crucial role of GPIb α in this mechanism [10].

In light of these studies, it seems that dabigatran might have pleiotropic effects beyond its target that could explain some of its clinical results, and that should be further explored together with their clinical relevance.

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