

Reply

Reply to the letter to the editor "Assessing the role of platelet activation in bevacizumab associated thrombosis"

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We appreciate the recent comments of Amirkhosravi and colleagues on our study [1, 2]. In response, we would like to take the opportunity to clarify some points in order to prevent further misunderstandings.

Our study was a clinical investigation aimed at understanding what happens in patients treated with bevacizumab. The research hypothesis was not only based on the work of Meyer et al. [3] but also on the experimental work of other groups such as Selheim et al. [4], who have described other VEGF-related mechanisms of platelet activation in the absence of heparin.

Amirkhosravi et al. argue that the PFA instrument has not been sufficiently evaluated. In our hands, however, the PFA-100 instrument has been useful in various in vivo studies. Thus, we have observed a shortened closure time, i.e. platelet activation, in the morning after wine drinking [5], after second hand smoke exposure [6], after particulate matter inhalation [7] and at high altitude [8], while a closure time prolongation i.e. platelet inhibition, has been seen after the infusion of propofol [9] or radiographic contrast media [10]. We have to accept that bevacizumab had neither of these effects.

We are of the impression that we have elucidated on the limitations of our study in great detail. In particular, we clearly stated in the discussion (on page 4 of the paper) that "This does not exclude some other form of platelet activation as described for other pathways such as ... immunocomplex-induced activation" and this statement is already in line with the recent comment of Amirkhosravi et al. [1, 2].

According to the experimental work of Meyer et al. unfractionated heparin is an essential component of the platelet activation via the Fc gamma receptor by bevacizumab containing immunocomplexes [3]. Amirkhosravi et al. have confirmed this in their comment [1]. However, patients treated with bevacizumab do not receive unfractionated heparin on a regular basis. Therefore, it remains unclear whether their elegantly demonstrated heparin-dependent pathomechanism can be relevant in clinical practice in the absence of heparin. Consequently, our conclusion that future research on the complications of bevacizumab should

also take other potential mechanisms into account – such as the interaction of bevacizumab with endothelial cell function or plasmatic coagulation – remains justified.

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