

## Editorial

# Regulation of Platelet Function by Statins

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**Received:** November 14, 2014; **Accepted:** November 15, 2014; **Published:** November 17, 2014

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Statins, among the most commonly prescribed drugs worldwide, are cholesterol-lowering agents used to manage and prevent cardiovascular and coronary heart diseases. Numerous studies have highlighted the fact that statins, besides their application in cardiovascular and coronary heart diseases as cholesterol-lowering agents, exhibit a wide range of pleiotropic effects, among these effect, their anti-platelet properties will be here discussed. Some of the statin effects in reducing cardiovascular events can be ascribed to their ability to prevent thrombus formation by exerting modulatory effects on profibrinolytic mechanisms, blood coagulation cascades and platelet functions. The first effects reported about reduced platelet activity by statin treatment documented decrease of the cholesterol content of the platelet membrane and decrease of the biosynthesis of thromboxane A<sub>2</sub>, however it might also be due to its inhibitory effect on Rho-GTPase family and on the activity of other signaling molecules, such as Erk2, NF-B, and Akt [1]. Statins can also decrease platelet activation by modulating the NO bioavailability [2] and rapidly reducing the CD36 and lectin-like ox-LDL receptor-1 [3], specific receptors for ox-LDL considered potent platelets agonists. Furthermore, statins inhibit the platelet-induced tissue factor expression by monocytes and macrophages [4], counteracting the pro-thrombotic complications of atherosclerosis. Indeed, statins, as agonists of PPAR- $\alpha$  and - $\gamma$  efficiently reduce platelet-mediated foam-cell generation via inhibition of matrix metalloproteinase 9 secretion [5]. Moreover, statins inhibit expression and release of collagen-induced platelet CD40 ligand, whose high levels have been found in atherothrombosis and in the major adverse cardiovascular events. Through this molecule, platelets can interact with endothelium and, simultaneously activate CD40-bearing immune cells and platelets themselves [6]. Statins and fibrates, by activating the PPAR system in platelets, may dampen the release of proinflammatory/prothrombotic mediators and aggregation [7]. Serebruanu et al [8] suggested for the first time that statins can also specifically target platelet thrombin protease-activated receptor-1, thereby modulating anti-platelet and antithrombotic properties. Furthermore, several

statins exhibited inhibitory effect of the platelet-activating factor and, can also exert their anti-platelet effects by reducing platelet adhesion to the vessel wall or the endocardium [9]. Beyond platelets, statins may inhibit plasmatic pathways of thrombus formation and affect fibrinolytic pathways. A first strong evidence of potential association between statins and reduced risk of thromboembolism has come from a case control study in postmenopausal women [10]. In this study, statin administration was associated with a slightly lower risk of venous thrombosis. Other case control studies [11] have also demonstrated reduction in the risk of venous thrombosis ranging from 26 to 58%. On the other hand, two additional observational studies suggested no association between statin use and the risk of venous thrombosis [12,13]. However, the recent randomized double blind Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study demonstrated that rosuvastatin significantly reduced the incidence of symptomatic venous thromboembolism in apparently healthy subjects without significant differences between treatment groups in the rates of bleeding episodes [14]. In conclusion, these data are quite promising; however, it remains to be elucidated to what extent these pleiotropic properties account for a potentially beneficial statin therapy in the clinical setting. Of note, a large population-based cohort study, evaluating a range of clinical outcomes found to be positively or negatively associated with statins, failed to confirm a protective action of statins on the risk of venous thromboembolism [15]. In our opinion, this prospective study was characterized by more potential confounders, and a different cut-off of statistical significance used for the analysis might have underestimated the potential positive secondary effects of statins. To date, we believe that, one of the more promising applications of statins in human seems to be related to their anti-inflammatory effects, mediated by both direct, via modulation of the immune-response and indirect, via inhibition of platelet functions, mechanisms. This is supported by evidence that statins may exert anti-platelet effects by interfering with redox signaling via inhibition of platelet NADPH oxidase-derived ROS formation. Indeed, experimental and clinical studies provided evidence that intra-platelet ROS formation is implicated in the process of thrombosis [16]. Future research is required to address the questions of the optimal type, timing and dosage of statin therapy as well as whether there are problems associated with abrupt withdrawal and adverse effects associated with long term use.

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