Journal of Blood Disorders

Open Access

Austin Publishing Group

Editorial

Regulation of Platelet Function by Statins

Maurizio Bifulco[1,2*] and Anna Maria Malfitano[1,2*]
[1]Department of Medicine, University of Salerno Medical School, Italy
[2]Department of Pharmacy, University of Salerno, Italy

***Corresponding author:** Anna Maria Malfitano, Department of Medicine and Surgery, University of Salerno Medical School, Italy and Department of Pharmacy, University of Salerno, Italy, Email: amalfitano@unisa.it

Maurizio Bifulc, Department of Medicine and Surgery, University of Salerno Medical School, Italy and Department of Pharmacy, University of Salerno, Italy, Email: mbifulco@unisa.it

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

Editorial

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 A2, 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-α and –γ 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]. Serebruany 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 statical 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.

References

1. Mitsios JV, Papathanasiou AI, Goudevenos JA, Tselepis AD. The antiplatelet and antithrombotic actions of statins. Curr Pharm Des. 2010; 16: 3808-3814.
2. Lee YM, Chen WF, Chou DS, Jayakumar T, Hou SY, Lee JJ, et al. Cyclic nucleotides and mitogen-activated protein kinases: regulation of simvastatin in platelet activation. J Biomed Sci. 2010; 17: 45.
3. Puccetti L, Sawamura T, Pasqui AL, Pastorelli M, Auteri A, Bruni F. Atorvastatin reduces platelet-oxidized-LDL receptor expression in hypercholesterolaemic patients. Eur J Clin Invest. 2005; 35: 47-51.
4. Puccetti L, Bruni F, Bova G, Cercignani M, Pompella G, Auteri A, et al. Role of platelets in tissue factor expression by monocytes in normal and

Citation: Bifulco M and Malfitano AM. Regulation of Platelet Function by Statins. J Blood Disord. 2014;1(4): 2.

hypercholesterolemic subjects. In vitro effect of cerivastatin. Int J Clin Lab Res. 2000; 30: 147-156.

5. Daub K, Lindemann S, Langer H, Seizer P, Stellos K, Siegel-Axel D, et al. The evil in atherosclerosis: adherent platelets induce foam cell formation. Semin Thromb Hemost. 2007; 33: 173-178.

6. Zhang S, Rahman M, Zhang S, Qi Z, Thorlacius H. Simvastatin antagonizes CD40L secretion, CXC chemokine formation, and pulmonary infiltration of neutrophils in abdominal sepsis. J Leukoc Biol. 2011; 89: 735-742.

7. Phipps RP, Blumberg N. Statin islands and PPAR ligands in platelets. Arterioscler Thromb Vasc Biol. 2009; 29: 620-621.

8. Serebruany VL, Miller M, Pokov AN, Malinin AI, Lowry DR, Tanguay JF, et al. Effect of statins on platelet PAR-1 thrombin receptor in patients with the metabolic syndrome (from the PAR-1 inhibition by statins [PARIS] study). Am J Cardiol. 2006; 97: 1332-1336.

9. Molins B, Pena E, Padro T, Casani L, Mendieta C, Badimon L. Glucose-regulated protein 78 and platelet deposition: effect of rosuvastatin. Arterioscler Thromb Vasc Biol. 2010; 30: 1246-1252.

10. Doggen CJ, Lemaitre RN, Smith NL, Heckbert SR, Psaty BM. HMG CoA reductase inhibitors and the risk of venous thrombosis among postmenopausal women. J Thromb Haemost. 2004; 2: 700-701.

11. Sorensen HT, Horvath-Puho E, Sogaard KK, Christensen S, Johnsen SP, Thomsen RW, et al. Arterial cardiovascular events, statins, low-dose aspirin and subsequent risk of venous thromboembolism: a populationbased case-control study. J Thromb Haemost. 2009; 7: 521–528.

12. Yang CC, Jick SS, Jick H. Statins and the risk of idiopathic venous thromboembolism. Br J Clin Pharmacol. 2002; 53: 101-105.

13. Smeeth L, Douglas I, Hall AJ, Hubbard R, Evans S. Effect of statins on a wide range of health outcomes: a cohort study validated by comparison with randomized trials. Br J Clin Pharmacol. 2009; 67: 99-109.

14. Glynn RJ, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. N Engl J Med. 2009; 360: 1851-1861.

15. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. BMJ. 2010; 340: c2197.

16. Violi F, Pignatelli P. Statins as regulators of redox signaling in platelets. Antioxid Redox Signal. 2014; 20: 1300-1312.

J Blood Disord - Volume 1 Issue 4 - 2014
ISSN 2379-8009 | www.austinpublishinggroup.com

Citation: Bifulco M and Malfitano AM. Regulation of Platelet Function by Statins. J Blood Disord. 2014;1(4): 2.