Atorvastatin and its collateral effects on microparticles

Silvia Montoro-García1,2; Gregory Y. H. Lip1; Eduard Shantsila1

1Haemostasis Thrombosis and Vascular Biology Unit, University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; 2Department of Cardiology, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain

Microparticles (MPs) are vesicular fragments that bud off cells during either activation or apoptosis. MPs have been postulated to play an important role in thrombosis, in part because phosphatidylserine on MP surfaces can be a site for catalytic assembly of the prothrombinase complex (1). Additionally, MPs, particularly those released from monocytes represent a rich source of circulating tissue factor, and they also express other surface proteins involved in the process of coagulation (2). Indeed, MPs have been found to be increased in blood of patients with various thrombotic and inflammatory disorders, including acute coronary syndromes, sickle cell disease, diabetes mellitus, thrombotic thrombocytopenic purpura, vasculitis, antiphospholipid antibody syndrome (1, 3–6).

As MPs (at least at high concentrations) have been shown to be related to thrombotic and inflammatory diseases, the modulation of their production might have important therapeutic implications (7–9). In this respect, there is increasing clinical attention towards the potential of pharmacological agents to modulate both levels of circulating MPs and their expression of prothrombotic markers (10). Statins are widely used in clinical practice, being the cornerstone of the current management of atherosclerosis. The beneficial net effect of statins on the rate of cardiovascular complications has largely been related to their ability to improve lipid profile. However, statins also possess additional (i.e. pleiotropic) biological properties, which are likely to facilitate their clinical success.

In the context of numerous lipid-independent effects of statins, it was therefore natural to explore their impact on circulating MPs. However, statins have been reported to exert controversial effects on MP levels and activation markers. Whilst Tramontano et al. (11) have reported inhibition of release of endothelium-derived MPs in the presence of fluvastatin, Diamant et al. (12) found that simvastatin increased the release of endothelium-derived MPs. Of note, both studies were restricted in vitro nature of the experiments and further research in the field was awaited. Nonetheless, a few studies reported the effects of lipid-lowering therapy in the expression of MPs markers in vivo (13).

Peripheral arterial occlusive disease is a clinical condition linked to excessive platelet activation, thrombin generation and endothelial dysfunction (14). Platelets are pivotal mediators of various endothelial, thrombotic and inflammatory responses and therefore are keys player in the initiation and progression of atherothrombosis (15). Platelet-derived MPs (PMPs) express on their surface several markers of platelet activation such as CD62P (P-selectin), apart from tissue factor (CD142), and the platelet-specific proteins, such as integrin CD61 (glycoprotein IIIa). Moreover, recently a cell-free form of CD36, a scavenger receptor associated with plaque instability, has been found not to be truly soluble but a constituent of MPs (16). This finding hints at the fact that several activation markers might be shed in the form of circulating MPs. This could have an important effect on thrombus propagation, related both to direct effects of MPs on platelet function and to their ability to facilitate thrombin generation by presenting tissue factor and serving as an assembly site for the prothrombinase complex.

In this issue of Thrombosis and Haemostasis, Mobarak et al. (17) carried out both in vivo and in vitro studies to explore the effects of atorvastatin on the expression of prothrombotic markers on PMPs and secondly, to analyse their possible effects of atorvastatin on the thrombin generation. These authors found that the expression of activation markers on PMPs and thrombin generation decreased with statin and aspirin treatment in patients with peripheral arterial occlusive disease, which again confirms the benefits of statins in prothrombotic diseases (18). Herein, the authors proposed PMPs as possible contributors of thrombin activation since the statin-related reduction in PMP expression of tissue factor and P-selectin diminished thrombin formation. Of note, these effects were not seen in placebo group, thus providing the evidence that the findings are truly attributable to the pleiotropic effects of atorvastatin. In order to provide further support of this novel concept, the authors showed that thrombotic effects of MPs could be blocked by the addition of anti-tissue factor and anti-phosphatidylserine polyclonal antibodies, thus confirming the capacity of MPs to reinforce thrombin generation. However, the present manuscript does not provide the proof per se of the direct implication (or causality) of PMPs in thrombin generation nor evidence of pathophysiological implication(s) of these processes in disease progression. Nonetheless, these findings again confirm the possibility that statins exert their beneficial effects acting beyond lipoprotein pathways.

As part of these additional effects, the authors speculate that the lower antigenic expression on PMPs in patients treated with statins might reflect a reduced platelet activation which could also contribute subsequently to reduced thrombin generation, as previously shown (19). Moreover, an additional point seems to be worth emphasising. The main procoagulant activity provided by MPs is usually attributable to the negatively charged surface (20). However, MP phosphatidylserine density has not
been found to be influenced by atorvastatin treatment (17). These observations support previous reports indicating significant phosphatidylserine-independent thrombogenicity of MPs (21). Thus, this study does not exclude the implication of PMPs in thrombin generation and therefore encourages the development of further in vivo and in vitro studies with special focus on inhibition of procoagulant MPs generation and their respective antigenic levels. Clearly, there is more to learn.

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Conflict of interest
None declared.

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