

# Stay Tuned on Statins: The New Panacea?

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Statins are widely used lipid-lowering drugs for the secondary prevention of cardiovascular disease. The HOPE-3 trial from 2016 even demonstrated a beneficial effect from a combination therapy of rosuvastatin, candesartan, and hydrochlorothiazide in the primary prevention of events.<sup>1</sup> Besides the widespread use of statins for cardiovascular risk management, there is increasing interest in their use in other diseases, including hematologic disorders. Endothelial cells play the role of the common denominator for the beneficial effects of statins in this perspective. Three recent articles in top journals have shown hematological clinical benefits of statins beyond lipid lowering.<sup>2-4</sup>

## Statins in allogeneic stem-cell transplantation

Endothelial complications after allogeneic stem-cell transplantation are major determinants of adverse outcomes, including thrombotic microangiopathy, veno-occlusive disease, acute graft-versus-host disease, and death. Recently, polymorphisms in the *CD40L* and thrombomodulin (*THBD*) genes have been found to be associated with an increased risk of transplant-associated thrombotic microangiopathy, overall nonrelapse mortality and nonrelapse mortality after acute graft-versus-host disease.<sup>2</sup> Both *CD40L* and *THBD* single nucleotide polymorphisms (SNPs) predicted adverse overall survival and overall nonrelapse mortality. By contrast, statin-based endothelial prophylaxis completely abolished the influence of the high-risk *CD40L* and *THBD* SNPs. These data suggest that statins might have a protective effect on endothelial cells and could be used as prophylaxis for endothelial protection.

## Statins in immune thrombocytopenia

Corticosteroid-resistant immune thrombocytopenia (ITP) forms a therapeutic challenge for most patients and physicians. Several second-line options are available, including immunoglobulins, rituximab, splenectomy, thrombopoietin-receptor agonists and a number of immunosuppressive agents. Making the right choice for a specific patient requires a well-balanced decision-making process. Although aforementioned treatment options all have substantial favorable outcomes, they come with considerable risks of adverse events and high costs.

Recently, researchers have explored the effect of atorvastatin and N-acetyl-L-cysteine (NAC) in patients with corticosteroid-resistant ITP.<sup>3</sup> In a small pilot study, they treated 13 patients with a daily dose of 20 mg of atorvastatin and 400 mg of NAC 3 times daily. The overall response rate was 69%, with 23% complete remissions. The median time to response was 25 days (range, 7–51). Platelet counts rose significantly from 21 to  $61 \times 10^9/L$  in patients with a response. Whether the response was due to atorvastatin, to NAC or to both was not investigated. As an explanation, the authors showed that bone marrow endothelial progenitor cells (BM EPCs) were reduced and functionally impaired in patients with corticosteroid-resistant ITP as compared to controls and to corticosteroid-sensitive ITP. Even more so, they demonstrated that both the number and function of BM EPCs improved in patients with a clinical response to treatment with statins and NAC. The suggested mechanism behind this beneficial effect of atorvastatin is the downregulation of the p38/MAPK pathway and the concomitant activation of AKT signaling.

## Statins in venous thrombosis

The effect of statins has also been investigated in the setting of venous thrombosis. Recently, the randomized START trial showed that 1 month of rosuvastatin at a dose of 20 mg/day improves coagulation profiles in patients with a prior venous thromboembolism (VTE).<sup>4</sup> This was especially true for FVIII levels. This favors the notion that statin use is associated with a reduced risk of first and recurrent VTE.<sup>5</sup> The authors explain this effect by statin-induced modification of

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endothelial function that is already evident after 28 days of treatment, when endothelial dysfunction is associated with a procoagulant state.

### Mechanisms of action beyond lipid lowering

Statins target hepatocytes and inhibit HMG-CoA reductase, the enzyme that converts HMG-CoA into mevalonic acid, a cholesterol precursor. Many processes involving intracellular signaling pathways are influenced by the use of statins.<sup>6</sup> Their effect on endothelial function has been shown to be independent of the reduction of lipid levels. An important aspect is the transcriptional activation and upregulation of the endothelial nitric oxide synthase (*eNOS*) gene through PI3 kinase/AKT signaling. In addition, inhibition of ox-LDL-induced endothelin-1 expression and the biological function of angiotensin II and its receptor subtype 1, inhibition of inflammatory markers including ICAM-1, VCAM-1, E-selectin, CD40, and stimulation of pre-existing endothelial cells and mobilization of EPCs from bone marrow, altering the profile of expression of certain adhesion molecules, have been described.<sup>7</sup>

The driver effects and benefits of statins continue to reveal their wide-ranging potential.

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