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Statins Increase Risk of Hemorrhagic Stroke by Inhibition of the PAR-1 Receptor

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In the PAR-1 Inhibition by Statins (PARIS) study, statins in general, and atorvastatin in particular selectively inhibited platelet-G-coupled α -thrombin protease-associated (PAR-1) receptors [1]. The PARIS trial was a small, randomized open-label clinical study which enrolled 70 participants with metabolic syndrome, and not taking any antiplatelet medications. Patients were randomly assigned to therapy with 1 of the 6 statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin) or to a 'no statin' group. Platelet expression of intact (SPAN-12 antibody) and cleaved (WEDE-15) PAR-1 thrombin receptors was assessed at baseline, week 4, and week 6 by flow cytometry. At baseline, there was no difference in receptor expression. However, after 4 weeks of treatment all statins significantly inhibited (46–55%) the activated epitope of PAR-1 expression and after 6 weeks there remained inhibition despite a slight rebound (22–37%). There was also a delayed pattern of inhibition of the intact PAR-1 epitope. The PAR-1 receptor is a cell-bound protein that links platelet activation and thrombin formation regulating primary hemostasis and coagulation [2]. In basic research, statins down-regulate both endothelial [3, 4] and platelet [5] PAR-1 expression. The clinical implications of inhibition of PAR-1 provide a plausible mechanism for the pleiotropy of statins in reducing ischemic vascular events [6].

In general, statins are capable of affecting inflammatory, oxidative, and vascular responses, therefore exhibiting the potential to diminish atherothrombosis, which may be responsible in part for the impressive results seen in the clinical trials. However, triaging the clinical advantages of such pleiotropy (if any) needs more primary evidence [7]. Based mostly on in vitro data and animal experiments, statins have been shown to improve vascular relaxation, promote new vessel formation, and stabilize unstable plaques [8]. They reduce glomerular injury, renal disease progression, insulin resistance, and bone resorption [9]. Other beneficial properties are protecting the vascular endothelium; decreasing low-density lipoprotein oxidation and inflammation; stabilizing atherosclerotic plaques and perhaps promoting regression; modulating smooth muscle growth; stimulating fibrinolysis, and improving blood viscosity and flow [10, 11].

It has been reported that hypercholesterolemia is directly related to the enhanced cell superoxide anion production including oxygen radical release from human platelets [12]. The contribution of the nitric oxide metabolism to the antiplatelet properties of statins has been suggested from a study of hypercholesterolemic patients treated with atorvastatin [13]. Statins may directly influence the platelet membrane lipid composition resulting in a decreased function. They are known to reduce CD40-CD40-ligand-dependent platelet-endothelial interactions inhibiting platelet-induced COX-2 expression in human endothelial cells [14].

Specifically, in the prospective Interaction of Atorvastatin and Clopidogrel Study (INTERACTION), point-of-care platelet activity testing was performed at baseline prior to the administration of clopidogrel in patients on various statins, as well as no statins, who were undergoing stent placement [15].

The INTERACTION study was aimed to investigate a previously raised concern that the antiplatelet effects of clopidogrel are inhibited by atorvastatin in patients undergoing coronary stenting. For this purpose, 75 patients undergoing coronary artery stenting were enrolled considering the P3A4-dependent and P3A4-independent mechanism of statin metabolism in the liver. The general finding of this trial was that statins in general, and atorvastatin in particular, do not affect the ability of clopidogrel to inhibit platelet function in patients undergoing coronary stenting. The conclusions produced by the INTERACTION study generated an extensive discussion.

With regard to the metabolic pathways of clopidogrel, the drug is extensively metabolized by the liver. Its main circulating metabolite is the carboxylic acid derivative, which has no apparent effects on platelet function. Results of in vitro studies in human liver microsomes and recombinant cytochromes P450 have shown that several cytochromes are involved in the oxidative metabolism of clopidogrel [16]. The cytochrome P450 enzyme system plays an important part in the metabolism of the statins, leading to clinically relevant interactions with other agents, particularly cyclosporin, erythromycin, itraconazole, ketoconazole and HIV protease inhibitors, which are also metabolized by this enzyme pathway [17, 18]. The findings of the INTERACTION and PARIS studies suggest that atorvastatin interference with clopidogrel metabolism is overridden by its internal antiplatelet activity. All these data contribute to the formulation of the hypothesis that statins increase the risk of hemorrhagic stroke. In numerous large-scale randomized trials and their meta-analyses [19, 20], patients assigned to statins had significantly decreased risks of myocardial infarction, stroke, and cardiovascular death. In the countries in which these trials were conducted, ischemic stroke accounts for about 80% and hemorrhagic stroke accounts for about 20% of total strokes. Two subgroup analyses from randomized trials also contribute to the formulation of the hypothesis that statins increase the risk of hemorrhagic stroke. Specifically, in the Stroke Prevention by Aggressive Reduction in Cholesterol

Levels (SPARCL) trial [21], patients were randomized to high-dose atorvastatin (80 mg) or placebo. In subgroup analyses of hemorrhagic stroke, although based on small numbers, the rates were 2.3% in the high-dose atorvastatin arm and 1.4% in the placebo arm (hazard ratio 1.66; $p = 0.02$). Further, in subgroup analyses from a meta-analysis, patients assigned at random to pravastatin also appeared to have an increased risk of hemorrhagic stroke [22, 23].

There is a controversy regarding the relationship between low levels of low-density lipoprotein and risks for hemorrhagic stroke. Several authors intended to consider a decrease in plasma low-density lipoproteins (induced or noninduced by statins) as an independent risk factor for hemorrhagic stroke [24], while the analysis of 52,421 patients enrolled in the Japan Lipid Intervention Trial has failed to demonstrate such an adverse association [25]. Also, there is no evidence that statins enhance other bleeding risks than intracranial hemorrhages.

Therefore, the subgroup analyses of the SPARCL study are useful to formulate but not test the hypothesis [26] that the trial findings may be related, at least in part, to the lack of uniform platelet activation among poststroke patients [27]. Moreover, endothelial cell mRNA levels of PAR-1 are significantly increased after stroke, but can be completely abolished by atorvastatin [28]. The most plausible alternative explanation for these observations is the play of chance because of the relatively small number of hemorrhagic strokes and the fact that the observations are based on subgroup analyses [27].

An additional intriguing but plausible alternative explanation derives from the fact that statins reduce ischemic stroke by about 25% [19, 20]. Such a circumstance might, at least in theory, lead to a spurious observed increase in hemorrhagic stroke. For example, in countries where 80% of total strokes are ischemic, the relative proportion of ischemic to hemorrhagic strokes is 4:1. Since statins prevent 1 in 4 ischemic strokes, the relative proportion of ischemic to hemorrhagic strokes will decrease from 4:1 to 3:1. In such a circumstance, there would be a relative increase in hemorrhagic stroke from 20 to 25% of total strokes, but statins *per se* would not cause an absolute increase in hemorrhagic stroke. On the other hand, if PAR-1 inhibition by statins does indeed cause increased bleeding, including an absolute increase in the risk of hemorrhagic stroke, then potential clinical implications might apply to patients receiving antiplatelet agents, especially dual therapy such as aspirin and clopidogrel. Indirect evidence to support this possibility derives from the INTERACTION study [15], in which the addition of statins to clopidogrel and aspirin yielded higher antiplatelet potency in patients undergoing coronary stenting. The hypothesis that statins increase the risk of hemorrhagic stroke by inhibition of the PAR-1 receptor, while plausible, requires detailed analysis in the large poststroke registry, with further direct testing in randomized trials designed a priori to do so.

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