

## Commentary: Effects of lipoprotein apheresis on PCSK9 levels

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### Article Info

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### PCSK9 protein

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) is a serine protease produced mainly in the liver and circulating in the blood. It is in part bound to LDL particles. It was first described in 2003 in patients suffering from hypercholesterolemia<sup>1</sup>. PCSK9 promotes the intracellular degradation of LDL receptors and in this way increases LDL-cholesterol (LDL-C) concentrations. Moreover, a PCSK9/apolipoprotein B (apoB) interaction resulted in increased production of apoB, possibly through the inhibition of intracellular apoB degradation via the autophagosome/lysosome pathway<sup>2, 3</sup>. Less atherosclerosis development was seen in mice not expressing PCSK9<sup>3</sup>. Additional effects of PCSK9 on the VLDL receptors, the epithelial cholesterol transporter (NPC1L1) and other targets have been described<sup>4</sup>.

### Role of PCSK9 levels for cardiovascular risk

It has been reported that serum PCSK9 levels were significantly higher in FH patients than in controls, and were correlated with serum LDL-C levels.

Moreover, serum PCSK9 levels were positively correlated with serum levels of lipoprotein(a) (Lp(a)); small, dense LDL; and oxidized LDL in patients with coronary artery disease<sup>5</sup>.

Compared with those of patients with coronary single-vessel or double-vessel disease, PCSK9 levels were significantly elevated in patients with multi-vessel disease<sup>6</sup>.

A meta-analysis summarizing the results of 32 studies provides evidence that the variant PCSK9 rs505151 allele confers increased triglyceride and LDL-C levels on the carrier, as well as increased cardiovascular risk<sup>7</sup>. Conversely, the variant rs11591147 allele protects against cardio-vascular disease susceptibility and is associated with lower total cholesterol and LDL-C levels<sup>7</sup>.

In the last years, monoclonal antibodies binding to PCSK9 have been introduced into medical practice<sup>8</sup>. These drugs (evolocumab, alirocumab) showed an effective reduction of LDL-C and of Lp(a) levels. Such an effect can also be acutely obtained by using an extracorporeal lipoprotein apheresis (LA) procedure<sup>9</sup>. This commentary focuses on the role of LA therapy on PCSK9 levels in dyslipidemic patients.

## The multi-center study measuring the effects of LA on PCSK9 concentrations

We performed a multicenter (US (4 centers) and Germany (2 centers)) observational study which did not have any influence on the therapeutic regimen in the patients<sup>10</sup>. The study was sponsored by Novartis Pharma Services AG, Basel (Switzerland).

Total serum PCSK9 levels were measured by an electrochemiluminescence immunoassay in 40 patients on a stable lipid-lowering drug therapy before and immediately after 3 LA sessions. The intervals between apheresis sessions were between 8 and 34 days (mean 15.8 days). Blood was also drawn on days between the LA procedures. Data were compared with two control groups: 1. Ten patients with an indication for LA who did not yet start the extracorporeal therapy, 2. 65 healthy people.

Patients with the lipid disorder being treated with LA or having at least the indication for LA showed higher serum PCSK9 concentrations than the healthy people. Apheresis sessions acutely reduced the PCSK9 level in the mean by 51 %, but on the next day, the pre-apheresis levels were reached again. In contrast, LDL-C concentrations returned to their pre-apheresis values much later (after 7 days). Triglycerides and HDL-cholesterol (HDL-C) were also acutely decreased but reached the pre-apheresis levels on the next day. No correlations between serum PCSK9 levels and lipid levels and between acute reduction rates of PCSK9 and of lipids were detected. Lp(a) levels have not been measured.

It could be shown that different LA methods had differing acute effects on PCSK9 concentrations: the highest reduction was seen with the heparin-induced extracorporeal LDL precipitation (HELP) method, the least reduction with the direct adsorption of lipids (DALI) system.

## Other studies looking at the influence of LA on PCSK9 levels

The first paper reporting the influence of LA on PCSK9 levels was published in 2013<sup>11</sup>.

In six patients with severe familial hypercholesterolemia (FH; according to Simone Broome's criteria) and a history of coronary artery disease (not taking any lipid-lowering drugs) treated with dextran-sulfate LA system the authors showed an acute 52 % reduction of plasma PCSK9 (on three consecutive treatment cycles with an interval of 2 weeks). Both LDL-bound PCSK9 and apoB-free PCSK9 were removed. PCSK9 bound to LDL was exclusively in the 62kDa monomeric active form, whereas the apoB-free fraction showed different molecular forms of PCSK9, mainly the smaller 55kDa band product of furin cleavage and also low levels of higher molecular weight bands

likely due to homo- and hetero-polymerization. There was a significant correlation between LDL and PCSK9 decreases.

Another publication appeared in 2015 and described data obtained in 18 patients with FH, including 7 homozygotes and 11 heterozygotes.<sup>12</sup> When using a dextran-sulfate LA method the mature and furin-cleaved PCSK9 fractions were, respectively, reduced by 56% and 55% in FH homozygotes by a single LA procedure<sup>12</sup>. The two forms of PCSK9 were decreased by 46% and 48% by a single LA procedure in FH heterozygotes. There was a high degree of correlation between the reduction of plasma LDL-C and the reduction of mature PCSK9 in both FH homozygotes and heterozygotes. In addition, there was a significant correlation between the reduction in plasma Lp(a) and that in mature PCSK9 in FH heterozygotes. The authors performed in 5 FH heterozygotes a crossover study comparing the treatment efficacy between dextran-sulfate and double membrane (DM) LA columns. With the DM method, the two PCSK9 forms were decreased by 56% and 48% by a single LA treatment.

## The significance of the effect of LA on PCSK9 levels

The elimination of the PCSK9 protein from the blood can be regarded as an additional pleiotropic effect of the LA therapy to prevent further cardiovascular events. All three studies showed a similar acute reduction of PCSK9 levels by LA sessions of about 50 %. The loss of LDL-bound PCSK9 is due to the removal of LDL, whereas the loss of LDL-free PCSK9 is likely due to the presence of interacting partner proteins.

Our American-German study differs from the other two in several aspects: 1. The number of participating patients was much higher; 2. PCSK9 levels in the apheresis patients were compared with healthy controls, 3. Several LA methods have been compared – the interpretation of these findings is not optimal due to limited patient numbers with certain LA methods, 4. Subfractions of PCSK9 have not been measured – it is known that furin-cleaved PCSK9 has less activity to regulate LDL receptors and serum LDL-C, 5. The rebound of PCSK9 levels has been followed – demonstrating that pre-apheresis levels have been reached on the day following the LA sessions.

The acute reduction of PCSK9 levels contributes to the lipid-lowering effect of LA. But taking the time course of this decrease into account, it becomes clear that it plays only a minor role. The rebound of LDL-C following LA sessions takes several days. Lipid-lowering drugs may have an effect on this LDL-C rebound. A combined application of LA and PCSK9 inhibitors appears to be a promising therapeutic approach in patients with extremely high LDL-C concentrations. When PCSK9 inhibitors are administered, PCSK9 levels remain low for several weeks.

Taking into account that PCSK9 levels reflect the atherogenic potential of this protein it can be suggested to measure these levels in high-risk patients in order to better characterize the atherogenic risk.

### PCSK9 as a drug target

Evidently, the effect of LA therapy on PCSK9 levels is of a limited value. But PCSK9 remains in the focus of new drug developments. PCSK9-targeted therapies include monoclonal antibodies (which are already used in the daily practice), adnectins, and mimetic peptides (which block the interaction between PCSK9 and the LDL receptors), CRISPR/Cas9 genome editing technology, antisense oligonucleotides (ASOs), siRNAs and small molecules (which inhibit PCSK9 expression), and drugs that interfere with PCSK9 secretion from the endothelial reticulum<sup>8,13,14</sup>.

### Conflicts of Interest

Honoraria from Aegerion, Amgen, Chiesi, Sanofi, Kaneka, Diamed, Fresenius Medical Care

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