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Statins and Lp(a) – the plot thickens

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In combination with a healthy lifestyle adoption promoted through an increasing awareness of its importance in healthy living, statins (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors) have contributed to the improved national trend seen in the prevalence of elevated levels of low-density lipoprotein cholesterol (LDL-C) [1]. In contrast to their well-established reducing effect on LDL-C levels, there has been a great deal of uncertainty to what extent statins impact lipoprotein(a) [Lp(a)] levels. At first glance this might seem contradictory in view of the structural similarity of the Lp(a) lipid core to LDL [cholesterol-rich lipid core firmly attached to apolipoprotein (apo) B-100]. However, the LDL receptor binding site in apoB is located close to the disulfide bond linking apoB and apo(a) in Lp(a) [2]. Given the large molecular size of apo(a) as well as its high carbohydrate content, the possibility of a steric configuration that impact access of Lp(a)-apoB for the LDL receptor seems possible. The paper by Yahya et al. in this issue of *Atherosclerosis* provides novel perspectives on this long-term puzzle [3].

Since their initial marketing in the 1980s, statins have become the most widely used therapy for hypercholesterolemia. In one of the first Lp(a) studies in this field, Kostner et al. reported that lovastatin dose dependently increased Lp(a) levels by ~33% [4]. The findings provided an initial indication that Lp(a), regardless of its structural similarity to LDL, maybe cleared from plasma via a different pathway, and further, that statins may impact Lp(a) metabolism independent of its effect on LDL receptor. Subsequent studies, however, produced mixed results ranging from no effect to significant increases in Lp(a) levels with statins [5–7], raising concerns about the robustness of findings. Further, a relatively large study in subjects with heterozygous familial hypercholesterolemia reported a reduction in Lp(a) levels using either atorvastatin or simvastatin [8]. Some factors contributing to difficulties to firmly establish the impact of statins on Lp(a) include variability of assays used and the extensive apo(a) size heterogeneity impacting levels, and in some cases, making smaller size studies challenging to interpret.

In recent years, a number of large scale studies on Lp(a) and its cardiovascular risk properties have been published making it possible to examine this issue in more detail. Several reviews and meta-analyses indicate an overall increase in Lp(a) levels during statin

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therapy, although the findings are not universally similar with no changes observed in some studies [9–11]. Furthermore, in many cases, there is a lack of consideration of Lp(a) genetic regulators, including the *LPA* gene size polymorphism and/or common single nucleotide polymorphisms (SNPs).

In this context, the study by Yahya et al. [3] offers opportunities for additional insights into the effect of statins on Lp(a) level by focusing on its major genetic regulator—the apo(a) size polymorphism. The authors compared subjects that initiated statin therapy versus subjects on stable therapy. Albeit based on a small group of hypercholesterolemic individuals, the authors showed that statins significantly increased Lp(a) levels in carriers of a small size apo(a) defined as ≤22K4 repeats (low molecular weight phenotype, LMW) initiating statin therapy. In this group, Lp(a) levels rose from 66.4 (IQR 23.5–148.3) to 97.4 (IQR 24.9–160.4) mg/dL (P=0.026). No significant changes were seen either in the stably treated group or among subjects initiating therapy who were non-carriers of a small size apo(a), i.e. having a high molecular weight phenotype (HMW). While a quantitative difference in Lp(a) increase during statin therapy between LMW and HMW carriers was reported in an earlier study by Klausen et al. [12], the present study suggests a qualitative difference.

The analytical approach used, SDS gel electrophoresis followed by immunoblotting, enabled determination of apo(a) protein size produced from each *LPA* allele, as opposed to other techniques generating a sum of the two *LPA* allele sizes. Reflecting the high-risk nature of the cohort, the prevalence of small apo(a) sizes (≤22K4 repeats) was higher (~35%) compared to those in the general population (~25%), facilitating a greater analytical power for between group difference. The authors further tested the relationship of statin-induced changes in Lp(a) levels with two common *LPA* SNPs present in their cohort (rs10455872 and rs41272110) and changes in LDL-C levels and found no interactions. Given the limited sample size, these observations should be interpreted with caution and need to be replicated in large-scale studies.

Mechanisms underlying the observed selective increase in Lp(a) levels during statin therapy in carriers of a small apo(a) are unclear and require further mechanistic studies. One hypothesis is that an overall increased awareness of the patients initiating stain therapy regarding heart healthy lifestyle may contribute. As mentioned by the authors, a decrease in the dietary saturated fat intake as part of healthy lifestyle may play a role. Indeed a reduction of saturated fat intake was associated with an increase in Lp(a) levels, whereas its addition was associated with a decrease in Lp(a) levels [13, 14]. Interestingly, studies have observed ethnic/racial differences in the response of Lp(a) levels, with greater changes in Blacks versus Whites, to replacement of dietary saturated fat with other macronutrients [15]. In this regard, it is worth to note that the patients in the study by Yahya et al. [3], were primarily of Caucasian origin, and that any statin effects on Lp(a) levels need to be tested across various ethnicity/race groups, including Blacks with the highest level of Lp(a).

In this context, it is interesting to draw parallels to findings regarding proprotein convertase subtilisin/kexin type 9 (PCSK9) and Lp(a) (Figure 1). While both PCSK9 and statins reduce LDL cholesterol levels through upregulation of LDL receptors, their effect on Lp(a) is vastly

different. One could postulate that while Lp(a) may perhaps have lower affinity for the LDL receptor than LDL, a reduced level of competition between Lp(a) and LDL as LDL-C levels decrease might increase the potential for receptor-mediated clearance of Lp(a) [16, 17]. However, this does not seem to fit with a statin-mediated increase in Lp(a). Given the well-documented and strong regulatory impact of apo(a) production on Lp(a) levels, a focus on apo(a) synthesis would seem appropriate. In their recent meta-analysis, Tsimikas et al. [11] included such a focus and reported that cell culture experiments using HepG2 cells resulted in a higher *LPA* mRNA level in response to several statins. Notably, a reduction in Lp(a)-associated apo(a) production was found during treatment with PCSK9 inhibitors [18], in keeping with the apparent divergent effect of these two LDL-C reducing agents on Lp(a).

The current study findings also add to the discussion whether Lp(a) levels should be measured before and after initiation of statin therapy and illustrate the need to evaluate variability in Lp(a)-increasing potential of various statin treatments as well as taking apo(a) properties into account. In this regard, identification of carriers of small apo(a) sizes (≤22K4 repeats) among statin users may help alleviate the residual risk through re-evaluation of treatment strategies and/or alternative approaches.

The role of statin-induced Lp(a) increase in residual CVD risk among statin-treated patients remains unclear and carefully designed future studies are required to address these uncertainties. The role of Lp(a) cholesterol levels versus LDL-C also deserves attention. While statins reduce LDL-C, an increase in Lp(a) levels would suggest an increase in Lp(a) cholesterol as well, resulting in a change in the ratio of LDL-C/Lp(a)-cholesterol among statin-treated patients, as pointed out by Scanu and Hinman [19]. Such changes may complicate the interpretation of what is commonly perceived as LDL-C (i.e. a combination of LDL-C and Lp(a) cholesterol) by both patients and practitioners monitoring statin therapy. Importantly, there is still a significant need for additional lipid-lowering therapy as recently noted in the American College of Cardiology/American Heart Association guideline of the presence of ~56 million adult Americans (40–75 years) eligible to receive statins [20] and a better understanding of the impact of statins on Lp(a) level is therefore of significant interest. Such studies might also open new opportunities to better understand Lp(a) metabolic properties.

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Abbreviations:

Apo(a)	apolipoprotein(a)
Lp(a)	lipoprotein(a)
LDL-C	low-density lipoprotein cholesterol
PCSK9i	proprotein convertase subtilisin/kexin type 9 inhibitor

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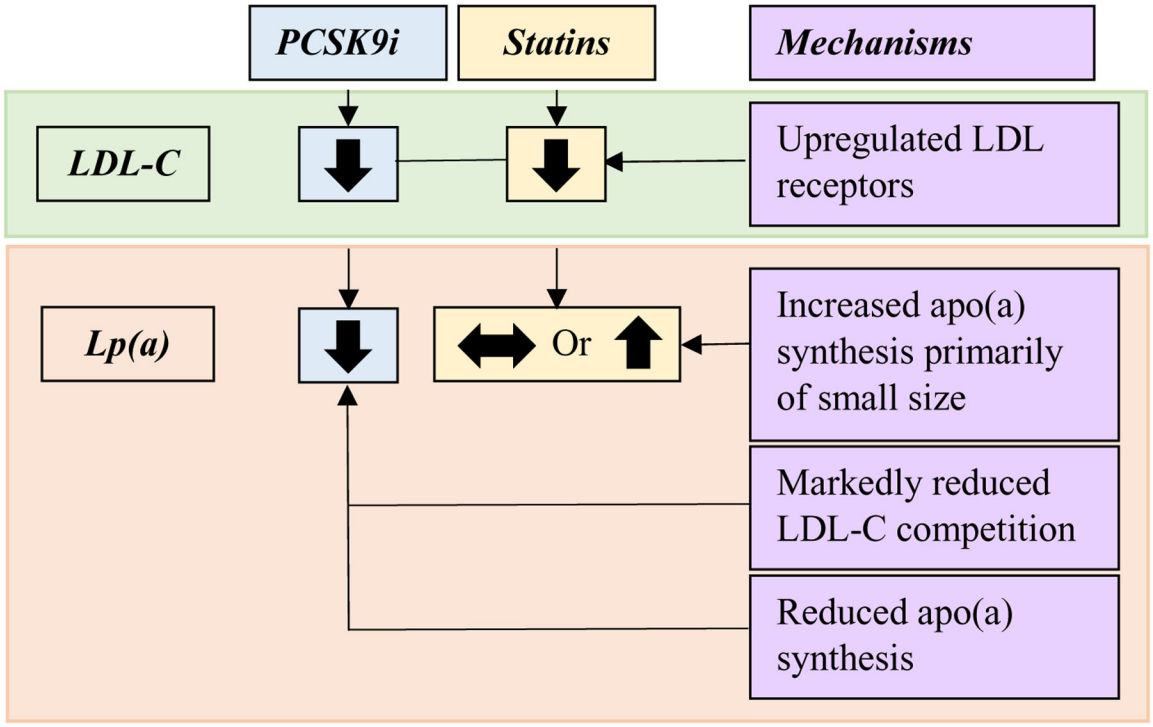

Figure 1. Statins versus PCSK9 inhibitors: Effects on LDL-C and Lp(a)

Both statins and PCSK9 inhibitors reduce LDL-C levels through mechanisms involving LDL receptor upregulation. In contrast, while PCSK9 inhibitors reduce Lp(a) levels, statins may increase Lp(a) levels. PCSK9-induced Lp(a) reduction maybe facilitated by markedly reduced competition from LDL-C for binding to LDL receptor and/or reduced production of apo(a) among patients taking PCSK9 inhibitors. On the other hand, increased production of apo(a), primarily of small sizes, may contribute to statin-induced Lp(a) elevation.