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# The complexity of lipoprotein (a) lowering by PCSK9 monoclonal antibodies

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## Abstract

Since 2012, clinical trials dedicated to proprotein convertase subtilisin kexin type 9 (PCSK9) inhibition with monoclonal antibodies (mAbs) have unambiguously demonstrated robust reductions not only in low-density lipoprotein (LDL) cholesterol (LDL-C) but also in lipoprotein (a) [Lp(a)] levels. The scientific literature published prior to those studies did not provide any evidence for a link between PCSK9 and Lp(a) metabolism. More recent investigations, either *in vitro* or *in vivo*, have attempted to unravel the mechanism(s) by which PCSK9 mAbs reduce circulating Lp(a) levels, with some showing a specific implication of the LDL receptor (LDLR) in Lp(a) clearance whereas others found no significant role for the LDLR in that process. This elusive pathway appears clearly distinct from that of the widely prescribed statins that also enhance LDLR function but do not lower circulating Lp(a) levels in humans. So how does PCSK9 inhibition with mAbs reduce Lp(a)? This still remains to be established.

**Key words:** lipoprotein (a), low-density lipoprotein (LDL) receptor, proprotein convertase subtilisin kexin type 9 (PCSK9), statins.

## INTRODUCTION

Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibition with monoclonal antibodies (mAbs), either as monotherapy or in combination with statins, recently emerged as a very promising strategy to lower circulating low-density lipoprotein (LDL) cholesterol (LDL-C) in patients with dyslipidaemia and cardiovascular disease (CVD) risk. PCSK9 is a natural circulating inhibitor of the LDL receptor (LDLR). It binds to the LDLR and after endocytosis targets the LDLR that would otherwise recycle back to the cell surface, towards lysosomal degradation. Like statins, anti-PCSK9 mAbs increase the abundance of the LDLR at the surface of hepatocytes and thereby promote an accelerated clearance of circulating LDL particles, thus lowering LDL-C levels.

But in contrast with statins, inhibiting PCSK9 with mAbs also promotes a reduction in lipoprotein (a) [Lp(a)] plasma levels. Lp(a) consists of a unique protein structurally similar

to plasminogen, apolipoprotein (a) [apo(a)], covalently tethered to the apolipoprotein B100 (apoB100) moiety of an LDL-like particle by a unique disulfide bond. Apo(a) is a high molecular mass glycoprotein (approximately 300–800 kDa), expressed exclusively by the liver. It contains 3 to more than 40 identical kringle IV<sub>2</sub> domains, and a strong inverse relationship exists between apo(a) isoform size and Lp(a) plasma concentration in humans.

Lp(a) is considered to be a highly atherogenic lipoprotein species, as elevated Lp(a) levels are independently and significantly associated with CVD. It is widely accepted that circulating Lp(a) concentrations are primarily controlled by synthesis rather than catabolism, but the molecular and cellular mechanisms governing apo(a)/Lp(a) hepatic production as well as Lp(a) catabolism are poorly understood. For instance, the potential physiological role for the LDLR in Lp(a) clearance remains extremely controversial. So how do anti-PCSK9 mAbs, unlike statins, reduce circulating Lp(a) levels in humans?

**Abbreviations:** apo(a), apolipoprotein (a); apoB, apolipoprotein B; apoB100, apolipoprotein B100; CVD, cardiovascular disease; FH, familial hypercholesterolaemia; Ho/He-FH, homozygote/heterozygote FH; LDL, low-density lipoprotein; LDL-C, LDL cholesterol; LDLR, LDL receptor; Lp(a), lipoprotein (a); mAbs, monoclonal antibodies; PCSK9, proprotein convertase subtilisin kexin type 9; Q2W, every 2 weeks; VLDL, very low-density lipoprotein.

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## PCSK9 AND Lp(a) IN OBSERVATIONAL AND EPIDEMIOLOGICAL STUDIES

Prior to reports of the initial phase I/II clinical trials in 2012 showing that PCSK9 inhibition with two fully human mAbs, namely alirocumab (Sanofi–Regeneron) and evolocumab (Amgen), yielded robust reductions in LDL-C as well as in Lp(a) levels, it had not been anticipated that this new class of drugs would significantly lower Lp(a) levels in humans. Indeed, the widely prescribed statins, that also increase LDLR expression, do not reduce circulating Lp(a) levels. Statins even appear to promote a small increase in plasma Lp(a) levels in clinical trials.

Furthermore, carriers of the PCSK9 loss-of-function mutations Y142X and C679X (all African Americans) display similar Lp(a) levels to non-carriers [ $99 \pm 53$  compared with  $98 \pm 78$  mg/dl respectively] [1], and patients with familial hypercholesterolaemia (FH) also carrying the PCSK9 loss-of-function mutation R46L had non-significantly increased Lp(a) levels compared with non-carriers [25 (6–36) compared with 16 (6–35) mg/dl] [2]. In the Danish population, however, the PCSK9–R46L mutation was associated with slightly reduced Lp(a) levels [8 (4–42) mg/dl for homozygous carriers, 9 (4–32) mg/dl for heterozygous carriers compared with 10 (5–30) mg/dl for non-carriers;  $P = 0.02$ ] [3]. The dominant negative loss-of-function PCSK9 V114A–R104C mutation carrier had no detectable plasma Lp(a) [4]. In addition, there was no difference in lipid profiles between carriers and non-carriers of the InsLeu PCSK9 genetic variant associated with reduced CVD, with Lp(a) levels of 19 (5.5–39.5) and 16 (7–38) mg/dl respectively [5].

In contrast, Lp(a) levels were increased among PCSK9–E32K gain-of-function mutation carriers ( $n = 42$ ) compared with 4015 normolipidemic controls [21.1 (11.7–34.9) compared with 11.8 (6.5–29.4) mg/dl respectively,  $P = 0.0011$ ] [6] and in two small groups of FH patients carrying PCSK9 gain-of-function mutations, Lp(a) levels were also slightly elevated [7]. Among four PCSK9–S127R gain-of-function mutation carriers followed in our institution [8], only one had strikingly elevated Lp(a) levels that was associated with a very small apo(a) isoform encompassing only three kringle IV<sub>2</sub> repeats (M. Krempf, M. Croyal and G. Lambert unpublished observation).

Interestingly, no positive association was found between circulating PCSK9 and Lp(a) levels in epidemiological studies. Thus, in the Dallas Heart Study (3138 persons), PCSK9 levels, that positively correlated with LDL-C ( $r = 0.24$ ,  $P < 10^{-4}$ ) and several other biomarkers of lipid and glucose metabolism, did not correlate with Lp(a) ( $r = 0.02$ ,  $P = 0.33$ ) [9]. In a study performed in 295 asymptomatic Australians, serum PCSK9 concentrations were not correlated with Lp(a) ( $r = -0.0138$ ) [10]. A study conducted in more than 4000 Stockholm inhabitants did not show higher plasma Lp(a) in individuals with higher PCSK9 levels, when analysed by quartiles [11]. Likewise, PCSK9 did not correlate with Lp(a) levels in 716 American women ( $r = -0.02$ ,  $P = 0.63$ ) [12]. In line with those studies, we recently reported a lack of association between plasma Lp(a) and PCSK9 levels in 161 statin-treated asymptomatic FH patients [13].

Together, the combined observations of gain- or loss-of-function PCSK9 mutation carriers as well as the lack of cor-

relation between PCSK9 and Lp(a) levels reported in several epidemiological studies do not provide any evidence of an association between PCSK9 and Lp(a) in humans.

## PCSK9 AND Lp(a) IN CLINICAL TRIALS

The link between PCSK9 and Lp(a) came from the first phase I/II clinical trials showing unambiguously that PCSK9 inhibition with alirocumab consistently reduced circulating Lp(a) levels by up to 30%, in monotherapy as well as on top of statins both in normolipidaemic volunteers and in dyslipidaemic individuals including heterozygous FH patients [14–17]. Similar observations were made in the initial phase I/II clinical trials of evolocumab, also published in 2012 [18–22]. Comprehensive assessment of Lp(a) lowering after 12 weeks of treatment with 140 mg evolocumab every 2 weeks (Q2W) showed mean reductions in Lp(a) of 32%, 2-fold lower than those observed for LDL-C (–65.5%) and apoB (–55.6%). There were significant associations between percent changes in Lp(a) and percent changes in LDL-C ( $r = 0.33$ ) or apoB ( $r = 0.36$ ) ( $P < 0.001$ , all) [23,24]. When LDL-C levels were corrected for the contribution of Lp(a)-cholesterol, the Spearman's correlation coefficient between changes in Lp(a) and changes in LDL-C after 12 weeks of evolocumab treatment was  $r = 0.49$ , and  $r = 0.36$  after 1 year of treatment ( $P < 10^{-4}$ ) [25]. Similar observations were made for alirocumab, also with positive correlations between changes in Lp(a) and changes in LDL-C ( $r = 0.23$ ,  $P < 0.05$ ) [26].

Interestingly, significant reductions in Lp(a) were not seen in the single phase I trial of ALN-PCS, a RNAi that reduces endogenous PCSK9 production, despite a 40% reduction in LDL-C [27,28]. Reductions in Lp(a) observed with mAbs targeting PCSK9 were sustained over time, regardless of baseline Lp(a) or LDL-C levels [29–32]. These reductions were of similar magnitudes in diverse patient populations, including heterozygous FH and Type 2 diabetics [32–41], as well as on top of various background lipid-lowering treatments [42]. Noteworthy, LDL-C and Lp(a) reductions appeared stronger in Japanese patients, at –68.6% and –50.6% with 140 mg evolocumab Q2W, and at –69.1% and –34.1% with 150 mg alirocumab Q2W respectively [43–45]. Encouraging interim reports published simultaneously in 2015 showed (i) a sustained reduction in LDL-C (–52%) associated with a cumulated incidence of cardiovascular events of 0.95% in the evolocumab arm compared with 2.18% in the placebo arm of the OSLER phase III study (Amgen) after 1 year [46] and (ii) a sustained reduction in LDL-C (–56%) and Lp(a) (–25.6%) associated with a cumulated incidence of cardiovascular events of 1.7% in the alirocumab arm compared with 3.3% in the placebo arm of the ODYSSEY phase III study (Sanofi–Regeneron) after 1.5 years [47]. Whether Lp(a) reductions induced by PCSK9 mAbs will per se translate into a decrease in CVD will be difficult to tease out from the anticipated beneficial effects of concomitant sharp reductions in LDL-C levels.

In addition to alirocumab and evolocumab, the clinical safety and efficacy of bococizumab (Pfizer) and of LY3015014 (Eli Lilly), two humanized mAbs targeting PCSK9, were reported in 2015. Treatment with 150 mg of bococizumab Q2W promoted

a 54.2% decrease in LDL-C but changes in Lp(a) were unfortunately not reported [48]. Treatment with 300 mg LY3015014 administered every 4 weeks promoted a 58.2% decrease in LDL-C and a 37.3% decrease in Lp(a) levels [49], in line with those reported with the fully human mAbs alirocumab and evolocumab [50].

Together, the results of clinical trials showing sustained effects of PCSK9 inhibition with mAbs on circulating Lp(a) levels provide strong evidence that PCSK9 plays a key role in Lp(a) metabolism. Since the mean reduction in Lp(a) with these new drugs is 2-fold lower than what is observed for LDL-C, and that changes in Lp(a) correlate modestly with changes in LDL-C, the mechanism(s) by which PCSK9 inhibition with mAbs lower Lp(a) levels appear(s) more complex than anticipated.

### PCSK9 AND Lp(a) IN THE PLASMA

PCSK9 is a secreted protein mainly expressed by the liver. PCSK9 circulates in the plasma either as a full-length 62 + 12 kDa form or as a furin-cleaved 55 + 12 kDa inactive form and can eventually generate dimers or trimers [51,52]. A significant proportion (up to 40%) of PCSK9 appears to be associated with LDL but not with VLDL or chylomicrons in human plasma [51,53,54]. In patients presenting with severe FH, LDL apheresis with dextran sulfate columns lowered circulating PCSK9 levels by 52% [both LDL bound (−81%) and apoB-free forms (−48%)] [55]. In Japanese homozygous and heterozygous FH patients, LDL apheresis similarly reduced full-length PCSK9 and furin-cleaved PCSK9 forms by 56% and 55% respectively [56].

We recently reported that PCSK9 is also bound to Lp(a) in the plasma, likely through direct interactions with apoB100 but not with apo(a). In individuals with elevated Lp(a) levels, PCSK9 showed a preferential association with Lp(a) than with LDL [57]. The physiological significance of PCSK9 binding to LDL and Lp(a) remains however to be established: it is a common event for PCSK9 (up to 40% is bound to lipoproteins) but a rare event for lipoproteins (less than 1% carry PCSK9). Nevertheless, the association between PCSK9 and Lp(a) underpins a specific role for PCSK9 in Lp(a) metabolism.

### A ROLE FOR THE LDL RECEPTOR

Given that (i) PCSK9 primarily targets the LDLR, and that (ii) inhibiting PCSK9 with mAbs lowers LDL and Lp(a) that both contain apoB100, a major ligand for the LDLR, it can be reasonably be hypothesized that the LDLR mediates the removal of Lp(a) from the circulation. In addition, among patients with hypercholesterolaemia, those presenting with LDLR defects appear to have higher Lp(a) levels [58,59], although this has not been unanimously observed [60–62]. In that respect, FH patients in whom the presence of mutations in the LDLR, apoB and PCSK9 has been excluded also display higher Lp(a) levels [63]. Furthermore, in the Copenhagen General Population Study, after adjusting LDL-C for Lp(a)-cholesterol levels (i.e. using corrected LDL-C values), the levels of Lp(a) were similar between

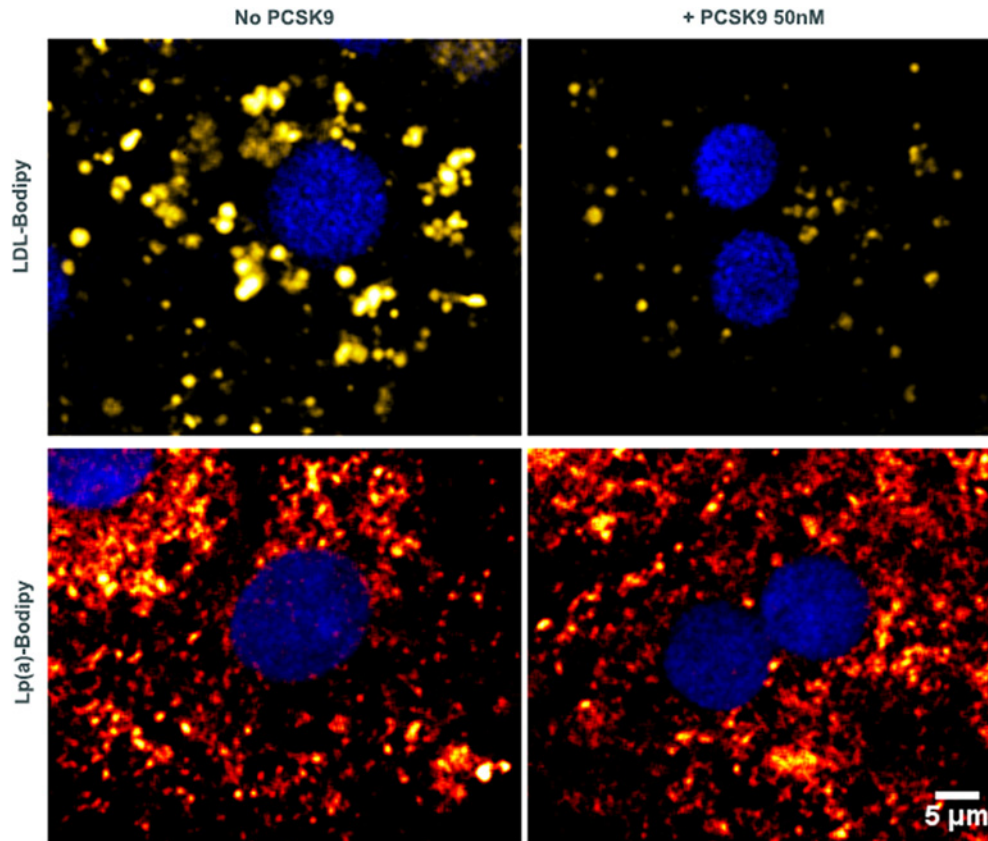
individuals unlikely to have FH (24 mg/dl,  $n = 43699$ ), those with possible FH (22 mg/dl,  $n = 2360$ ) and those with probable or definite FH (21 mg/dl,  $n = 141$ ,  $P_{\text{trend}} = 0.46$ ), suggesting that the LDLR is unlikely to remove Lp(a) from the circulation [64].

Initial reports trying to unravel the mechanism of Lp(a) catabolism using dermal fibroblasts isolated from homozygote FH (Ho-FH) patients and control individuals are contradictory. One study showed that the LDLR is of minor importance, if any, for Lp(a) binding to and internalization in human fibroblasts [65], whereas Lp(a) was shown by others to bind to fibroblasts only with a slightly reduced affinity compared with LDL, presumably via the LDLR [66–68]. An Lp(a)-like complex, consisting of a recombinant form of apo(a) encompassing 17 kringle IV<sub>2</sub> domains associated on to an LDL particle, was also found to undergo cellular binding and uptake via the LDLR in fibroblasts and HepG2 hepatoma cells [69]. In that study, the plasminogen receptor was proposed to represent a significant pathway for removal of free apo(a).

*In vivo* Lp(a) turnover studies conducted in humans also yielded conflicting results. Thus, the fractional catabolic rate of Lp(a) appeared reduced in one homozygous FH patient totally lacking the LDLR [68], whereas the Lp(a) fractional catabolic rates of five Ho-FH, four heterozygote FH (He-FH) and eight non-FH controls were similar in another study [70]. In both studies, LDL fractional catabolic rates were sharply reduced in FH patients.

In 2015, PCSK9 was shown to inhibit Lp(a) uptake in the HepG2 hepatoma cell line and in dermal fibroblasts via a mechanism involving mainly the clathrin machinery and the LDLR [62]. In contrast with Lp(a), the catabolism of apo(a) alone did not appear to occur via the LDLR in that study. The authors proposed that PCSK9 inhibition with mAbs promotes a supra-physiological increase in LDLR expression at the hepatic surface thereby allowing Lp(a) uptake. In another study, Lp(a) cell association with HepG2 was shown to parallel the levels of LDLR expression modulated either by PCSK9, anti-LDLR antibodies or by the amount of serum in the culture medium [25].

In sharp contrast with those studies, we recently reported that Lp(a) cellular uptake is not mediated by the LDLR in dermal fibroblasts isolated from non-FH, heterozygous and homozygous FH patients [71–73], as well as in human primary hepatocytes isolated from two unrelated donors [74]. Figure 1 illustrates one of the major conclusions of our study: lowering LDLR expression with PCSK9 sharply reduces the cellular uptake of fluorescent LDL but not that of fluorescent Lp(a) in human hepatocytes. We also showed that alirocumab did not modulate Lp(a) uptake in fibroblasts and hepatocytes [74]. We are uncertain how to explain the discrepancies between our study and that of Romagnuolo et al. [62] beyond the different methodologies used [e.g. hepatoma cell line compared with primary hepatocytes; different isolation/purification procedures for Lp(a); Lp(a) containing apo(a) of variable lengths; flow cytometry/confocal microscopy compared with Western blots; variable concentrations of PCSK9; apoE genotype of Lp(a) donors]. Our results are however concordant with the observations that up-regulating LDLR expression even with the most potent statins does not reduce Lp(a) levels *in vivo* [75], and that PCSK9 inhibition with evolocumab reduces Lp(a) in two out of three homozygous FH totally lacking the LDLR,



**Figure 1** Inhibiting LDLR expression with PCSK9 does not significantly affect Lp(a) uptake in human primary hepatocytes. Human primary hepatocytes grown in Millicell EZ slides were treated with or without recombinant PCSK9 (50 nM) for 24 h. Fluorescent LDL-bodipy (yellow) or fluorescent Lp(a)-bodipy (red-hot) was added to the culture medium for 3 h. Cells were washed extensively with ice-cold PBS containing 1% BSA, fixed in PBS containing 4% paraformaldehyde for 10 min, and rinsed twice with PBS. Nuclei were stained with Hoechst 33258 (blue) and cells were visualized on a confocal fluorescent microscope.

despite no reduction in LDL-C [76,77]. We also showed that PCSK9 enhances the secretion of apo(a)/Lp(a) from primary hepatocytes, an effect totally blunted by alirocumab [74]. This observation is in line with several *in vitro* and animal studies showing that PCSK9 modulates the synthesis and secretion of other apoB containing lipoproteins from the liver [78–80] and the intestine [81,82]. We therefore propose that PCSK9 inhibition with mAbs lowers Lp(a) at least in part by acting on Lp(a) hepatic synthesis, secretion and/or assembly.

## CONCLUSION

All together, the studies reviewed above do not provide a definitive answer to the following question: by which pathway(s) or mechanism(s) does PCSK9 inhibition with mAbs consistently lower circulating Lp(a) in clinical trials? More frustrating were the opposite conclusions communicated in May 2016 at the Lp(a) satellite meeting held in Innsbruck (Austria) from *in vivo* Lp(a) turnover studies conducted in humans. One study showed that PCSK9 inhibition with alirocumab increased Lp(a) fractional catabolic rates, thus Lp(a) catabolism, although this was not sig-

nificant, whereas the other showed that PCSK9 inhibition with evolocumab in normolipaeamic individuals decreased Lp(a) production rates, thus Lp(a) synthesis.

One can only conclude with certainty that combined research efforts from our various labs are needed to better understand the intriguing and complex metabolism of the fascinating Lp(a).

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