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Update on PCSK9 inhibitors, lipoprotein(a) and cardiovascular risk

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Lipoprotein(a) STRUCTURE AND ASSOCIATED CARDIOVASCULAR RISK

Lipoprotein (a) (Lp(a)) is constituted of an low-density lipoprotein (LDL)-particle whose apoB is covalently linked to apo(a). The latter contains several 'kringle' domains analogous to those of plasminogen. Moreover, the number of kringle IV type 2 repeats is variable, under genetic control, and inversely related to the plasma concentration of Lp(a) [1]. An increased risk of coronary artery disease (CAD) has been reported in carriers of LPA genetic variants, associated with elevated Lp(a) and reduced kringle IV-2 repeats [2]. In general, population-based prospective studies have demonstrated a continuous association of Lp(a) concentration with the risk of CAD and ischemic stroke [3]. Likewise, in patients with established cardiovascular (CV) disease treated with statins, higher levels of Lp(a) were associated with further CV events, independently of LDL-cholesterol (LDL-C) [4**,5]. A 20 mg/dL greater Lp(a) would be associated with an 8% increase in CV risk [5,6]. Conversely, in patients on secondary prevention, lowering Lp(a) levels by 50mg/dl should reduce CV diseases by 20% [7**].

Several mechanisms have been proposed to explain the effects of Lp(a) on atherothrombosis. Due to its homology with plasminogen, Lp(a) can in-vitro inhibit fibrinolysis. This might favor thrombosis at vulnerable arterial plaques [1]. Besides, Lp(a) has long been described in human coronary atheroma lesions, colocalized with macrophages. These cells might participate to Lp(a) clearance, since Lp(a) is only partly catabolized through the LDL receptor (LDL-R).

Recently, elevated Lp(a) and oxidized phospholipids (ox-PL) were found associated with more prevalent aortic valve stenosis (AVS) and microcalcification, documented by positron emission tomography [8*]. In patients with moderate AVS, elevated Lp(a) and ox-PL conferred greater progression of valve calcification and increased risk of valve replacement or cardiac death [9,10**]. Similar observations were made in hypercholesterolemic patients [11]. Ox-PL and Lp(a) are linked in arterial and aortic valve lesions. This complex might promote lipid deposition, endothelial dysfunction, inflammation, osteogenic differentiation and calcification [10**].

PROPROTEIN CONVERTASE SUBTILISIN/ KEXIN TYPE 9 AND ANTI-PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9

Proprotein convertase subtilisin/kexin type 9 structure, functions and association to cardiovascular risk.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a secretory serine protease mainly expressed in the liver and to a lesser extent in kidney, lung, intestine, central nervous system, inflammatory and blood vessel cells. The PCSK9 gene encodes for a 72 kDa inactive protein (pro-PCSK9) containing a signal peptide. Pro-PCSK9 is cleaved to form the mature 62 kDa PCSK9 protein. The PCSK9 gene expression is regulated by different transcription factors among which sterol-response element-binding protein 2 (SREBP2) which also regulates LDL-R expression [12,13*].

PCSK9 was first discovered as a genetic determinant of some forms of familial hypercholesterolemia (FH). In approximately 1% of cases, FH with severely elevated LDL-C levels results from the presence of 'gain-of-function' mutations on PCSK9. Conversely, PCSK9 loss-of-function mutations are associated with very low plasma levels of LDL and to a lesser CV risk [14]. High circulating PCSK9 is significantly associated with increased risk of major adverse cardiovascular events (MACE) [15*]. PCSK9 binds to the LDL-R at the surface of hepatocytes and prevents its recycling after endocytosis, leading to its lysosomal degradation. Overexpression of PCSK9 results in a reduced clearance and an accumulation of LDL in the circulation [13*]. Recent findings demonstrate that PCSK9 is also involved in the pathophysiology of atherosclerosis, independently from LDL-R cleavage, by actively modulating inflammation, plaque formation and thrombosis [13*,16].

Proprotein convertase subtilisin/kexin type 9 inhibitors, effects on the cardiovascular risk

Given its established role as a major LDL-R inhibitor, PCSK9 has become a prime therapeutic target to lower LDL-C. Currently, two main approaches are used to decrease circulating PCSK9: binding of PCSK9 with human monoclonal antibodies (alirocumab or evolocumab) or inhibiting its hepatic synthesis with a small interfering RNA (inclisiran). With any of these strategies, PCSK9 inhibitors (PCSK9i) impair LDL-R degradation and lower LDL-C by 50 – 60%. Consequently, they reduce the risk of MACE when added to statins [17].

Unexpectedly and unlike statins, PCSK9i lower plasma Lp(a) levels by 27% on average [18*]. The mechanisms involved in this effect of PCSK9i remain unclear, although several hypotheses have been proposed: an enhanced clearance of Lp(a) through the LDL-R, an enhanced Lp(a) clearance via other receptors (LDL-R related protein 1, cluster of differentiation 36 receptor, toll-like receptor 2, scavenger receptor-BI and plasminogen receptors) and a reduction of apo(a) production or of Lp(a) assembly [19]. A high frequency of discordant LDL-C/Lp(a) responses to alirocumab was reported, suggesting that this PCSK9i reduces plasma Lp(a) through alternative mechanisms to the LDL-R [20*]. In the same way, recent kinetic studies using stable isotopes tracer methodologies have shown that PCSK9i do not modulate hepatic uptake of Lp(a) by LDL-R [21*,22], except when combined with statins [21*,23]. In contrast, PCSKi reduce Lp(a) levels by lowering apo(a) production rate [21*,24].

In the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial, evolocumab significantly reduced the risk of CV death, myocardial infarction (MI) or urgent revascularization in patients with established CV disease. The risk reduction was greater in patients with higher baseline Lp(a) [4**]. In the ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial, in patients with the recent acute coronary syndrome, Lp(a) lowering by alirocumab reduced the total burden of CV events independently of LDL-C decrease. Each 5-mg/dL reduction in Lp(a) predicted a 2.5% relative reduction in CV events [25**]. Alirocumab-induced decrease of Lp(a) predicted the risk reduction of a first primary outcome event (CV deaths, nonfatal MI, unstable angina or ischemic stroke) [26], of a first major peripheral artery disease [27] and also of recurrent events [25**]. These clinical trials were conducted in a secondary prevention setting, and primary prevention trials regarding the protective effects of Lp(a) reduction are still lacking. Moreover, it remains difficult to dissociate the protective effects of PCSK9i through LDL-C lowering and/or Lp(a) lowering. A treatment that selectively lowers Lp(a) should provide a real proof of causality between Lp(a) lowering and CV risk reduction. An antisense oligonucleotide (pelacarsen) targeting apo(a) mRNA reduces mean Lp(a) levels by 80%. It is currently under evaluation in the phase 3 HORIZON (Assessing the Impact of Lipoprotein(a) Lowering With TQJ230 on Major Cardiovascular Events in Patients With CVD) trial to assess the impact of Lp(a) lowering on MACE in patients with CV disease [28].

Proprotein convertase subtilisin/kexin type 9, proprotein convertase subtilisin/kexin type 9 inhibitors and calcified aortic stenosis

Besides Lp(a), PCSK9 itself had been found in human aortic valves and may participate to calcium deposition [29]. Incubation of valve interstitial cells in an osteogenic medium stimulates PCSK9 synthesis and secretion, concomitant with a rise in intracellular calcium. This latter effect is blocked by a neutralizing anti-PCSK9 antibody [30**]. In a large meta-analysis [30**], the common PCSK9 (R46L) loss of function variant has been associated with a 20% lower risk of calcified AVS. In the prospective FOURIER trial, evolocumab reduced aortic stenosis events by 50% beyond one year treatment [31].

Beyond low-density lipoprotein cholesterol, effects of proprotein convertase subtilisin/kexin type 9 inhibitors on plasma lipoproteins

The impact of PCSK9i on the lipoprotein profile was recently determined by nuclear magnetic resonance [32]. Evolocumab induced a decrease of small and medium-sized LDL particles, potentially associated with a reduction of CV risk. A decrease of all subtypes of very-low density lipoprotein was also observed, which may reflect an accelerated catabolism of those particles [32]. In a recent study, anti-PCSK9 antibodies led to a more atheroprotective high-density lipoprotein (HDL) profile, with a rise in total and medium HDL particles, and a decrease of large HDL [33*]. Furthermore, under PCSKi, medium and small HDL were found enriched in esterified cholesterol but depleted in triglycerides, which might result from a reduced cholesteryl ester transfer protein activity due to lower availability of apoB-containing lipoproteins [33*]. Interestingly, small and medium-sized HDL particles appear as preferred acceptors of excess cell cholesterol.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

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