Chapter 5
Contemporary Aspects of Lp(a) Metabolism and Therapies Based on Tracer Kinetic Studies in Humans

Dick C Chan, Jing Pang, and Gerald F Watts

Bullet Points

- Lipoprotein(a) [Lp(a)] is an inherited and causal risk factor for atherosclerotic cardiovascular disease (ASCVD) and aortic valve stenosis.
- Use of stable isotope tracers and compartmental modelling has provided deeper understanding of the physiology and pathophysiology of Lp(a) metabolism in humans.
- Plasma Lp(a) concentration is predominantly determined by the rate of production of Lp(a) particles, irrespective of apo(a) isoform size and background therapy with statins.
- Niacin and cholesteryl ester transfer protein inhibitors lower plasma Lp(a) concentration by increasing the clearance or catabolism of apo(a).
- ApoB antisense oligonucleotides lower plasma Lp(a) concentration by decreasing hepatic production.
- Proprotein convertase subtilisin kexin type 9 inhibitors can lower plasma Lp(a) concentration by a dual mode of action involving both increased clearance and decreased production of apo(a),
- Further studies should investigate nucleic acid-based inhibitors for apo(a), angiopoietin-like 3 and apoC-III inhibitors on the metabolism of Lp(a) and other lipoproteins.

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Introduction

Lipoprotein(a) [Lp(a)] is one of the most important genetically determined risk factors for atherosclerotic cardiovascular disease (ASCVD) and aortic valve stenosis (Nordestgaard and Langsted 2016; Saleheen et al. 2017; Tsimikas et al. 2018; Cegla et al. 2009; Arsenault and Kamstrup 2022; Reyes-Soffer et al. 2022). Large clinical trials have consistently shown that patients with elevated Lp(a), even when treated with statins, are at an increased risk of ASCVD (Khera et al. 2014; Nicholls et al. 2010). The metabolic pathways governing the metabolism of Lp(a) have been extensively studied in cellular and animal model systems (McCormick and Schneider 2019; Boffa and Koschinsky 2022; Chemello et al. 2022a). However, only scare information is available on the metabolism of this lipoprotein in humans. Use of stable isotopically labelled tracers and compartmental modelling has greatly enhanced our understanding of Lp(a) metabolism (Chan et al. 2004; Barrett et al. 2006). In the present chapter, we review use of these techniques and its contribution to key knowledge of the physiology and pathophysiology of Lp(a) metabolism in humans. We focus on subjects with elevated Lp(a) and the mode of action of lipid-regulating agents.

Structure and Genetics of Lipoprotein(a) in Brief

Lp(a) is composed of one molecule of a highly polymorphic apolipoprotein(a) [apo(a)] particle covalently linked to one molecule of a low-density lipoprotein (LDL)-like particle containing apoB-100 by a single disulphide bond (Schmidt et al. 2016). Apo(a) is composed of 10 types of kringle 4 (KIV) domains related to plasminogen kringle 4, followed by a KV domain and an inactive protease-like domain. KIV_2 exists in variable numbers (from 3 to >30), which gives rise to Lp(a) isoform size heterogeneity (Marcovina et al. 1996; Kronenberg and Utermann 2013).

The gene encoding apo(a), *LPA*, is located on the long arm of chromosome 6 at 6q2.6–2.7, adjacent to the human plasminogen gene. While the control of *LPA* expression is at present not well understood, certain factors, such as estrogen, hepatocyte nuclear factor 4α, interleukin-6 and tumour necrosis factor alpha, influence the expression of *LPA* (Kronenberg and Utermann 2013). Plasma Lp(a) concentration is largely controlled by the *LPA* gene locus. Up to 90% of its variation in Lp(a) concentration is attributable to genetic factors (Lamon-Fava et al. 1991; Austin et al. 1992; Boerwinkle et al. 1992), with approximately 30–70% explained by a variable number of KIV_2 repeats in the *LPA* gene (Kronenberg and Utermann 2013). The unexplained genetic variance in Lp(a) concentration can be contributed by other genetic factors outside KIV_2 repeat variation. Several single nucleotide polymorphisms (SNPs) in the *LPA* gene, such as rs3798220 (CT/CC) and rs10455872 (AG/

GG), are strongly associated with an elevated Lp(a) concentration (Clarke et al. 2009). Genome-wide association studies (GWAS) have also identified many common genetic variants of small effect which can aggregately influence Lp(a) concentration (Coassin and Kronenberg 2022). Accordingly, a polygenic risk score for predicting Lp(a) concentration has recently been reported, explaining approximately 60–70% of the variance in Lp(a) levels in the EPIC-Norfolk and UK Biobank cohorts (Wu et al. 2021). *APOE* gene is one of the most important genetic factors modulating Lp(a) concentrations (Li et al. 2015; Zekavat et al. 2018; Mack et al. 2017; Chemello et al. 2022b); the ε2 allele is associated with reduced Lp(a) concentrations, whereas the ε4 allele is associated with increased Lp(a) concentrations compared with the ε3 allele (Moriarty et al. 2017). Several physiological states, such as kidney, thyroid and liver disease, and ancestry, also contribute to the variability in Lp(a) concentration (Enkhmaa and Berglund 2022).

Stable Isotopic Tracer Methodologies

Plasma Lp(a) concentration in the circulation is determined by a balance between the rates of production and catabolism of Lp(a) particles. Stable isotope tracer studies using endogenous labelling of apolipoproteins with amino acid precursor molecules (isotopomers) and mathematical modelling have been employed to study Lp(a) kinetics (Barrett et al. 2006). This approach has provided better understanding of Lp(a) homeostasis and of the pathogenesis of elevated Lp(a), as well as the kinetic effects of statin and newer lipid-regulating agents, such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.

Briefly, stable isotopically labelled amino acids (such as D3-leucine) are administered intravenously as a bolus or primed infusion with serial blood sampling over several days to assess the turnover of apo(a). Enrichment data (tracer/tracee ratio) are generated by gas- or liquid-chromatography mass spectrometry (GCMS or LCMS, respectively) analysis after separation of apo(a) from plasma (Chan et al. 2004). A novel LCMS method for quantification of apo(a) enrichment has recently been established by employing a synthetic peptide (LFLEPTQADIALLK) that targets the proteolytic domain of apo(a) following a standardized sample trypsin digestion procedure (Croyal et al. 2015, 2018). This method is more sensitive and less labour-intensive than the traditional approach based on immunoprecipitation and Western blotting. Enrichment data are then analysed via multicompartmental modelling, from which the fractional turnover rate of apo(a) in the circulation is derived. Fractional catabolic (or clearance) rate (FCR) refers to the fraction of trace lost from a defined plasma pool per day. From these primary kinetic data, together with the corresponding plasma pool size of apo(a), absolute transport rates in the circulation are calculated. We have detailed these methods elsewhere (Chan et al. 2004; Barrett et al. 2006). Figure 5.1 shows a multicompartmental model for the metabolism of Lp(a)-apo(a) and Lp(a)-apoB-100.

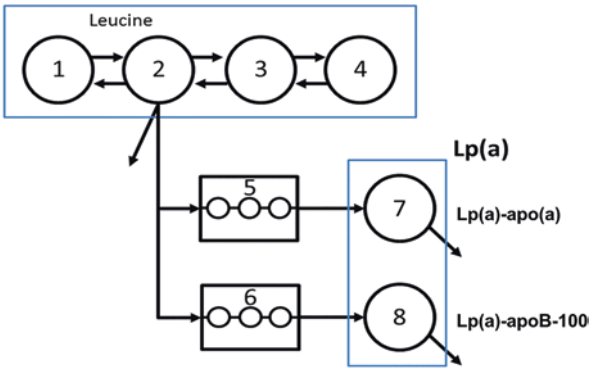

Fig. 5.1 Compartmental model to describe Lp(a)-apo(a) and Lp(a)-apoB-100 tracer kinetics. Plasma leucine kinetics are described by a four-compartment model, which is connected to intrahepatic delay compartments (compartments 5 and 6) that accounts for the synthesis and secretion of Lp(a)-apo(a) and Lp(a)-apoB-100, with compartments 7 and 8 describing the plasma kinetics of Lp(a)-apo(a) and Lp(a)-apoB-100, respectively

Metabolism of Lipoprotein(a)

Synthesis, Assembly and Secretion

Apo(a) is exclusively synthesized by the liver (Schmidt et al. 2016). However, details of the assembly process have not been fully elucidated. The site of Lp(a) assembly may occur in hepatocytes, extracellularly in the space of Disse, or in the circulation (plasma space) (Hoover-Plow and Huang 2013; Youssef et al. 2022). Several pathways for Lp(a) assembly and secretion have been suggested. Apo(a) and apoB are assembled intrahepaticaly, forming an Lp(a) particle which is subsequently secreted into plasma. The Lp(a) particle may also be assembled in the circulation (e.g. on the hepatocyte surface) from its constituent protein; these are then independently secreted from the liver into plasma. There is also uncertainty concerning whether the kinetics in plasma of the two protein components of Lp(a) are coupled, and specifically whether apo(a) is recycled or cleared with apoB-100 as an Lp(a) holoparticle. Using stable isotope tracers and compartmental modelling, we demonstrated that in individuals with a wide range of plasma Lp(a) concentrations, Lp(a)-apoB-100 and Lp(a)-apo(a) have identical isotopic enrichment curves in plasma and similar FCRs (Watts et al. 2018). This finding was confirmed in another kinetic study of statin-treated patients (Ma et al. 2019a) (Fig. 5.2). Hence, these kinetic data generally support that newly synthesized Lp(a)-apoB-100 and Lp(a)-apo(a) are secreted as a holoparticle with tightly coupled apo(a) and apoB100 residence times in the circulation. However, it remains unclear whether the covalent binding of apo(a) to apoB-100 takes place in the liver or in the circulation.

Another outstanding issue concerning the assembly of Lp(a) particles is the extent to which the binding of apo(a) to triglyceride-rich lipoproteins (TRLs) contributes to the formation of Lp(a) particles in the circulation (Nassir et al. 1998;

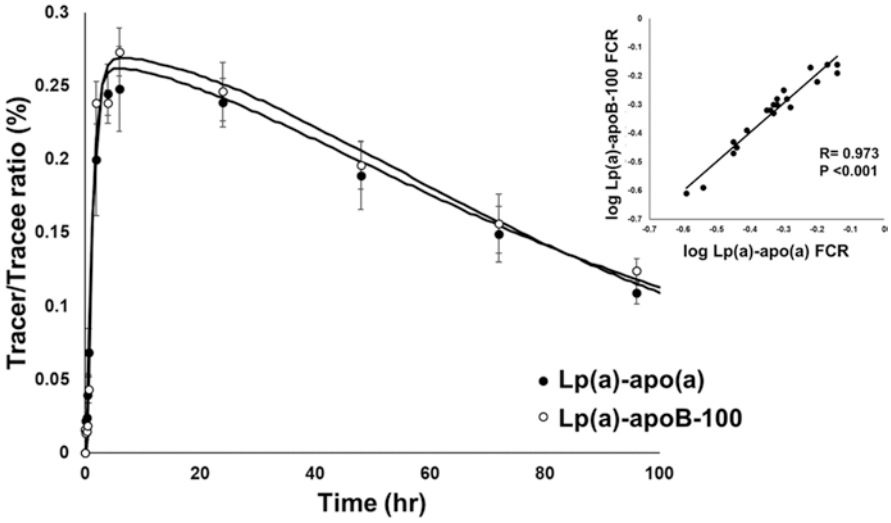

Fig. 5.2 Lp(a)-apo(a) and Lp(a)-apoB tracer-tracee ratio (%) in 20 statin-treated subjects including association of Lp(a)-apo(a) and Lp(a)-apoB-100 fractional catabolic rates (FCR)

Ramos-Cáceres et al. 2022). Earlier radiolabelled kinetic studies suggest that apo(a) is unlikely to be adducted to a triglyceride-rich very low-density lipoprotein (VLDL) as a precursor of Lp(a) in the LDL/HDL density range (Krempler et al. 1980). In contrast, apo(a) can be associated with TRLs, such as chylomicrons and chylomicron remnants, after oral ingestion of a fatty meal (Bersot et al. 1986). This is supported by experimental evidence that the apoB-100-apo(a) complex within Lp(a) particles have a high affinity for TRL particles (Marcoux et al. 1997). A significant proportion of Lp(a) particles can bind non-covalently to TRLs in the hypertriglyceridemic state. Consistent with this, we and others have demonstrated a redistribution of a significant portion of apo(a) protein from Lp(a) to the TRL fraction, particularly in the postprandial state (Cohn et al. 1991; Ying et al. 2022). In a recent study of FH, we found that the impaired postprandial TRL-apo(a) response to a fat load was partially corrected by fish oil supplementation (Ying et al. 2022). The reduction in postprandial TRL-apo(a) with fish oil supplementation in response to the fat load was significantly associated with the corresponding reduction in postprandial triglyceride response. Hence, interaction with TRLs may influence the metabolism or catabolism of Lp(a). The underlying kinetic mechanism remains to be investigated employing stable isotopes and compartmental modelling.

Clearance and Catabolism

It is well established that the liver is the main site of Lp(a) clearance and, to a much lesser extent, the kidney and the arterial wall (McCormick and Schneider 2019). The mechanisms of Lp(a) clearance from the circulation and the catalytic pathways

involved remain uncertain, however. Several cellular receptors have been proposed to mediate the clearance of Lp(a) from the liver. These include LDL receptor and other members of the LDL-receptor family such as VLDL receptor, LDL receptor-related protein 1 (LRP1), megalin/gp330, scavenger receptor class B type 1 (SR-BI) and plasminogen receptor (McCormick and Schneider 2019).

The role of the LDL receptor in Lp(a) clearance remains controversial. Several experimental studies have demonstrated that LDL receptor can facilitate Lp(a) binding and uptake (Havekes et al. 1981; Reblin et al. 1997; Romagnuolo et al. 2015), and in mice overexpressing LDL receptor the clearance of Lp(a) particles is significantly increased (Hofmann et al. 1990). Very few kinetic studies have specifically investigated the metabolism of Lp(a) in patients with LDL receptor defects, such as familial hypercholesterolemia (FH). Using exogenous radiolabelled tracers, Rader et al. found that the clearance of Lp(a) did not differ significantly among homozygous FH patients, heterozygous FH parents and non-FH control subjects (Rader et al. 1995). Using endogenous stable isotope tracers, Croyal et al. reported that the FCRs of Lp(a)-apo(a) were similar in patients with PCSK9 gain-of-function mutations and control subjects (Croyal et al. 2020). Hence, defects in LDL receptor function do not appear to result in delayed clearance of Lp(a). In a study of healthy normolipidemic men, there was no significant association between the FCRs of apo(a) and LDL-apoB-100 (Chan et al. 2019). These kinetic findings suggest under physiological conditions that the LDL receptors may not play a major role in Lp(a) clearance. As discussed later, LDL receptor could play a role in Lp(a) clearance in a supraphysiological condition in which the activity of LDL receptors is markedly upregulated, such as in patients who are treated with a combination of statins and PCSK9 inhibitors (Watts et al. 2018).

Kinetic Determinants of Plasma Lipoprotein(a) Concentrations

Production Rate vs. Fractional Catabolic Rate

In a kinetic study of healthy normolipidemic men with a wide range of plasma Lp(a) concentration, Lp(a) particle concentration was significantly and positively associated with apo(a) production rate (PR) and inversely with apo(a) FCR (Chan et al. 2019). In another study of statin-treated subjects, plasma concentration of apo(a) was significantly and positively associated with apo(a) PR in patients with both normal and elevated Lp(a) concentrations (Ma et al. 2019b). However, there was no significant association between plasma apo(a) concentration and FCR in either of the groups. Hence, these observations reinforce the notion that plasma concentrations of Lp(a) are primarily determined by the rates of production and not clearance, irrespective of background statin use. Accordingly, plasma concentration and PR of apo(a) were significantly higher in statin-treated patients with elevated Lp(a)

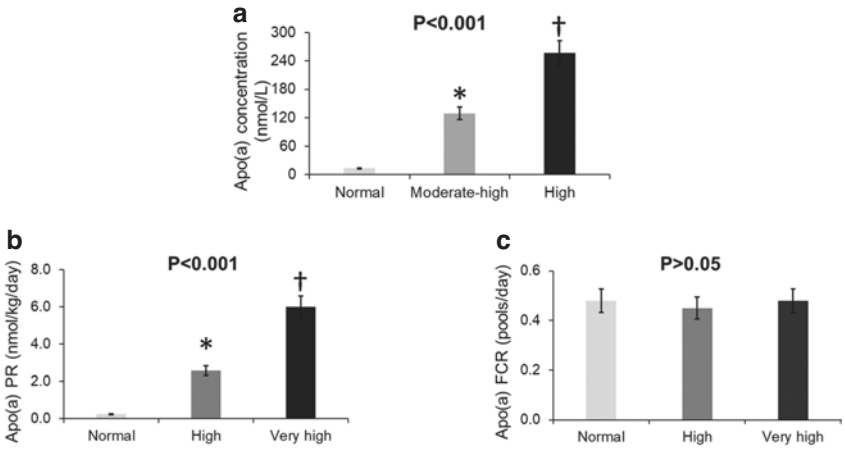

Fig. 5.3 Kinetic parameters of apo(a) in statin-treated subjects with (**a**) normal (<75 nmol/L), (**b**) high (75–145 nmol/L) and (**c**) very high apo(a) concentrations (>145 nmol/L). Data presented as mean ± SEM. *Apo* apolipoprotein, *FCR* fraction catabolic rate, *PR* production rate. $^{*}P < 0.001$ compared with normal apo(a) group. $^{\dagger}P < 0.001$ compared with normal and moderate-high apo(a) group using ANOVA

compared with those with normal Lp(a) (Fig. 5.3a, b). The FCR of apo(a) did not differ significantly between the groups (Fig. 5.3c). This finding suggests that elevated plasma Lp(a) concentration is a consequence of increased hepatic production of Lp(a) particles in patients with elevated Lp(a). In a constant-feeding study of healthy individuals, patients with high Lp(a) had increased apo(a) PR and reduced FCR compared with those without elevated Lp(a) concentration (Jenner et al. 2005). Plasma concentrations of Lp(a) were correlated significantly with both apo(a) PR and negatively with apo(a) FCR. These findings implicate a role of Lp(a) catabolism in determining Lp(a) plasma concentrations in the fed state.

Apo(a) Isoform Size

As discussed earlier, the plasma concentrations of Lp(a) is dependent on genetic variations in the number of KIV_2 repeats (Marcovina and Koschinsky 1999; Kronenberg and Utermann 2013). Experimental data have suggested that the size of the apo(a) transcripts is inversely associated with hepatic *LPA* mRNA concentration (Wade et al. 1991; White et al. 1994) and by implication apo(a) production. Smaller apo(a) isoforms have been shown to have a shorter retention time in the endoplasmic reticulum and probably lesser intracellular apo(a) proteasome degradation, resulting in a more efficiently secretion from hepatocytes (White et al. 1994; Brunner et al. 1996; Lobentanz et al. 1998). On the other hand, Lp(a) with apo(a)

isoforms of different sizes may have different binding affinities for the LDL receptor or other receptors (März et al. 1993). Lp(a) particles with larger isoform size have been shown to be more effectively removed via LDL receptor independent pathways.

In a study of healthy normolipidemic subjects, subjects with smaller apo(a) isoform sizes (≤22 KIV repeats) had significantly higher apo(a) concentration and PR, and lower apo(a) FCR than those with larger sizes (Chan et al. 2019). Plasma apo(a) concentration was significantly associated with apo(a) PR, but not with FCR in subjects with smaller apo(a) isoform size. In contrast, both apo(a) PR and FCR were significantly associated with plasma apo(a) concentrations in subjects with larger isoforms. Similar observations were observed in patients who were on statin (Ma et al. 2019c). Taken together, these findings again suggest that the plasma Lp(a) concentration is predominantly determined by the rate of production of Lp(a) particles, irrespective of apo(a) isoform size and background statin use. Lp(a) particle catabolism may only play a modest role in determining Lp(a) concentration in subjects with larger apo(a) isoform size. These observations also support the clinical use of agents that target the hepatic production and secretion of Lp(a) (Tsimikas 2017).

As discussed earlier, *APOE* genotype can influence the concentration of Lp(a) (Moriarty et al. 2017; Croyal et al. 2020; Chemello et al. 2022a). However, the effect of *APOE* genotype, particularly the presence of apoE2 and apoE4, on Lp(a) concentrations is known to be affected by the size of apo(a) (Klausen et al. 1996; Blanchard et al. 2021). Accordingly, the effect of apoE genotype on the metabolism of Lp(a) in subjects with large and small apo(a) isoform merits further investigation.

Mechanisms of Action of Lipid-Regulating Agents on Lipoprotein(a) Metabolism

A major challenge in managing patients with elevated Lp(a) is a lack of effective and specific treatment for lowering Lp(a) concentrations (Tsimikas 2017; Tsimikas et al. 2018; Reyes-Soffer et al. 2022; Schwartz and Ballantyne 2022). Diet and lifestyle interventions, such as weight loss or physical activity, do not seem to influence Lp(a) concentrations. Lipoprotein apheresis is the only FDA approved treatment for elevated Lp(a). Currently, there are no approved pharmacologic therapies that specifically target Lp(a) concentrations (Cegla et al. 2009; Tsimikas 2017). The kinetic effect of several established and newer therapies, including statins, niacin, PCSK9 inhibitors, cholesteryl ester transfer protein (CETP) inhibitors and apoB antisense oligonucleotides (ASO), on Lp(a) metabolism are discussed below and in Table 5.1, with specific reference to the mechanisms of action.

Table 5.1 Mechanisms of several pharmacological interventions in regulating lipoprotein(a) metabolism

Author (year)	Subjects	Agents	Principal results		
			Concentration	FCR	PR
Watts et al. (2018)	Healthy normolipidaemic men	Atorvastatin	⟺	⟺	⟺
Ooi et al. (2015)	Statin-treated men with type 2 diabetes	Extended-release niacin	↓↓	⟺	↓↓
Croyal et al. (2015)	Non-diabetic, obese men with hypertriglyceridaemia	Extended-release niacin	↓↓	↓↓	↓↓↓
Reyes-Soffer et al. (2017)	Healthy normolipidaemic men and women	Alirocumab	↓	↑	⟺
Watts et al. (2020)	Statin-treated men and women with high Lp(a)	Alirocumab	↓↓	↑↑	⟺
Ying et al. (2022)	Statin-treated men and women with very high Lp(a)	Alirocumab	↓↓↓	↑↑	↓↓
Watts et al. (2018)	Healthy normolipidaemic men	Evolocumab	↓↓	⟺	↓↓
Watts et al. (2018)	Healthy normolipidaemic men	Evolocumab + Atorvastatin	↓↓	↑↑	⟺
Thomas et al. (2017)	Mildly hypercholesterolaemic men and women	Anacetrapib (CETP inhibitor)	↓↓	⟺	↓↓
Nandakumar et al. (2018)	Healthy normolipidaemic men and women	Mipomersen (ApoB ASO)	↓↓	↑↑	⟺

apo apolipoprotein, *ASO* antisense oligonucleotide, *CETP* cholesteryl ester transfer protein, *FCR* fractional catabolic rate, *PR* production rate
↑↑: mild increase; ↓↓: mild decrease; ↓↓↓: marked decrease; ⟺: no change

Statins

The value of statins in lowering LDL-cholesterol is well recognized. Statins competitively inhibit HMG CoA reductase, thereby decreasing cholesterol biosynthesis, reciprocally upregulating hepatic LDL receptors and enhancing clearance of LDL and other apoB-100-containing particles, including TRLs (Ginsberg 2006). Given the structural similarities between LDL and Lp(a), one would speculate that statins could lower Lp(a) concentration by increasing the clearance of Lp(a). However, the effect of statins on Lp(a) levels is conflicting: some studies show a neutral role (Wang et al. 2021; de Boer et al. 2022), while others report a decrease (Takagi and Umemoto 2012) or increase of plasma Lp(a) levels (Tsimikas et al. 2020). It appears that the influence of stains on Lp(a) level may depend on the type of statins; atorvastatin and rosuvastatin increase Lp(a) levels whereas pitavastatin has no impact or

may tend to decrease plasma Lp(a) concentrations (Tsimikas et al. 2020). The statin-induced increase in Lp(a) level is supported by experimental evidence in HepG2 cells showing a higher *LPA* mRNA level in response to atorvastatin (Tsimikas et al. 2020). In a study of healthy normolipidemic subjects, atorvastatin (80 mg daily) did not significantly alter the FCR or PR of apo(a) (Watts et al. 2017). This finding does not support a role of LDL receptor in the regulation of apo(a) FCR under physiological condition. However, it remains unclear whether statin has a potential impact on Lp(a) metabolism in subjects with high Lp(a) concentration. There is also evidence showing that statins increase Lp(a) levels exclusively in patients with a small size apo(a) defined as $\leq$22 KIV repeats (Yahya et al. 2019). The precise mechanisms of action of this effect on Lp(a) metabolism remain to be investigated.

Niacin

Niacin is one of few agents that can significantly lower plasma Lp(a) concentrations. Experimental data suggest that niacin decreases the expression of *LPA* mRNA (Chennamsetty et al. 2012). This is consistent with a kinetic study showing that niacin lowered Lp(a) concentration by decreasing the production of apo(a) in non-diabetic, obese and hypertriglyceridemic men (Croyal et al. 2015). The lowering of the PR of apo(a) by niacin was confirmed in another postprandial kinetic study in statin-treated patients with type 2 diabetes (Ooi et al. 2015). In this study, extended-release niacin (1–2 g/day) significantly decreased plasma Lp(a) concentration and the production rates of apo(a), with greater treatment effect in individuals with elevated Lp(a) concentration. This is consistent with another study showing that extended-release niacin was more effective in lowering Lp(a) level in subjects with small apo(a) isoform than those with large isoform (Artemeva et al. 2015).

PCSK9 Inhibitors

Inhibition of PCSK9 in combination with statins and/or ezetimibe provides a highly effective approach for lowering LDL-cholesterol concentrations in patients with hypercholesterolemia (Duprez et al. 2020; Ying et al. 2021; Ferri et al. 2020). Monoclonal antibodies (mAbs) targeting PCSK9, such as evolocumab and alirocumab, have been consistently known to significantly lower plasma LDL-cholesterol and the incidence of ASCVD outcomes (Sabatine et al. 2017; Schwartz et al. 2018; Deedwania et al. 2021). PCSK9mAbs can similarly lower plasma Lp(a) concentration. The effectiveness of PCSK9 mAbs in reducing ASCVD events is also found to be most pronounced in patients with high Lp(a) and that the reduction

in Lp(a) could also partly mediate the cardiovascular benefit of PCSK9 mAbs (Bittner et al. 2020; Schwartz et al. 2021).

In a kinetic study of healthy normolipidemic men, evolocumab monotherapy significantly decreased plasma Lp(a) concentration chiefly by reducing the PR of apo(a) with no effect on the corresponding FCR (Watts et al. 2018). This effect is consistent with a tracer study conducted in non-human primates in which alirocumab decreased the PR of apo(a) (Croyal et al. 2018). The mechanistic effect of evolocumab may involve reduced hepatic production of Lp(a) by decreasing the assembly of Lp(a) particles through the reduction of apo(a) binding with LDL on the surface of hepatocytes (Lambert et al. 2017). This speculation is supported by in vitro studies showing that PCSK9 induces Lp(a) intracellular assembly and secretion, whereas PCSK9 mAbs reduce the extracellular release of Lp(a) (Villard et al. 2016).

However, as combination therapy with high-dose atorvastatin, evolocumab reduced the plasma concentration of Lp(a) chiefly by a significant increase in the FCR of apo(a) (Watts et al. 2018). The PR of Lp(a) was not significantly altered with the combination. Similar results were also found in another kinetic study in healthy individuals receiving alirocumab treatment (Reyes-Soffer et al. 2017). However, the increase in apo(a) FCR in the latter study was not statistically significant, probably owing to greater variability in study subject characteristics (e.g. mixed race and gender). The mechanistic effect of evolocumab in combination with atorvastatin may involve supraphysiological upregulation of the activity of LDL receptors and decreased competition of Lp(a) with very low concentrations of LDLs for clearance by these receptors. This mechanism suggests that the LDL receptor likely plays a significant role in mediating Lp(a) clearance only when its expression is markedly upregulated and when LDL plasma levels are substantially lowered, allowing decreased competition between LDL and Lp(a) for receptor-mediated uptake in the liver.

The mechanism of action of PCSK9 inhibition has recently been studied in statin-treated patients with high Lp(a). Using stable isotopes, PCSK9 inhibition with alirocumab-lowered plasma Lp(a) concentration by increasing apo(a) FCR in patients with elevated Lp(a) receiving maximally tolerated statin therapy (Watts et al. 2020). However, in patients with very high-Lp(a) concentration, alirocumab significantly lowered plasma Lp(a) concentration by a dual mode of action involving both increased clearance and decreased production of apo(a) (Ying et al. 2022). Taken together, the mechanistic action of PCSK9 mAbs on the PR and FCR of apo(a) appears to be dependent on background statin use and Lp(a) concentration at baseline.

Unlike evolocumab or alirocumab, small interfering RNA on PCSK9 mRNA transcript (e.g. Inclisiran) is a new approach to targeting PCSK9 intracellularly (German and Shapiro 2020; Smith and White 2022). This novel agent was shown to inhibit hepatic synthesis of the PCSK9 protein, and lower apoB-100-containing lipoproteins, including Lp(a) (Ray et al. 2020; Raal et al. 2020). This implies that the effect of PCSK9 inhibition on Lp(a) is irrespective of mode of inhibition of

PCSK9 (intracellular or extracellular. However, the mechanisms of action of inclisiran on Lp(a) metabolism remain to be elucidated.

CETP Inhibitors

CETP plays an important role in lipoprotein metabolism, primarily by its ability to facilitate transfer of esterified cholesterol from high-density lipoproteins (HDL) to apoB-containing lipoproteins (Tall 1993). Treatment with CETP inhibitors, either alone or in combination with statin, can lower Lp(a) concentrations up to 30% (Schmidt et al. 2021). In a kinetic study of patients with hypercholesterolaemia (Thomas et al. 2017), CETP inhibition with anacetrapib lowered Lp(a) concentration by reducing the PR of apo(a) with no effect on the corresponding FCR. However, there is no clear explanation for the reduction in apo(a) PR with anacetrapib which merits further investigation. Despite these metabolic changes, CETP inhibitors did overall not have clinically meaningful effects in large clinical trials. While several CETP inhibitors, including torcetrapid, evacetrapid, dalcetrapid and anacetrapid, have fallen after disappointing clinical trial outcomes (Berberich et al. 2017; Schwartz et al. 2012; Lincoff et al. 2017; Schmidt et al. 2021), two clinical trials with a newer CETP inhibitor obicetrapib (TA-8995; 10 mg) has been shown to increase HDL-cholesterol by 160%, and reduce LDL-cholesterol, apoB and Lp(a) levels approximately by 50–60%, 30–50% and 25–50%, respectively, in patients treated with atorvastatin or rosuvastatin (Hovingh et al. 2015; Ray 2022). The mechanisms of action of this agent on Lp(a) and other lipoproteins merit investigation.

ApoB Antisense Oligonucleotides

Mipomersen is an antisense oligonucleotide (ASO) directed to liver mRNA of apoB that inhibits apoB synthesis (Parham and Goldberg 2019). Accordingly, mipomersen has been shown to significantly lower plasma concentrations of apoB-containing lipoproteins including LDL and Lp(a). In a kinetic study of healthy volunteers, treatment with mipomersen caused a significant decrease of plasma Lp(a) levels that was associated with a significant increase in the FCR of Lp(a), with no effect on corresponding apo(a) PR (Nandakumar et al. 2018). These results were unexpected because inhibition of apoB synthesis with mipomersen would reduce the availability of apoB100 substrate for the assembly of hepatic apoB with apo(a) to form an Lp(a). It is noteworthy that mipomersen also did not reduce VLDL apoB secretion in the same subjects studied (Reyes-Soffer et al. 2016). These observations appear to support the presence of spare apoB pool in the liver that would be utilized for the assembly of Lp(a) in order to maintain hepatic homeostasis for apoB. However, this speculation requires further investigation. In the same study, the increase in Lp(a) FCR observed was similar to the 30% increase in the FCR of LDL apoB100,

supporting a role for the LDL receptors or related receptors in the clearance of Lp(a) particles.

Other Therapies

Lipoprotein apheresis effectively lowers Lp(a) and LDL levels by approximately 60–70%. Kinetic studies, using stable isotope methods, have shown inconsistent findings when comparing Lp(a) and LDL FCRs in patients undergoing apheresis (Parhofer et al. 1999; Armstrong et al. 1989; Kroon et al. 2000). In studying the rebound of Lp(a) and LDL particle concentration following lipoprotein apheresis (Ma et al. 2019c), the clearance of Lp(a) is significantly slower than that of LDL-apoB in patients with elevated Lp(a) and ASCVD. These findings suggest that the clearance pathways for Lp(a) differ from those of LDL-apoB.

Selective thyroid hormone receptor (THR) agonists (such as Resmetirom) can effectively lower plasma Lp(a) concentrations (Hovingh et al. 2022). Activation of THR has been shown to increase LDL receptor expression, resulting in reduced circulating LDL particles (Erion et al. 2007). Whether the lowering effect of Lp(a) is mediated by upregulating the activity of LDL receptor remains unclear and merits further investigation.

Administration of aspirin has been shown to lower Lp(a) levels in patients with high-Lp(a) concentrations irrespectively of apo(a) isoform size (Akaike et al. 2002). This observation is supported by experimental data in HepG2 cells that aspirin reduced Lp(a) production in H2G cell via the reduction of apo(a) gene transcriptional activity with suppression of apo(a) mRNA expression (Kagawa et al. 1999). However, no kinetic studies have yet specified investigated the effect of aspirin on Lp(a) metabolism in humans.

Lomitapide is a small molecule that inhibits lipid transfer by direct binding to microsomal triglyceride transfer protein (MTP) in the liver and intestine (Berberich and Hegele 2017). By inhibiting MTP in hepatocytes and enterocyte, lomitapide reduces VLDL assembly and secretion, and lowers plasma levels of all apoB-1con-taining lipoproteins, including VLDL, LDL and Lp(a) independent of LDL receptor (Cuchel and Rader 2013; Harada-Shiba et al. 2017). Accordingly, lomitapide is specifically approved for lowering LDL-cholesterol in homozygous FH (Berberich et al. 2017). Kinetic studies showed a marked reduction in the production of LDL-apoB-100 (Cuchel et al. 2007). Whether lomitapide reduces Lp(a) concentrations by decreasing apo(a) PR remains to be investigated.

Conclusions and Future Perspectives

Lp(a) is associated with an increased risk of ASCVD, even in patients on intensive lipid-lowering therapy. However, elevated Lp(a) remains an under-recognized, under-treated and under-researched condition with an extremely high risk of

ASCVD. This atherogenic disorder has received little attention due to a significant knowledge gap in understanding Lp(a) pathophysiology. Stable isotope tracer methods provide unique information of the dynamics of Lp(a) particles in the circulation. The interferences from these studies are important for understanding the metabolism of Lp(a) and for developing new therapies. Knowledge of the mode of action of therapeutic interventions is also important for informing shared-decision making and improving adherences to therapies. Future research is still needed to understand whole body metabolism of Lp(a), including the stability of the covalent bonding between apo(a) and apoB-100, the potential recycling of apo(a) in the circulation, the possible formation of Lp(a) complexes with TRLs, and the relative roles of hepatic and renal receptors in the clearance of Lp(a) particles. The precise modes of action of CETP inhibitors, apoB ASO and THR agonists on the metabolism of Lp(a), particularly in patients with high Lp(a), also merit further clarification.

While several therapeutic interventions can lower plasma Lp(a) concentrations (Korneva et al. 2021), it is uncertain that it would mitigate the adverse effects of elevated Lp(a) on ASCVD. Nevertheless, some of the cardiovascular benefit of PCSK9 mAbs in clinical outcome trials are known to be mediated by the lowering of Lp(a) independently of the concurrent reduction in LDL cholesterol. More aggressive treatment strategies involve use of multiple lipid-regulating agents to treat elevated Lp(a). This approach harnesses the complementary mechanisms of action of the different agents. Possible combinations include PCSK9 inhibitor with niacin, CETP inhibitor or THR agonist. Inhibiting hepatic apo(a) synthesis with nucleic acid therapeutics has emerged as a potent approach to reduce plasma Lp(a) levels up to 90% which is not affected by *LPA* gene variants and isoform size (Karwatowska-Prokopczuk et al. 2021). The effect of this novel and specific agent on the metabolism of Lp(a) and other apoB-containing lipoproteins warrants investigation. Further studies are required to characterize the mode of action of newer lipid-regulating agents on the metabolism TRLs and Lp(a). These include inhibitors of angiopoietin-like protein 3 (ANGPTL3) and apoC-III (antibodies and/or nucleic acid-based ASO therapies) (Ward et al. 2022).

Conflicts of Interest GFW has received honoraria for lectures and advisory boards or research grants from Amgen, Arrowhead, AstraZeneca, Esperion, Kowa, Novartis, Regeneron and Sanofi. DCC has nothing to declare.

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