Lipoprotein(a), Interleukin-6 inhibitors, and atherosclerotic cardiovascular disease: Is there an association?

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ABSTRACT

Background and aims: Lipoprotein(a) [Lp(a)] and interleuking-6 (IL-6), an inflammation biomarker, have been established as distinct targets of the residual atherosclerotic cardiovascular disease (ASCVD) risk. We aimed to investigate the association between them, and the potential clinical implications in ASCVD prevention.
Methods: A literature search was conducted in PubMed until December 31st, 2022, using relevant keywords.
Results: Elevated lipoprotein(a) [Lp(a)] levels constitute the most common inherited lipid disorder associated with ASCVD. Although Lp(a) levels are mostly determined genetically by the LPA gene locus, they may be altered by acute conditions of stress and chronic inflammatory diseases. Considering its resemblance with low-density lipoproteins, Lp(a) is involved in atherosclerosis, but it also exerts oxidative, thrombotic, antifibrinolytic and inflammatory properties. The cardiovascular efficacy of therapies lowering Lp(a) by >90% is currently investigated. On the other hand, interleukin (IL)-1b/IL-6 pathway also plays a pivotal role in atherosclerosis and residual ASCVD risk. IL-6 receptor inhibitors [IL-6(R)i] lower Lp(a) by 16–41%, whereas ongoing trials are investigating their potential anti-atherosclerotic effect. The Lp(a)-lowering effect of IL-6(R)i might be attributed to the inhibition of the IL-6 response elements in the promoter region of the LPA gene.
Conclusions: Although the effect of IL-6(R)i on Lp(a) levels is inferior to that of available Lp(a)-lowering therapies, the dual effect of the former on both inflammation and apolipoprotein (a) synthesis may prove of equal or even greater significance when it comes ASCVD outcomes. More trials are required to establish IL-6(R)i in ASCVD prevention and elucidate their interplay with Lp(a) as well as its clinical significance.

1. Introduction

Elevated lipoprotein(a) [Lp(a)] is the most common inherited lipid disorder associated with atherosclerotic cardiovascular disease (ASCVD) [1,2]. Lp(a) is a low-density lipoprotein (LDL) particle in which apolipoprotein B (ApoB) is covalently bound to apo(a), a protein that resembles plasminogen [3]. Lp(a) inheritance follows an autosomal dominant pattern, and is mostly influenced by a single gene, the *LPA* gene, located in chromosome 6q23 [4,5]. Lp(a) levels double within the first year of life as the apo(a) gene reaches full expression between the first and second year of life [1]. Onwards, Lp(a) levels are minimally affected by diet, physical activity, and other environmental factors [1, 3]. On the contrary, Lp(a) may be altered by conditions of stress, such as infections and sepsis, as well as chronic inflammatory diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and psoriasis [1,3]. Traditionally, the threshold for elevated Lp(a) levels is set at >30 mg/dL (>75 nmol/L), with almost 20% of the general population having Lp(a) > 50 mg/dL (>125 nmol/L) [1,6]. Of note, Lp

(a) measurement remains challenging, mainly due to the variability in Kringle IV repeats and apo(a) structure [1,5]. Although clinical assays identifying a unique non-repetitive epitope in apo(a), recognizing each Lp(a) particle once and reporting levels as nmol/L would be ideal, most assays incorporate polyclonal antibodies recognizing different epitopes, and thus potentially underestimate or overestimate Lp(a) levels depending on the presence of small or large isoforms, respectively [1,5]. A plethora of experimental, observational, and genetic studies have shown a linear relationship between Lp(a) levels and the development of ASCVD, as well as heart failure and calcific aortic valve stenosis [1,7,8]. Interestingly, there is a debate whether this increased ASCVD risk is persistent only in individuals with residual inflammatory risk, as indicated by the presence of elevated high-sensitivity C reactive protein (hsCRP >2 mg/L) [9–12].

Currently, there is no approved Lp(a)-lowering treatment [1,3]. Statins tend to increase Lp(a) levels by 10%, while proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are associated with a 20–30% decrease [1,3]. Recently, novel treatments have shown promising results. Specifically, anti-sense oligonucleotides (ASOs) and small interfering RNAs (siRNAs) inhibiting hepatic apo(a) synthesis decrease Lp(a) levels by more than 90% and, presently, they are being investigated in cardiovascular outcome trials [13,14].

Monoclonal antibodies directed against either IL-6 or its receptor [IL-6(R)i], which are widely used in RA and other autoimmune diseases, have also shown a potential Lp(a)-lowering effect [1,15–17]. Of note, the literature has indicated a proatherogenic role of IL-6 in ASCVD, and thus the role of IL-6 inhibition in cardiovascular prevention is being investigated by randomized controlled trials (RCTs) [16,17].

This review aims to discuss relevant evidence on the relationship between Lp(a), IL-6(R)i, and ASCVD, as well as the underlying mechanisms.

2. Methods

For the present state of the art literature review a thorough search was conducted on PubMed until December 31st, 2022, using the following keywords and their combinations: "interleukin-6", "IL-6", "IL-6 inhibitor", "IL-6R inhibitor", "anti-IL-6 monoclonal antibody", "anti-IL-6R monoclonal antibody", "lipoprotein(a)", "Lp(a)" and "atherosclerotic cardiovascular disease". References of eligible articles were scrutinized for relevant articles.

3. Lipoprotein (a) and inflammation

3.1. Lipoprotein(a) and interleukin-6 axis in inflammation

Lp(a)-induced atherosclerosis and the processes of foam cell formation, smooth muscle fiber proliferation and plaque development, have been mostly attributed to the high content of oxidized phospholipids (OxPL) in the Lp(a) particle which increase arterial wall inflammation by activating circulating monocytes and endothelial cells, and less to its atherogenic lipid content, which is considerably lower than that of LDL [18,19]. Lp(a) has been additionally linked to systemic inflammation, including the IL-6 axis [1].

IL-6 is a hormone-like cytokine which participates in innate and adaptive immunity and exhibits both pro- and anti-inflammatory properties. IL-6 is produced mainly by T cells, but also by monocytes, fibroblasts, and endothelial cells, usually at sites of inflammation [20]. Apart from inflammation, IL-6 has a metabolic role, including regulation of lipid metabolism and insulin resistance [20]. IL-6 binds to either soluble or membrane-bound receptors, as well as to glycoprotein 130 (gp130) to create a hexameric complex [20]. Upon receptor activation, intracellular signaling is initiated via the janus kinase as well as the signal transducer and activator of transcription (JAK-STAT) pathway, ultimately leading to target gene transcription [20]. This gives rise to both local and systemic inflammation, sequelae of which are

dysregulation of the balance between regulator and effector T and B cells, as well as immunoglobulin and acute-phase protein production [20].

The Lp(a) gene (*LPA*) has several response elements to IL-6; c.-46 to c.-40 is the most important one to be associated with apo(a) upregulation in the presence of IL-6 [21]. Thus, in the IL-6 milieu, apo(a) and subsequently Lp(a) may act as acute phase reactants [22]. On the other hand, IL-6-mediated induction of apo(a) and Lp(a) can be reversed by other cytokines, namely transforming growth factor β1 and tumor necrosis factor-a (TNF-a), which are also increased during inflammatory conditions [23]. This evidence underlines the complex nature of Lp(a) regulation, which is maintained by the opposing actions of stimulatory and inhibitory cytokines. Of note, inflammatory conditions like RA, SLE, Crohn's disease as well as coronavirus disease 2019 (COVID-19) have been associated with elevated Lp(a) levels [24–29].

Müller et al. incubated human hepatocytes separately with IL-6 and tocilizumab, an IL-6(R)i, and this led to over- and under-expression of the *LPA* gene, respectively. On the contrary, an anti-TNF agent (adalimumab) did not change Lp(a) levels [21]. Another study examined the association between IL-6 and Lp(a) showing that the −174G/C single nucleotide polymorphism of the IL-6 gene is associated with high Lp(a) levels [30].

In this context, IL-6(R)i could potentially lower Lp(a) by inhibiting the effect of IL-6 on the promoter region of the *LPA* gene and, thus, leading to decreased apo(a) production.

3.2. Lipoprotein(a) and interleukin-6 inhibitors

A few studies have investigated the association between IL-6(R) inhibition and Lp(a) levels (Table 1) [31–40]. These were post-hoc analyses of RCTs handling IL-6(R)i or prospective cohorts including patients with RA, except for 1 study which included patients with chronic kidney disease (CKD). The intervention arms included tocilizumab, sarilumab or ziltivekimab, while the comparator groups comprised of placebo or other immunomodulating drugs; follow-up period ranged from 12 to 48 weeks.

As shown in Table 2, all studies demonstrated decreases in Lp(a) levels following IL-6(R)i administration. Inter-group statistical significance was shown in 7 studies, while significant changes from baseline were seen in 4 intervention groups. In the intervention group, Lp(a) changes ranged from −5 to −26.4 mg/dL, while Lp(a) changes varied between −0.2 and −1.1 mg/dL in the comparator groups. Overall, IL-6(R)i reduced Lp(a) levels by 16–41%, and this reduction was dose-dependent in a study with ziltivekimab.

Of note, none of the studies using tocilizumab or sarilumab evaluated major adverse cardiovascular events (MACE). On the contrary, Ridker et al. [38] reported 1 non-fatal myocardial infarction in the ziltivekimab 7.5 mg group, 1 non-fatal myocardial infarction in the ziltivekimab 15 mg group, and 1 cardiovascular death in the placebo group.

4. Interleukin-6 inhibitors and atherosclerotic cardiovascular disease

4.1. Interleukin-6 axis and atherosclerosis

Chronic inflammation and ASCVD risk are linked mostly via the NLRP3 inflammasome – IL-1 – IL-6 axis [16,17].

The NLRP3 inflammasome is a multimeric cytosolic protein complex, which is assembled by pathogen-associated molecular patterns (PAMPs) and DAMPs that activate the NLRP3 cytoplasmic receptor [16,41]. In the context of atherosclerosis, special emphasis has been placed on DAMPs, which include LDL, cholesterol crystals, calcium pyrophosphate crystals, uric acid crystals, glucose, disturbed blood flow, and hypoxia [16,41]. The NLRP3 inflammasome is also activated by neutrophil extracellular traps (NETs), which are pro-atherosclerotic, cytotoxic, nucleus-derived, net-like chromatin formations released extracellularly [16,41,42].

Table 1
Characteristics of studies investigating the association between IL-6(R) inhibition and Lp(a) levels.

First Author	Year	Study Type	Population	Sample size	Duration (weeks)	Intervention	Comparator
Ferraz-Amaro [31]	2019	Prospective	RA	27	48	TCZ (8 mg/kg, IV, q4w)	N/A
Gabay [32]	2016	Post hoc analysis of an RCT (phase IV) [ADACTA]	RA	324	24	TCZ (8 mg/kg, IV, q4w)	ADA
Gabay [33]	2020	Post hoc analysis of an RCT (phase III) [MONARCH]	RA	307	24	Sarilumab (200 mg, SC, q2w)	ADA
Garcia-Gomez [34]	2017	Cross-sectional analysis of a prospective study [CARMA]	RA	441	N/A	TCZ	Anti-TNF Other biologic (RTX, ABA) Non-biologic
Lee [35]	2016	Substudy of an RCT (phase III) [MEASURE]	RA	20	12	TCZ (8 mg/kg, IV, q4w)	N/A
McInnes [36]	2015	RCT, phase III	RA	132	24	TCZ (8 mg/kg, IV, q4w)	Placebo
Pierini [37]	2021	Prospective	RA	28	12	TCZ (4–8 mg/kg, IV, q4w or 162 mg SC)	N/A
Ridker [38]	2021	RCT, Phase II	CKD	264	24	Ziltivekimab (7.5–30.0 mg, SC, q4w)	Placebo
Schultz [39]	2010	Prospective	RA	11	12	TCZ (8 mg/kg, IV, q4w)	N/A
Virone [40]	2019	Ancillary study of an RCT, Phase III [ROC]	RA	203	24	TCZ (500 mg, IV, q4w)	Anti-TNF

ABA: Abatacept; ADA: Adalimumab; CKD: Chronic kidney disease; IV: intravenous; N/A: Not applicable; RA: Rheumatoid arthritis; RCT: Randomized controlled trial; RTX: Rituximab; SC: subcutaneous; TCZ: Tocilizumab; TNF: Tumor necrosis factor; q2w: every 2 weeks; q4w: every 4 weeks.

Table 2
Effect of IL-6(R) inhibitors on Lp(a) levels.

First Author (Year)	Intervention				Comparator				P value
	Agent	Sample size (females, %)	Age (years)	Lp(a) - change from baseline (mg/dL)	Agent	Sample size (females, %)	Age (years)	Lp(a) - change from baseline (mg/dL)	
Ferraz-Amaro (2019) [31]	TCZ	27 (88)	52 ± 11	At 12 w: 6 (−33, −0)	N/A	N/A	N/A	N/A	0.008[e]
Gabay (2016) [32]	TCZ	162 (80)	54 ± 13	At 8 w: 7.6 (12)[a]	ADA	162 (82)	53 ± 12	At 8 w: -1.1 (15.1)[a]	N/A
Gabay (2020) [33]	Sarilumab	153 (84)	50 ± 13	At 12 w: -5.9 (−13.4, −1.3) At 24 w: -6.03 (−15.7, −2.1) −41%	ADA	154 (79)	53 ± 12	At 12 w: -0.2 (−5.4, 2.8) At 24 w: -0.45 (−4.0, 2.8) −2.8%	<0.0001[de]
Garcia-Gomez (2017) [34]	TCZ	21 (89)	43 ± 14	8.5 (6.0–15.5)[b]	Anti-TNF Other biologic Non-biologic	131 (76) 24 (66) 265 (75)	43 ± 13 43 ± 15 48 ± 13	15.4 (6.0–32.3)[b] 10.8 (2.2–26.3)[b] 16.7 (7.2–40.0)[b]	0.05[d]
Lee (2016) [35]	TCZ	20 (79)	59 (54–62)	At 12 w: -12.2 (−17.2, −7.2) −41%	N/A	N/A	N/A	N/A	0.000[c]
McInnes (2015) [36]	TCZ	69 (83)	57 (49–62)	At 12 w: -37% At 24 w: -38%	Placebo	63 (75)	57 (50–64)	At 12 w: -0.3% At 2 4w: -0.4%	<0.0001[df]
Pierini (2021) [37]	TCZ	28 (89)	61 ± 14	At 12 w: -26.4	N/A	N/A	N/A	N/A	<0.01[c]
Ridker (2021) [38]	Ziltivekimab	7.5 mg: 66 (48)	70 (60–74)	At 12 w: -16%	Placebo	66 (44)	66 (60–74)	At 12 w: 0%	<0.0001[d]
		15 mg: 66 (55)	66 (59–74)	−20%					<0.0001[d]
		30 mg: 66 (48)	68 (61–76)	−25%					<0.0001[d]
Schultz (2010) [39]	TCZ	11 (64)	51 ± 4	At 4 w: -10.2[a] At 12 w: -14.6[a]	N/A	N/A	N/A	N/A	<0.05[cg]
Virone (2019) [40]	TCZ	47 (80)	N/A	At 24 w: -5 (−11, 1)	Anti-TNF	96 (83)	56 (45–64)	At 24 w: -1 (−2.0, 1.0)	<0.001[d]

Abbreviations: ADA: Adalimumab; N/A: Not applicable; TCZ: Tocilizumab; TNF: Tumor necrosis factor.
[a] Values represent mean values; the rest of the Lp(a) values are expressed as median.
[b] Values represent Lp(a) measurements post-treatment, not changes from baseline.
[c] In comparison with baseline.
[d] In comparison with control group(s).
[e] At week 24.
[f] At week 12.
[g] At both weeks 4 and 12.

During the process of pyroptosis, the NLRP3 inflammasome produces IL-1b and IL-18, which are potent mediators of systemic inflammation [16,41]. IL-1b is initially produced as pro-IL-1b, and, upon activation of the NLRP3 inflammasome, it is cleaved into its active form by caspase-1 [16, 41]. IL-1b has autocrine, paracrine, and endocrine effects, and is implicated in the pathogenesis of autoinflammatory diseases, gout, diabetes, atherosclerosis, and neurodegenerative diseases. IL-1b induces its own production, together with that of IL-6 [16, 41]. IL-6 may also be induced by other factors such as TNF, toll-like receptors, prostaglandins, adipokines, and stress [43]. During acute inflammation, IL-6 promotes the hepatic synthesis of various acute-phase proteins, such as fibrinogen, plasminogen activator inhibitor-1 (PAI-1), serum amyloid A (SAA) and CRP, implicated in host immune responses, but also in thrombogenesis [16,41]. Of note, an IL-6-mediated increase in the risk of MACE has been noted in patients with COVID-19 [29]. Persistently elevated IL-6 levels result in a shift to chronic inflammation and, subsequently, to tissue damage [44]. Effects on the cardiovascular system include endothelial dysfunction, arterial stiffness, microvascular flow dysfunction, and atherosclerosis [16]. An example of persistent systemic inflammation where IL-6 has a pivotal role is RA. RA is the most common autoimmune disease associated with accelerated atherosclerosis, and, in fact, this effect occurs even in the absence of classic cardiovascular risk factors [45–47].

In this context, therapeutic strategies aiming at upstream molecules of this axis, and primarily at IL-6 and IL-1b, have been developed [17,48, 49].

4.2. Cardiovascular outcome trials handling anti-inflammatory drugs targeting the NPLR3 inflammasome and the IL-1b/IL-6 pathway

Recently, several RCTs have assessed the effect of the NPLR3 inflammasome – IL-1b – IL-6 pathway inhibitors on atherosclerosis [48]. The first RCT providing robust evidence on the inflammatory hypothesis was Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) [50]. This proof-of-concept study showed that the administration of the highest dose (300 mg) of canakinumab, an anti-IL-1b monoclonal antibody, in addition to lipid-lowering therapy was associated with MACE reduction by 15% in patients with established ASCVD and elevated hsCRP (hazard ratio, HR: 0.85, 95% CI: 0.74–0.98) [50]. However, canakinumab was associated with a higher incidence of fatal infection vs placebo [50]. The next major study to provide evidence on the association between inflammation and ASCVD was Cardiovascular Inflammation Reduction Trial (CIRT). Low-dose methotrexate (15–20 mg weekly) did not reduce levels of interleukin-1β, interleukin-6, or CRP, and was not associated with cardiovascular event reduction compared with placebo [51]. On the other hand, Colchicine Cardiovascular Outcomes Trial (COLCOT) evaluated the efficacy of low-dose colchicine (0.5 mg qd), an NLRP3 inflammasome inhibitor, on MACE reduction after myocardial infarction (MI). Colchicine administration within 30 days of MI reduced MACE (HR: 0.77, 95% CI: 0.61–0.96), and this finding was subsequently verified in individuals with chronic coronary artery disease in the LoDoCo2 trial (HR: 0.69; 95% CI: 0.57–0.83) [52,53]. Likewise, CLEAR-SYNERGY is currently investigating the effect of colchicine (0.5 mg, twice daily) with or without spironolactone (25 mg, once daily) and SYNERGY stent in patients with acute MI [54].

The fact that the cardioprotective effects of canakinumab, as demonstrated by CANTOS, were largely mediated by IL-6 inhibition indicates a potential atheroprotective role of IL-6(R)i in ASCVD patients. Specifically, a sub-analysis of CANTOS showed that inflammatory risk, as defined by high levels of hsCRP and IL-6, was higher in CKD patients than in patients with normal renal function [55]. Therefore, CKD patients might benefit more from IL6(R)i treatment. Other RCTs investigating the use of IL6(R)i in ASCVD prevention include Randomized Evaluation of Patients with Stable Angina Comparing Utilization of Noninvasive Examinations (RESCUE) and Ziltivekimab Cardiovascular Outcomes Study (ZEUS), as well as the phase II RCT of single-dose TCZ

in non-ST elevation MI by Kleveland et al., and the ASSessing the Effect of Anti-IL-6 Treatment in Myocardial Infarction (ASSAIL) trial, which evaluated the effect of single-dose TCZ on myocardial salvage in acute ST-elevation MI patients [38,56,57]. Specifically, RESCUE trial, a phase II multicenter RCT including patients with stage 3–5 CKD and high hsCRP levels, showed that ziltivekimab (7.5–30 mg, every 4 weeks) reduces both hsCRP and Lp(a) levels in a dose-dependent manner [38]. Given its promising results, ziltivekimab was further advanced into ZEUS, a large ongoing cardiovascular outcome trial including patients with established ASCVD, stage 3–4 CKD, and high hsCRP [49]. Other ongoing trials of IL-6(R)i in non-rheumatic patients with ASCVD include GLORIOUS-II, a multifactorial design trial of TCZ in post-open heart surgery patients, and DOBERMANN, a trial of dobutamine and single-dose TCZ in acute MI patients with cardiogenic shock [58,59].

Interestingly, a recent meta-analysis with 26 RCTs comparing anti-inflammatory therapies with placebo in patients with established ASCVD or at high cardiovascular risk has shown that anti-inflammatory treatment, especially that targeting IL-6 pathway may serve as promising treatment strategies to ameliorate the risk of myocardial infarction (relative risk, RR: 0.93, 95% CI: 0.88–0.98 and RR: 0.83, 95% CI: 0.74–0.93, respectively) [60].

Finally, considering that the comorbidities of included study participants, namely established ASCVD and CKD, could be associated with elevated Lp(a) levels, additional analyses could help elucidate the effect of IL-6(R)i on Lp(a) and associated ASCVD risk.

5. Clinical implications of Interleukin-6 inhibitors in Lipoprotein(a) management

Lp(a) is an independent, causal, and measurable risk factor of ASCVD. Ongoing trials are investigating the cardiovascular efficacy of novel therapies inhibiting apo(a) synthesis and lowering Lp(a) over 90% [1]. In the absence of approved Lp(a)-lowering treatment, current guidelines recommend early intensive risk factor modification in patients with elevated Lp(a) levels [1]. Another approach towards Lp (a)-associated ASCVD risk reduction might be the inhibition of the IL-6 pathway, which could not only modestly lower Lp(a) levels, but mostly ameliorates the accompanying inflammatory effect [28]. A post-hoc analysis of the ODYSSEY OUTCOMES study showed that treatment with alirocumab mostly benefited acute coronary syndrome patients with elevated hsCRP and Lp(a) levels compared to those with one or none increased [9]. Similar results were also found by another RCT, the Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High Risk for Vascular Outcomes (ACCELERATE) trial [10]. In the setting of primary ASCVD prevention, MESA (Multi-Ethnic Study of Atherosclerosis) showed that elevated Lp(a) was associated with increased cardiovascular disease (CVD) risk in individuals with elevated hsCRP (Hazard Ratio, HR: 1.36; 95% CI: 1.02–1.81 for Lp(a): 50–99.9 mg/dL, and HR: 2.09; 95% CI: 1.40–3.13 for Lp(a) ≥100 mg/dL) [11]. Although isolated elevations of either Lp(a) or hsCRP had no effect on CVD risk, the combination of elevated Lp(a) ≥50 mg/dL and hsCRP ≥2 mg/L contributed significantly to ASCVD risk (HR: 1.62; 95% CI: 1.25–2.10) and all-cause mortality (HR: 1.39; 95% CI: 1.12–1.72) [11]. On the contrary, the Copenhagen General Population Study has recently shown that high Lp(a) remained a significant factor for ASCVD and aortic valve stenosis, regardless of CRP levels (HR: 1.61, 95% CI: 1.43–1.81 for those with CRP <2 mg/L and HR: 1.57, 95% CI: 1.36–1.82) [12]. Considering these controversial results, the theory that patients with elevated Lp(a) levels may profit from anti-inflammatory treatment with IL-6(R)i needs to be addressed by relevant RCTs.

6. Perspectives

Although the effect of IL-6(R)i on Lp(a) levels is not similar to that of ASOs or siRNAs, the dual effect of the former on both inflammation and

apo(a) synthesis may prove of equal or even greater significance when it comes to CVD outcomes. A similar hypothesis was confirmed with statins in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial [61]. After enrolling 17,802 apparently healthy men and women with LDL-C <130 mg/dL and hsCRP ≥2.0 mg/L, JUPITER showed that treatment with rosuvastatin 20 mg qd was associated with a significant reduction in MACE when compared with placebo (HR: 0.56, 95% CI: 0.46–0.69) [61]. Interestingly, this effect was greater in individuals who achieved the greatest reductions in LDL-C (<70 mg/dL) and hsCRP (<2 mg/L) (HR: 0.35, 95% CI: 0.23–0.54) [61].

Furthermore, a topic of interest for future clinical trials would be the assessment of the cardiovascular efficacy of anti-inflammatory and Lp (a)-lowering combination therapies. Would the addition of an IL-6R(i) to Lp(a)-lowering therapies lead to greater ASCVD reduction? Nevertheless, Lp(a)-related ASCVD risk management is currently under evaluation and optimal therapeutic modalities are yet to be discovered.

7. Conclusions

Although Lp(a) is mostly genetically determined, it can be increased in acute and chronic inflammatory conditions. Evidence derived from observational studies and RCTs has shown that treatment with IL-6(R)i decreases Lp(a) levels. According to experimental evidence, this could be attributed to the inhibition of IL-6, which promotes apo(a) production. This comes to mark a new era in ASCVD prevention, which focuses on the inflammatory pathway of atherosclerosis. Ongoing RCTs investigating the role of IL-6(R)i in secondary ASCVD prevention could help elucidate the interaction between these drugs and Lp(a), as well as the corresponding effect on clinical outcomes.

Author contributions

Anastasios Makris and Fotios Barkas have contributed equally: conceptualization, methodology, validation, formal analysis, investigation, writing – original draft, visualization; Petros P. Sfikakis: writing – review & editing, supervision; Evangelos Liberopoulos: writing – review & editing, supervision; Theodosios D. Filippatos: writing – review & editing, supervision; Kausik K. Ray: writing – review & editing, supervision; Aris P. Agouridis: conceptualization, methodology, writing – review & editing, supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Fotios Barkas has received honoraria from Amgen, Novartis, Novo Nordisc and Viatris.Petros P Sfikakis has received consultant fees from Actelion, Pfizer, Genesis, MSD, UCB, Boehringer Ingelheim, Enorasis, Farmaserv-Lilly, Gilead, Abbvie, and Novartis. He has received grants and research support from Abbvie, Roche, Pfizer, Faran, Amgen, Jannsen, Boehringer Ingelheim, and Gilead.Evangelos Liberopoulos reports personal fees and non-financial support from Amgen, personal fees from Servier, personal fees from Boehringer-Ingelheim, personal fees and non-financial support from AstraZeneca, personal fees from MSD, personal fees from Lilly, personal fees and non-financial support from Bayer, personal fees from Novartis, personal fees from Chiesi, outside the submitted work.Theodosios D. Filippatos reports participation in advisory board for Lilly and lecture honoraria from Boehringer Ingelheim, Mylan, Astra Zeneca, Lilly, Recordati, Bausch Health, Servier, Viatris, Omega-Pharma and Innovis.Kausik K. Ray has received honoraria for consulting, lectures from Kowa, Amgen, Regeneron Pharmaceuticals, Sanofi, Daiichi Sankyo, Pfizer, Viatris, AstraZeneca, Eli Lilly, Esperion, New Amsterdam Pharma, Novartis, Silence Therapeutics, Bayer, Boehringer Ingelheim, Novo Nordisk, SCRIBE, CRISPR, Cargene, Vaxxinity, Abbott, Resverlogix. In addition, he has received research

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