Beyond Lipoprotein(a) plasma measurements: Lipoprotein(a) and inflammation

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Abstract

Genome wide association, epidemiological, and clinical studies have established high lipoprotein(a) [Lp(a)] as a causal risk factor for atherosclerotic cardiovascular disease (ASCVD). Lp(a) is an apoB100 containing lipoprotein covalently bound to apolipoprotein(a) [apo(a)], a glycoprotein. Plasma Lp(a) levels are to a large extent determined by genetics. Its link to cardiovascular disease (CVD) may be driven by its pro-inflammatory effects, of which its association with oxidized phospholipids (oxPL) bound to Lp(a) is the most studied. Various inflammatory conditions, such as rheumatoid arthritis (RA), systemic lupus erythematosus, acquired immunodeficiency syndrome, and chronic renal failure are associated with high Lp(a) levels. In cases of RA, high Lp(a) levels are reversed by interleukin-6 receptor (IL-6R) blockade by tocilizumab, suggesting a potential role for IL-6 in regulating Lp(a) plasma levels. Elevated levels of IL-6 and IL-6R polymorphisms are associated with CVD. Therapies aimed at lowering apo(a) and thereby reducing plasma Lp(a) levels are in clinical trials. Their results will determine if reductions in apo(a) and Lp(a) decrease cardiovascular outcomes. As we enter this new arena of available treatments, there is a need to improve our understanding of mechanisms. This review will focus on the role of Lp(a) in inflammation and CVD.

Keywords

Inflammation; Atherosclerosis; Lipoprotein(a); Cardiovascular diseases

1. Introduction

Genome wide association, epidemiological, and clinical studies have established high lipoprotein(a) [Lp(a)] as a causal risk factor for atherosclerotic cardiovascular disease (ASCVD) \cite{1,2}. Lp(a) contains several proteins \cite{3}. Its main protein components are apolipoprotein(a) [apo(a)] and apolipoprotein B100 (apoB100) which are bound by covalent

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Conflicts of Interest

None.
and non-covalent bonds [4]. Lp(a) also contains cholesterol, phospholipids, and triglycerides [5]. High plasma levels of Lp(a) are linked to atherosclerosis, thrombosis, and arterial calcification [6], which may be driven by its pro-inflammatory effects [7]. Lp(a) has been found in atherosclerotic plaques [8]. Several studies have suggested that Lp(a) itself may enhance inflammation in endothelial cells, monocytes, and macrophages, via the oxidized phospholipids (oxPL) that are bound to Lp(a) [9–11]. Previous studies point to both the apoB component and the apo(a) moiety as drivers of inflammation that can result in ASCVD [3,12]. Proteomic studies have also identified a large number of apolipoproteins on Lp(a), as well as platelet-activating acetylhydrolase (PAF-AH) and paraoxinase-1 (PON-1) [3,13,14], which may link Lp(a) to disease states. Some currently identified proteins and their function are listed in Table 1.

Plasma Lp(a) levels are to a large extent determined by genetics [15,16]. The LPA gene is derived from a duplication of the plasminogen gene, but apo(a) has no plasminogen-like activity and so, in addition to its apoB containing lipoprotein structure, it may compete with plasminogen for binding to fibrin, thereby impairing fibrinolysis and promoting thrombosis at sites of endothelial breakdown [17,18]. Recent data suggest ex vivo measures of fibrinolysis are not affected in subjects with high Lp(a). However, in vivo studies are lacking [19].

High Lp(a) levels have also been reported in various inflammatory conditions, such as rheumatoid arthritis (RA), systemic lupus erythematosus, acquired immunodeficiency syndrome, chronic renal failure, and pulmonary arterial hypertension [20–31]. Differences in Lp(a) levels have also been observed in pregnancy [32,33], and diabetes [34,35], inflammatory conditions that will not be addressed in this review.

Large data sets pointing to Lp(a) as a top genetic marker for cardiovascular disease [36,37] have increased interest in the identification of pathways and involved culprits of disease. Importantly, there are various treatments that lower Lp(a) levels. Non-lipid altering treatments affect Lp(a) levels, including niacin [1,6,11,38–40]. PCSK9 inhibitors modestly lower Lp(a) levels [9,41], as do additional apoB lowering therapies [42,43]. Apharesis lowers Lp(a) and other apoB containing lipoproteins, and is FDA approved for severe elevations of Lp(a) levels [11,44]. Studies assessing risk reduction of apharesis are ongoing (NCT02791802). There are three ongoing studies examining the effect of apo(a) lowering with novel targeted therapies (NCT0404606602-SLN360, NCT04023552-TQJ230, and NCT04270760-AMG 890) [10,45–49]. As we enter a new arena of available treatments, there is a need to improve our understanding of mechanisms downstream of Lp(a) and mechanisms that regulate plasma Lp(a) levels. This review will focus on the role of Lp(a) in inflammation and cardiovascular disease (CVD).

2. Inflammation and CVD

The CANTOS (canakinumab anti-inflammatory thrombosis outcomes study) trial has for the first time provided direct evidence that inflammation enhances CVD events in humans, by showing that antagonism of interleukin (IL)-1β decreases the incidence of recurrent CVD events in patients with high levels of C reactive protein (CRP) [50], irrespective of
 effects on plasma lipid levels. IL-1β is a main regulator of inflammation and cytokine secretion, including IL-6 [51,52]. Mendelian Randomization studies and meta-analyses have shown a link between IL-6R polymorphisms and CVD [53,54]. In a subgroup of CANTOS participants screened for IL-6 plasma levels (n = 4833), decreases in plasma levels of IL-6 downstream of IL-1β antagonism by canakinumab were associated with a reduction of CVD events [55]. Moreover, the residual CVD risk in this subgroup of the CANTOS trial was proportional to plasma IL-6 levels [56]. Together, these studies indicate an important role for IL-6 in CVD events, independent of plasma lipid levels. Other trials evaluating anti-inflammatory drugs (methotrexate and colchicine) in CVD include the CIRT (cardiovascular inflammation reduction trial), LoDoCo (low dose colchicine), COLCOT (colchicine cardiovascular outcomes trial), and LoDoCo2 (low dose colchicine 2) trials. While low-dose methotrexate was ineffective in reducing CVD events, leading to CIRT being stopped prematurely, the effects of colchicine on CVD are still being evaluated in ongoing research studies [57–61]. The outcome of these trials has recently been reviewed [62].

The above observations suggest that IL-6R blockade by tocilizumab, which is used as a therapy for RA, would have beneficial effects in CVD. However, tocilizumab treatment increases plasma LDL-cholesterol in RA patients [20,63–67], which has been attributed to decreased hepatic LDL receptor levels, as shown in HepG2 cells [65]. In three USA databases, as well as in studies in Japan and Italy, treatment with tocilizumab had no effects on major adverse cardiovascular events (MACE) [68–71]. Perhaps this was due to the study populations mainly consisting of RA patients that generally have higher levels of inflammation and lower LDL-cholesterol levels [63,72]. Two small trials assessed the role of tocilizumab in myocardial infarction (MI) directly, in patients that did not have RA. A clinical trial in non-ST-elevation myocardial infarction (nSTEMI) patients showed that tocilizumab did not affect MI [73] and the ASSAIL-MI (ASSessing the Effect of Anti-IL-6 Treatment in Myocardial Infarction) trial (NCT03004703) testing a role for tocilizumab in STEMI patients is ongoing [74]. In sum, the CANTOS trial has provided direct evidence for a role of inflammation in CVD, which has mainly been attributed to decreases in plasma IL-6 downstream of IL-1β signaling. A role for IL-6 in CVD is supported by Mendelian Randomization studies and meta-analyses showing links between IL-6R polymorphisms and CVD. Whether IL-6R blockade by tocilizumab decreases the incidence of CVD has only been studied in one small population of MI patients. The ASSAIL-MI trial, which is currently ongoing, is likely to provide additional insights as to whether tocilizumab decreases the incidence of CVD.

3. IL-6 regulates Lp(a) plasma levels

As previously stated, in addition to genetic control [15,16], various inflammatory diseases including RA have been linked to high Lp(a) levels. Studies using drugs to target inflammatory pathways in RA patients have provided insights into these links. IL-6R blockade by tocilizumab, but not tumor necrosis factor α (TNFa) blockade by adalimumab, decrease plasma Lp(a) levels by ~30–40% in RA patients [20,63,64,75]. These data thus suggest that decreased IL-6R signaling and not TNFa signaling, reduces plasma Lp(a) levels. Conversely, the IL-6 promoter polymorphism (~174 G/C), which is associated with
high plasma IL-6 levels, correlates positively with plasma Lp(a) [76], as do plasma levels of IL-6 as demonstrated in ~1153 human subjects [77]. The latter was confirmed in a subgroup of subjects (n = 635) without chronic inflammatory disease, suggesting a positive relationship between plasma IL-6 and Lp(a) in the general population [77]. This subgroup showed a positive correlation of IL-6 responsive genes with LPA mRNA expression in liver biopsies, further supporting a positive association between IL-6 and Lp(a) [77]. In vitro experiments in hepatocytes transfected with a plasmid for LPA substantiated that IL-6 enhances LPA expression, mediated by binding of STAT3 to the LPA promoter [77]. Hence, multiple lines of evidence show regulation of plasma Lp(a) levels by IL-6.

However, a clinical trial in nSTEMI patients showed that tocilizumab did not affect Lp(a) levels, measured at day 1, 3, and months 3 and 6 after tocilizumab treatment [73]. Statin-therapy, which may increase Lp(a) levels, was suggested to explain why tocilizumab did not decrease Lp(a) levels in this specific cohort [73]. Indeed, a recent meta-analysis from six randomized trials (n = 5256 patients) using a single well-established method for Lp(a) measurements has shown that statins increase Lp(a) levels (11.6–20.4% for pravastatin and 18.7–24.2% for atorvastatin) [78]. Mechanistically, atorvastatin increased LPA mRNA levels and apolipoprotein(a) in HepG2 cells [78], via an as yet unidentified mechanism. In summary, signaling downstream of the IL-6R affects Lp(a) levels in RA patients. Whether this is also the case for CVD remains to be elucidated, although one study found no differences, perhaps because the tocilizumab effect on Lp(a) is compromised by statin-therapy. Nonetheless, the statin effects may not be the complete explanation for this outcome. In future studies, it would be of interest to evaluate whether IL-6R polymorphisms that associate with CVD risk affect plasma Lp(a) levels.

Apart from inflammation, Lp(a) inversely correlates with levels of bile acids in plasma in patients with biliary obstructions [79]. Mechanistic studies in animal models and hepatocytes revealed that activation of the Farnesoid X Receptor (FXR) by bile acids suppressed LPA mRNA transcription, irrespective of effects on inflammatory gene expression [79]. In support of these findings, a later study showed that therapy with the FXR agonist chenodeoxycholic acid (CDCA) for gallstone disease over a period of three weeks decreased plasma Lp(a) levels significantly [80]. In sum, both IL-6 and FXR pathways have been shown to regulate plasma Lp(a) levels.

4. **Tocilizumab, Lp(a), and COVID-19 (SARS-CoV 2)**

IL-6 is elevated during the cytokine storm in COVID-19 patients [81–83]. It has been hypothesized that Lp(a) levels, as a result thereof, may also be upregulated, and that high Lp(a) could contribute to inflammation and thrombosis observed in COVID-19 [84]. Importantly, studies in 9005 UK Biobank participants found that plasma levels of apoB, a component of Lp(a), was not associated with COVID-19 [85]. The link between IL-6, Lp(a), and COVID-19 is of interest, particularly in view of studies addressing whether tocilizumab suppresses symptoms and complications associated with COVID-19. Potential anti-inflammatory effects of tocilizumab could be mediated by decreases in Lp(a). The effect of tocilizumab on reducing symptoms and mortality related to COVID-19 has been investigated extensively. Some studies, though small in terms of number of patients, have
shown clinical benefit [81–83], while others did not [86–88]. A recent meta-analysis and meta-regression has suggested that tocilizumab is associated with clinical meaningful improvements in COVID-19 [89]. This is supported by recent results in a larger group of 4116 COVID19 patients in the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial, that, although preliminary, showed that tocilizumab improves survival in hospitalized COVID19 patients with hypoxia and systemic inflammation [90]. Lp(a) may be elevated during the cytokine storm in COVID-19 and could contribute to an increased incidence of thrombosis [84].

5. Lp(a), oxidized phospholipids, and CVD risk

Lp(a) has been found to enhance inflammation, presumably due to oxidized phospholipids (oxPL) bound to Lp(a). In addition to Lp(a), oxPL circulate on oxidized LDL (oxLDL) and apoptotic cells [91]. This was found using E06, an antibody that binds to the phosphocholine head-group of most oxPL, but not PL [91]. E06 blocks the uptake of oxLDL, but not LDL by macrophages, as well as their ingestion of apoptotic cells, but not viable cells [91]. A landmark study by the Witztum Laboratory has shown that E06 suppresses inflammation and atherosclerosis in Ldlr−/− mice, providing direct evidence that oxPL, in mice either derived from oxLDL or apoptotic cells, accelerates atherosclerosis [92].

Using the E06 and apoB-100/E06 assays, several studies have shown a positive relationship between oxPL and acute coronary syndrome (ACS), CVD events, and MI [93–95], indicating that oxPL is a clear pro-atherogenic factor in humans. Whether the positive relationship between oxPL and CVD is driven by oxPL bound to LDL and/or Lp(a), has been reviewed in detail [93]. A positive correlation between Lp(a) and plasma oxPL in plasma of patients from several CVD cohorts support a role of oxPL association with Lp(a) [93].

Lp(a) concentrations correlate inversely with the size of the apo(a) isoform, and the small apo(a) isoform has high affinity for oxPL [93,96,97]. This may explain the higher affinity of apo(a) for oxPL when Lp(a) concentrations are high [7,96,98,99]. Mendelian Randomization studies have shown that the small isoform of apo(a) associated with Lp(a) plasma levels > 50 mg/dL, increases CVD risk by 2–2.5-fold compared to the large apo(a) isoform [36,100]. These studies are limited to white cohorts and Lp(a) levels vary by ethnicity [101,102]. Importantly, not all subjects with Lp(a) plasma levels > 50 mg/dL develop CVD, suggesting that additional factors may be required for CVD to develop in the setting of high plasma Lp(a) levels.

Inflammation has been suggested to potentiate CVD risk mediated by Lp(a) and oxPL [103]. This was investigated by assessing the correlation between Lp(a) or apoB-bound-oxPL and CVD risk in carriers and non-carriers of an IL-1 haplotype that is associated with increased inflammation [103]. In this study a positive relationship between Lp(a) or apoB-bound-oxPL and CVD risk was shown in subjects carrying this IL-1 haplotype, but not in non-carriers [103]. This positive relationship was strengthened in subjects with high levels of CRP. These findings suggest that Lp(a) and oxPL enhance CVD in the presence of IL-1 induced inflammation, particularly when this results in high CRP levels.
6. Clinical implications of high Lp(a) linked to inflammation

The role of Lp(a) in inflammation has been evaluated extensively in *in vitro* studies. Early studies have shown that Lp(a) is a chemoattractant for monocytes and upregulates IL-6 secretion in these cells [104–106]. Lp(a) also enhances the expression of vascular cell adhesion molecule (VCAM–1), intracellular adhesion molecule (ICAM–1), E-selectin, IL-6, and IL-8 in human endothelial cells, as well as IL-8 in macrophages [107–110]. In line with these data, Lp(a) increases monocyte adhesion to human endothelial cells, and monocyte transmigration through the endothelial layer, early events in the development of atherosclerotic plaques [110,111]. In studies with E06 antibodies and apo(a)-mutated peptides that show reduced affinity for oxPL binding, all effects of Lp(a) on enhancing expression of adhesion molecules and cytokines were shown to be dependent on oxPL [109–111].

The role of Lp(a) in vascular inflammation has been studied in subjects with either high or low Lp(a) plasma levels. These subjects were not on statins, not smoking, and were matched for age, sex, and body mass index. They did not show differences in leukocyte levels or blood pressure [111]. Essentially, the only difference between these groups were the plasma Lp(a) levels. Using positron emission tomography/computed tomographic (PET/CT) imaging, subjects with high Lp(a) levels (average ~108 mg/dL) showed an increase in 18 F-fluorodeoxyglucose (FDG) uptake in the arterial wall of the carotid artery and ascending aorta in comparison to subjects with low Lp(a) (average ~7 mg/dL), reflecting an increase in arterial inflammation [111]. Normalized wall index of the carotid artery was not different between the groups as shown by magnetic resonance imaging (MRI) [111]. Subjects with high Lp(a) had high oxPL-apoB as well as oxPL-Lp(a) levels compared to the low Lp(a) group. Elegant 99mTc-labeling studies of autologous peripheral blood mononuclear cells (PBMCs) revealed an increase in PBMC accumulation in the arterial wall of the carotid and the aorta in subjects with high Lp(a) [111].

These studies for the first time provided solid evidence, in the human setting, that Lp(a) enhances arterial wall inflammation, presumably by enhancing monocyte entry. The latter could be the consequence of increased monocyte activation and/or endothelial activation. It has been shown in monocytes from patients included in the PET/CT study that an increase in plasma Lp(a) was accompanied by increases in C-C chemokine receptor 7 (CCR7), CD62L (L-selectin), the integrins CD11b, CD11c, and CD29 on the surface of monocytes, which reflect monocyte activation [111]. Monocytes from patients with high Lp(a) showed an increase in endothelial transmigration as well as cytokine secretion; the latter being mediated by oxPL on Lp(a) [111]. This likely explains the enhanced monocyte entry in the arterial wall in the subjects with high plasma Lp(a) levels.

Currently, antisense-based approaches to lower plasma apo(a) levels are in clinical trials. IONIS-APO(a)LRx decreases apo(a) plasma levels by ~72% and oxPL-Lp(a) levels at 85 days after injection compared to day 0 [45]. Interestingly, incubation of plasma from patients who received IONIS-APO(a)LRx with healthy aortic endothelial cells suppressed ICAM-1, VCAM-1, monocyte chemoattractant protein-1 (MCP-1), and IL-6 expression, compared to plasma from placebo treated patients, suggestive of suppression of endothelial activation by
antisense oligonucleotides to apo(a) [110]. These data support the therapeutic potential of these drugs for decreasing CVD, in particular when CVD is driven by inflammation.

Further studies examining the monocyte activation phenotype by the same group have shown that elevated Lp(a) plasma levels in otherwise healthy individuals were associated with an increase in interferon α (IFNα) and IFNγ responsive genes in monocytes, compared to individuals with low Lp(a) [112]. These differences were exacerbated in monocytes from CVD patients with high Lp(a) plasma levels that also showed an increase in TNFα signaling pathways [112]. Additional studies showed that lowering Lp(a) levels by ~47% via an antisense-based approach (AKCEA-APO(a)-LRx) in CVD patients led to suppression of IFNα, IFNγ, and Toll like receptor (TLR) responsive genes in monocytes [112]. AKCEA-APO(a)-LRx treatment also suppressed CCR2, CX3C chemokine receptor 1 (CX3CR1), and Toll like receptor 2 (TLR2) surface expression on monocytes, decreasing their trans-endothelial migratory capacity. These data support the findings in earlier studies [111] that Lp(a) enhances monocyte entry into atherosclerotic plaques, which may be mediated by direct effects on monocytes, and endothelial cells [110].

In the same study showing anti-inflammatory effects of AKCEA-APO(a)-LRx on monocytes [112], also monocytes from the ANITSCHKOW trial had been included. This trial included patients with high plasma levels of LDL-cholesterol and high Lp(a) (~80 mg/dL) [113]. While the PCSK9 antibody evolocumab lowered plasma LDL-cholesterol by ~60%, it reduced plasma Lp(a) by only ~14% [113]; and as a consequence did not affect arterial inflammation or inflammatory gene expression in monocytes [112,113]. These effects were attributed to Lp(a) reduction being only minimal after evolocumab treatment and reduction of LDL-cholesterol not affecting inflammation under conditions of high plasma Lp(a) levels [113]. A large percentage of patients with Familial Hypercholesterolemia (FH) also show Lp(a) levels > 50 mg/dL [114,115], While PCSK9 antibodies reduce Lp(a) in these patients [114,115], the outcome of the ANITSCHKOW trial suggests that in the context of high Lp(a) levels (~80 mg/dL), reduction of Lp(a) by evolocumab is insufficient to suppress arterial wall inflammation or inflammatory gene expression in monocytes [112,113]. In a recent study, Santos et al. examined the long-term effects of evolocumab in patients with FH [116]. Evolocumab has similar efficacy in FH as in non-FH populations if patients have at least 1 normal LDLR allele. In this study, they did find lower than expected CV event rate of 2.7% per year vs. a range of 4–5% in previous studies [116].

However, subgroup results from the Studies of PCSK9 Inhibition and the Reduction of vascular Events (SPIRE) program, showed that statin-treated FH patients had a similar magnitude of risk reduction for hard cardiovascular events with the PCSK9 inhibitor bococizumab as did patients without FH, with no evidence of statistical heterogeneity [115]. The benefits of Lp(a) lowering using targeted apo(a) lowering treatments, in addition to LDL-cholesterol lowering therapies in this population are yet to be determined.

7. Concluding remarks

Collectively, it has been shown that Lp(a) enhances arterial inflammation, by stimulating monocyte entry, mediated by oxPL [110–112]. OxPL is a clear pro-atherogenic factor [93–
95], and the small apo(a) isoform has high affinity for oxPL [93, 96, 97], and is associated with high Lp(a) levels that have been linked with CVD in Mendelian Randomization studies [36,100]. Additional work is needed to elucidate mechanisms linking Lp(a) to inflammatory phenotypes. The association of the small apo(a) isoform with high Lp(a) levels, and its high affinity for oxPL binding may lead to further understanding and discovery of pathways that link Lp(a) to inflammation. The role of the large apo(a) isoform in CVD remains understudied. Additional studies will be needed to elucidate whether the Lp(a) particle itself starts an inflammatory signal or existing inflammatory conditions drive the particle and its components to participate in pathways driving inflammation.

Since not all subjects with plasma Lp(a) levels > 50 mg/dL are at CVD risk, questions remain as to the additional risk factors that determine the pro-atherogenic and pro-thrombotic capacity of Lp(a). IL-1 induced inflammation may contribute to the effects of Lp(a) on CVD events [103]. Nonetheless, in this particular study [103], IL-1 may have increased plasma Lp(a) by increasing IL-6 expression, which complicates its interpretation.

Since several clinical trials on lowering plasma Lp(a) levels are ongoing [10, 45–49], questions remain as to which patients may benefit from Lp(a) lowering, especially since not all patients with elevated Lp(a) are at risk for CVD. These could include patients with elevated Lp(a) and high levels of inflammatory cytokines such as CRP, which is more routinely measured. In that regard, it would also be of interest to investigate whether anti-inflammatory drugs, such as canakinumab, or colchicine lower plasma Lp(a) levels, and as such are more effective in reducing CVD in patients with elevated Lp(a). One complication, as observed in a small trial with tocilizumab [73], is that several CVD patients are on statins, which have been associated with elevated Lp(a) [78]. Since tocilizumab treatment decreases plasma Lp(a) levels, and several lines of evidence indicate that Lp(a) is being produced downstream of IL-6 signaling, it will be of interest whether tocilizumab lowers plasma Lp(a) in the ASSAIL-MI trial [74] and whether this affects CVD events. Moreover, recent studies have shown that IL-6 inhibition with ziltivekimab in the Trial to Evaluate Reduction in Inflammation in Patients With Advanced Chronic Renal Disease Utilizing Antibody Mediated IL-6 Inhibition (RESCUE) has anti-inflammatory effects and decreases plasma Lp(a) dose-dependently. Ziltivekimab may be tested in a cardiovascular outcome trial [139]. Findings from the RESCUE trial suggest that its anti-inflammatory effects could be due to Lp(a) lowering.

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References

[1]. Tsimikas SFS, Ferdinand KC, Ginsberg HN, Koschinsky ML, Marcovina SM, Moriarty PM, Rader DJ, Remaley AT, Reyes-Soffer G, Santos RD, Thanassoulis G, Witztum JL, Danthi S, Olive M, Liu L, NHLBI working group recommendations to reduce lipoprotein(a)-mediated risk of cardiovascular disease and aortic stenosis, J. Am. Coll. Cardiol 71 (2) (2018) 177–192. [PubMed: 29325642]
[2]. Nordestgaard BG, Chapman MJ, Ray K, Borjén J, Andreotti F, Watts GF, Ginsberg H, Amarenco P, Catapano A, Descamps OS, Fisher E, Kovánen PT, Lesnik P, Masana L, Reiner Z, Taskinen M-R, Tokgözoglu L, Tybjerg-Hansen A, Panel aEASC. Lipoprotein(a) as a cardiovascular risk factor: current status, Eur. Heart J 31 (2010) 2844–2853. [PubMed: 20965889]

[3]. von Zychlinski A, Williams M, McCormick S, Kleffmann T. Absolute quantification of apolipoproteins and associated proteins on human plasma lipoproteins, J. Proteom 106 (2014) 181–190.

[4]. Kostner KM, Kostner GM. Lipoprotein (a): a historical appraisal, J. Lipid Res 58 (1) (2017) 1–14. [PubMed: 27821413]

[5]. White AL, Rainwater DL, Hixson JE, Estlack LE, Lanford RE. Intracellular processing of apo(a) in primary baboon hepatocytes, Chem. Phys. Lipids 67–68 (1994) 123–133.

[6]. Witztum JL. Lipoprotein HNG, (a): Coming of age at last, J. Lipid Res 57 (3) (2016) 336–339. [PubMed: 26839334]

[7]. Bergmark C, Dewan A, Orsoni A, Merki E, Miller ER, Shin MJ, Binder CJ, Horkko S, Krauss RM, Chapman MJ, Witztum JL, Tsimikas S. A novel function of lipoprotein [a] as a preferential carrier of oxidized phospholipids in human plasma, J. Lipid Res 49 (10) (2008) 2230–2239. [PubMed: 18594118]

[8]. Sotiriou SN, Orlova VV, Al-Fakhri N, Ihanus E, Economopoulou M, Isermann B, Bdeir K, Nawroth PP, Preissner KT, Gahmberg CG, Koschinsky ML, Chavakis T. Lipoprotein(a) in atherosclerotic plaques recruits inflammatory cells through interaction with Mac-1 integrin, FASEB J. 20 (3) (2006) 559–561. [PubMed: 16403785]

[9]. Hoogeveen RC, Ballantyne CM. Residual cardiovascular risk at low LDL: remnants, lipoprotein(a), and inflammation, Clin. Chem 67 (1) (2021) 143–153. [PubMed: 33257928]

[10]. Swerdlow DI, Rider DA, Yavari A, Lindholm MW, Campion GV, Nissen SE. Treatment and prevention of lipoprotein(a)-mediated cardiovascular disease: the emerging potential of RNA interference therapeutics, Cardiovasc. Res (2021).

[11]. Cybulska B, Klosiewicz-Latoszek L, Benson PE, Banach M. What do we know about the role of lipoprotein(a) in atherogenesis 57 years after its discovery? Prog. Cardiovasc Dis 63 (3) (2020) 219–227. [PubMed: 32277995]

[12]. Torzewski M, Rayandi A, Yeang C, Edel A, Bhindi S, Kath S, Twardowski L, Schmid J, Yang X, Franke UF, Witztum JL, Tsimikas S. Lipoprotein(a) associated molecules are prominent components in plasma and valve leaflets in calcific aortic valve stenosis, JACC Basic Transl. Sci 2 (3) (2017) 229–240. [PubMed: 29147686]

[13]. Rodger EJ, Porteous CM, Jones GT, Legge M, Kleffmann T, McCormick SPA. Proteomic analysis of liver from human lipoprotein(a) transgenic mice shows an oxidative stress and lipid export response, Biomed. Res. Int 2018 (2018), 4963942. [PubMed: 30596094]

[14]. Capoulade R, Torzewski M, Mayr M, Chan KL, Mathieu P, Bossé Y, Dumesnil JG, Tam J, Teo KK, Burnap SA, Schmid J, Gobel N, Franke UF, Sanchez A, Witztum JL, Yang X, Yeang C, Arsenault B, Després JP, Piharot P, Tsimikas S, ApoCIII-Lp(a) complexes in conjunction with Lp(a)-OxPL predict rapid progression of aortic stenosis, Heart (Br. Card. Soc.) 106 (10) (2020) 738–745.

[15]. Boerwinkle E, Leffert CC, Lin J, Lackner C, Chiesa G, Hobbs HH. Apolipoprotein(a) gene accounts for greater than 90% of the variation in plasma lipoprotein(a) concentrations, J. Clin. Investig 90 (1) (1992) 52–60. [PubMed: 1386087]

[16]. Mooser V, Scheer D, Marcovina SM, Wang J, Guerra R, Cohen J, Hobbs HH. The Apo(a) gene is the major determinant of variation in plasma Lp[a] levels in African Americans, Am. J. Hum. Genet 61 (2) (1997) 402–417. [PubMed: 9311746]

[17]. Boffa MBKM. Lipoprotein (a): truly a direct prothrombotic factor in cardiovascular disease? J. Lipid Res 57 (5) (2016) 745–757. [PubMed: 26647358]

[18]. Hoff HF, O’Neil J, Yashiro A. Partial characterization of lipoproteins containing apo[a] in human atherosclerotic lesions, J. Lipid Res 34 (1993) 789–798. [PubMed: 8509717]

[19]. Boffa MB, Marat TT, Yeang C, Viney NJ, Xia S, Witztum JL, Koschinsky ML, Tsimikas S. Potent reduction of plasma lipoprotein (a) with an antisense oligonucleotide in human subjects does not affect ex vivo fibrinolysis, J. Lipid Res 60 (12) (2019) 2082–2089. [PubMed: 31551368]
[20]. Garcia-Gomez C, Martin-Martinez MA, Castaneda S, Sanchez-Alonso F, Uriarte-Ecenarro M, Gonzalez-Juanatey C, Romera-Baures M, Santos-Rey J, Pinto-Tasende JA, Quesada-Masachs E, Tornero-Molina J, Martinez-Gonzalez O, Cobo-Ibanez T, Chamizo-Carmona E, Manrique-Arija S, Fabregas-Canales D, Diaz-Gonzalez F, Llorca J, Gonzalez-Gay MA, C.P.C. Group, Lipoprotein(a) concentrations in rheumatoid arthritis on biologic therapy: results from the CARdiovascular in rheuMATology study project, J. Clin. Lipidol 11 (3) (2017) 749–756, e743. [PubMed: 28476652]

[21]. Govindan KP, Basha S, Kumar CN, Swathi S, A comparative study on serum lipoprotein (a) and lipid profile between rheumatoid arthritis patients and normal subjects, J. Pharm. Bioallied Sci 7 (Suppl 1) (2015). S22–25. [PubMed: 26015716]

[22]. Dursunoglu D, Evrengul H, Polat B, Tanriverdi H, Cobankara V, Kaftan A, Kilic M, Lp(a) lipoprotein and lipids in patients with rheumatoid arthritis: serum levels and relationship to inflammation, Rheuma Int. 25 (4) (2005) 241–245.

[23]. Koutroubakis IE, Malliaraki N, Vardas E, Gamotakis E, Margioris AN, Manousos ON, Kouroumalis EA, Increased levels of lipoprotein (a) in Crohn’s disease: a relation to thrombosis? Eur. J. Gastroenterol. Hepatol 13 (12) (2001) 1415–1419. [PubMed: 11742189]

[24]. Missala I, Kassner U, Steinhagen-Thiessen E, A systematic literary review of the association of lipoprotein(a) and autoimmune diseases and atherosclerosis, Int. J. Rheuma 2012 (2012), 480784.

[25]. Asanuma Y, Kawai S, Aoshima H, Kaburaki J, Mizushima Y, Serum lipoprotein (a) and apolipoprotein(a) phenotypes in patients with rheumatoid arthritis, Arthritis Rheum. 42 (3) (1999) 443–447. [PubMed: 10088766]

[26]. Kronenberg F, Konig P, Neyer U, Auinger M, Pribasnig A, Lang U, Reitinger J, Pinter G, Utermann G, Dieplinger H, Multicenter study of lipoprotein(a) and apolipoprotein(a) phenotypes in patients with end-stage renal disease treated by hemodialysis or continuous ambulatory peritoneal dialysis, J. Am. Soc. Nephrol. JASN 6 (1) (1995) 110–120. [PubMed: 7579063]

[27]. Thillet J, Doucet C, Issad B, Allouache M, Chapman JM, Jacobs C, Elevated Lp(a) levels in patients with end-stage renal disease, Am. J. Kidney Dis 23 (4) (1994) 620–621. [PubMed: 8154052]

[28]. Mooser V, Marcovina SM, Wang J, Hobbs HH, High plasma levels of apo(a) fragments in Caucasians and African-Americans with end-stage renal disease: implications for plasma Lp(a) assay, Clin. Genet 52 (5) (1997) 387–392. [PubMed: 9520131]

[29]. Borba EF, Santos RD, Bonfa E, Vinagre CG, Pileggi FJ, Cossermelli W, Maranhao RC, Lipoprotein(a) levels in systemic lupus erythematosus, J. Rheumatol 21 (2) (1994) 220–223. [PubMed: 8182628]

[30]. Van den Hof M, Klein Haneveld MJ, Blokhuis C, Scherpierb HJ, Jansen HPG, Kootstra NA, Dallinga-Thie GM, Van Deventer SJH, Tsimikas S, Pajkrt D, Elevated lipoprotein(a) in perinatally HIV-infected children compared with healthy ethnicity-matched controls, Open Forum Infect. Dis 6 (9) (2019) 301, ofz301.

[31]. Santos RD, Foronda A, Ramires JA, Maranhao RC, Levels of lipoprotein (a) in pulmonary arterial hypertension, Cardiol. Young 11 (1) (2001) 25–29. [PubMed: 11233393]

[32]. Aydemir B, Behice Serinkan Cinemre F, Cinemre H, Tuten A, Aytaç Yuksel M, Yilmaz N, Kaya B, Akdemir N, Erdogan E, Madazli R, Paraoxonase 1 (PON1) Q192R and L55M polymorphisms, lipid profile, lipid peroxidation and lipoprotein-a levels in Turkish patients with pregnancy-related disorders, Gynecol. Endocrinol 35 (5) (2019) 417–421. [PubMed: 30654664]

[33]. Fanshawe AE, Ibrahim M, The current status of lipoprotein (a) in pregnancy: a literature review, J. Cardiol 61 (2) (2013) 99–106. [PubMed: 23165148]

[34]. Saeed A, Sun W, Agarwala A, Virani SS, Nambi V, Coresh J, Selvin E, Boerwinkle E, Jones PH, Ballantyne CM, Hoogeveen RC, Lipoprotein(a) levels and risk of cardiovascular disease events in individuals with diabetes mellitus or prediabetes: the atherosclerosis risk in communities study, Atherosclerosis 282 (2019) 52–56. [PubMed: 30685442]

[35]. Koschinsky ML, Marcovina SM, The relationship between lipoprotein(a) and the complications of diabetes mellitus, Acta Diabetol. 40 (2) (2003) 65–76. [PubMed: 12861403]
[36]. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG, Genetically elevated lipoprotein(a) and increased risk of myocardial infarction, JAMA: J. Am. Med. Assoc 301 (22) (2009) 2331–2339.

[37]. Langsted A, Kamstrup PR, Nordestgaard BG, High lipoprotein(a) and high risk of mortality, Eur. Heart J 40 (33) (2019) 2760–2770. [PubMed: 30608559]

[38]. Sereni A, Sticchi E, Gori AM, Magi A, Della Latta D, Volta A, Murri A, Jamagidze G, Chiappino D, Abbate R, Gensini GF, Marcucci R, Sofi F, Giusti B, Genetic and nutritional factors determining circulating levels of lipoprotein(a): results of the “Montignoso Study”, Intern. Emerg. Med 15 (7) (2020) 1239–1245. [PubMed: 31993950]

[39]. Ferretti G, Bacchetti T, Simental-Mendía LE, Reiner Ž, Banach M, Sahebkar A, Raloxifene lowers plasma lipoprotein(a) concentrations: a systematic review and meta-analysis of randomized placebo-controlled trials, Cardiovasc. Drugs Ther 31 (2) (2017) 197–208. [PubMed: 28265881]

[40]. A S, Ž R, LE S-M, G F, AF C, Effect of extended-release niacin on plasma lipoprotein(a) levels: a systematic review and meta-analysis of randomized placebo-controlled trials, Metab. Clin. Exp 65 (11) (2016) 1664–1678. [PubMed: 27733255]

[41]. Reyes-Soffer G, Pavlyha M, Ngai C, Thomas T, Holleran S, Ramakrishnan R, Karmally W, Nandakumar R, Fontanez N, Obunike JC, Marcovina SM, Lichtenstein AH, Matthau NR, Matta J, Marocca M, Becue F, Poitiers F, Swanson B, Cowan L, Sasaiya WJ, Surks HK, Ginsberg BN, Effects of PCSK9 inhibition with alirocumab on lipoprotein metabolism in healthy humans, Circulation 135 (2017) 352–362. [PubMed: 27986651]

[42]. Nandakumar R, Matveyenko A, Thomas T, Pavlyha M, Ngai C, Holleran S, Ramakrishnan R, Ginsberg BN, Karmally W, Marcovina SM, Reyes-Soffer G, Effects of mipomersen, an apolipoprotein B100 antisense, on lipoprotein (a) metabolism in healthy subjects, J. Lipid Res 59 (12) (2018) 2397–2402. [PubMed: 30293969]

[43]. Thomas TZH, Karmally W, Ramakrishnan S, Holleran S, Liu, James P, Wagner JA, Hubbard B, Previs SF, Roddy T, Johnson-Levonas AO, Gutstein DE, Marcovina SM, Rader DJ, Ginsberg BN, Millar JS, Reyes-Soffer GCETP, Cholesteryl ester transfer protein inhibition with anacetrapib decreases production of lipoprotein(a) in mildly hypercholesterolemic subjects, Arterioscler. Thromb. Vasc. Biol 37 (9) (2017) 1770–1775. [PubMed: 28729361]

[44]. Thompson G, Parhofer KG, Current role of lipoprotein apheresis, Curr. Atheroscler. Rep 21 (7) (2019) 26. [PubMed: 31041550]

[45]. Viney NJ, van Capelleveen JC, Geary RS, Xia S, Tami JA, Yu RZ, Marcovina SM, Hughes SG, Graham MJ, Crooke RM, Crooke ST, Witzum JL, Stroes ES, Tsimikas S, Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials, Lancet 388 (10057) (2016) 2239–2253. [PubMed: 27665230]

[46]. Tsimikas S, Stroes ESG, The dedicated “Lp(a) clinic”: a concept whose time has arrived? Atherosclerosis 300 (2020) 1–9. [PubMed: 32234580]

[47]. Gencer B, Mach F, Potential of lipoprotein(a)-lowering strategies in treating coronary artery disease, Drugs 80 (3) (2020) 229–239. [PubMed: 31916186]

[48]. Tsimikas S, Moriarty PM, Stroes ES, Emerging RNA therapeutics to lower blood levels of Lp(a): JACC focus seminar 2/4, J. Am. Coll. Cardiol 77 (12) (2021) 1576–1589. [PubMed: 33766265]

[49]. Page MM, Watts GF, Contemporary perspectives on the genetics and clinical use of lipoprotein(a) in preventive cardiology, Curr. Opin. Cardiol 36 (3) (2021) 272–280. [PubMed: 33741767]

[50]. Rüdker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Gunn RJ, C.T. Group, Antiinflammatory therapy with canakinumab for atherosclerotic disease, N. Engl. J. Med 377 (12) (2017) 1119–1131. [PubMed: 28845751]

[51]. Lopponow H, Libby P, Adult human vascular endothelial cells express the IL6 gene differentially in response to LPS or IL1, Cell Immunol. 122 (2) (1989) 493–503. [PubMed: 2788520]
[52]. Loppnow H, Libby P. Proliferating or interleukin 1-activated human vascular smooth muscle cells secrete copious interleukin 6. The Journal of clinical investigation. 1990;85(3):731–738. [PubMed: 2312724]

[53]. Collaboration IRGCEERF, Sarwar N, Butterworth AS, Freitag DF, Gregson J, Willeit P, Gorman DN, Gao P, Saleheen D, Rendon A, Nelson CP, Braund PS, Hall AS, Chasman DI, Tybjærg-Hansen A, Chambers JC, Benjamin EJ, Franks PW, Clarke R, Wilde AA, Tripe MD, Steri M, Witteman JC, Qi L, van der Schoot CE, de Faire U, Erdmann J, Stringham HM, Koenig W, Rader DJ, Melzer D, Reich D, Psaty BM, Kleber ME, Panagiotakos DB, Willeit J, Wennberg P, Woodward M, Adamovic S, Ohlsson C, Tissen A, Ljunggren O, Reilly MP, Hamsten A, Ingelsson E, Cambien F, Hung J, Thomas GN, Boehnke M, Schunkert H, Asselbergs FW, Kastelein JJ, Gallacher J, Cushman M, Tracy RP, Kauhanen J, Karlsson M, Salonen JT, Wilhelmsen L, Amouyel P, Cantin B, Best LG, Ben-Shlomo Y, Watson H, Watkins WH, Ouwehand WH, Samani NJ, Kaptoge S, Di Angelantonio E, Harari O, Danesh J. Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies, Lancet 379 (9822) (2012) 1205–1213. [PubMed: 22421339]

[54]. Interleukin-6 Receptor Mendelian Randomisation Analysis C, Swerdlow DI, Holmes MV, Kuchenbaecker KB, Engmann JE, Shah T, Sofat R, Guo Y, Chung C, Peasey A, Pfister R, Mooijaart SP, Ireland HA, Leusink M, Langenberg C, Li KW, Palmen J, Howard P, Cooper JA, Drenos F, Hardy J, Nalls MA, Li YR, Lowe G, Stewart M, Bielsinska SJ, Peto J, Timpponen MJ, Gallacher J, Dunlop M, Houlston R, Tomlinson I, Tzoulaki I, Luan J, Boer JM, Forouhi NG, Onland-Moret NC, van der Schouw YT, Schnabel RB, Hubacek JA, Kubinova R, Bacevic M, Tamosiunas A, Pakar A, Topor-Madry R, Malyutina S, Demajtric BL, Tremblay E, de Faire U, Ferrucci L, Bandenelli S, Tanaka T, Meschia JF, Singleton A, Navis G, Mateo Leach I, Bakker SJ, Ganevoort RT, Ford I, Epstein SE, Burnett MS, Devaney J, Jukema JW, Westendorp RJ, Jan de Borst G, van der Graaf Y, de Jong PA, Mailand-van der Zee A., Klungel OH, de Boer A, Doevendorf PA, Stephens JW, Eaton CB, Robinson JG, Manso J, Fowkes FG, Frayling TM, Price JF, Whincup PH, Morris RW, Lawlor DA, Smith GD, Ben-Shlomo Y, Redline S, Lange LA, Kumari M, Wareham NJ, Verschuren WM, Benjamin EJ, Whittaker JC, Hamsten A, Dudbridge F, Delaney JA, Wong A, Kuh D, Hardy R, Castillo BA, Connolly JJ, van der Harst P, Brunner EJ, Marmot MG, Wessels CL, Humphries SE, Talmud PJ, Kivimaki M, Asselbergs FW, Voedselaer M, Bobak M, Vikhart H, Wilson JG, Hakonarson H, Reiner AP, Keating BJ, Sattar N, Hingorani AD, Casas JP, The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis, Lancet 379 (9822) (2012) 1214–1224. [PubMed: 22421340]

[55]. Ridker PM, Libby P, MacFadyen JG, Thuren T, Ballantyne C, Fonseca F, Koenig W, Shimokawa H, Everett BM, Glynn RJ. Modulation of the interleukin-1beta signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). Eur. Heart J 39 (38) (2018) 3499–3507. [PubMed: 30165610]

[56]. Ridker PM, MacFadyen JG, Thuren T, Libby P. Residual inflammatory risk associated with interleukin-18 and interleukin-6 after successful interleukin-1beta inhibition with canakinumab: further rationale for the development of targeted anti-cytokine therapies for the treatment of atherothrombosis, Eur. Heart J (2019).

[57]. Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, Mam V, Hasan A, Rosenberg Y, Iturriondo E, Gupta M, Tsigoulis M, Verma S, Clearfield M, Libby P, Goldhaber SZ, Seagle R, Ofori C, Saklayen M, Butman S, Singh N, Le May M, Bertrand O, Johnston J, Paynter NP, Glynn RJ. Investigators C. Low-dose metformax for the prevention of atherosclerotic events, N. Engl. J. Med 380 (8) (2019) 752–762. [PubMed: 30416510]

[58]. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL, Low-dose colchicine for secondary prevention of cardiovascular disease, J. Am. Coll. Cardiol 61 (4) (2013) 404–410. [PubMed: 23265346]
[59]. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, The SHK, Xu XF, Ireland MA, Lenderink T, Latchem D, Hoogslag P, Jerzewski A, Nierop P, Whelan A, Hendriks R, Swart H, Schaap J, Kuiper AFM, van Hessen MWJ, Saklani P, Tan I, Thompson AG, Morton A, Juddins C, Bax WA, Dirksen M, Alings M, Hankey GJ, Budgen Q, Tijsen JGP, Cornel JH, Thompson PL., LoDoCo2 Trial I. Colchicine in patients with chronic coronary disease, N. Engl. J. Med 383 (19) (2020) 1838–1847. [PubMed: 32865380]

[60]. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, Berry C, Lopez-Sendon J, Ostadal P, Koenig W, Angoulvant D, Gregoire JC, Lavoie MA, Dube MP, Rahind D, Provencher M, Blondeau L, Orfanes A, L’Allier PL, Guertin MC, Roubille F. Efficacy and safety of low-dose colchicine after myocardial infarction, N. Engl. J. Med 381 (26) (2019) 2497–2505. [PubMed: 31733140]

[61]. Reiner Z, Sirtori CR, Banach M, Ruscia M, Sahebkar A. Methotrexate for cardiovascular risk reduction: the right choice? Angiology 71 (2) (2020) 105–107. [PubMed: 31185727]

[62]. Samuel M, Tardif JC. Lessons learned from large cardiovascular outcome trials targeting inflammation in cardiovascular disease (CANTOS, CIRT, COLCOT and LoDoCo2), Future Cardiol. 17 (3) (2021) 411–414. [PubMed: 33687270]

[63]. Gabay C, McInnes IB, Kavanaugh A, Klearman M, Pulley J, Sattar N, Comparison of lipid and lipid-associated cardiovascular risk marker changes after treatment with tocilizumab or adalimumab in patients with rheumatoid arthritis, Ann. Rheum. Dis 75 (10) (2016) 1806–1812. [PubMed: 26613768]

[64]. McInnes IB, Thompson L, Giles JT, Bathon JM, Salmon JE, Beaulieu AD, Codding CE, Carlson TH, Delles C, Lee JS, Sattar N. Effect of interleukin-6 receptor blockade on surrogates of vascular risk in rheumatoid arthritis: MEASURE, a randomised, placebo-controlled study, Ann. Rheum. Dis 74 (4) (2015) 694–702. [PubMed: 24365814]

[65]. Strang AC, Biscoendial RJ, Koorte RS, Schulte DM, Dallinga-Thie GM, Levels JH, Kok M, Vos K, Tas SW, Tietje UJ, Muller N, Laudes M, Gerlag DM, Stroes ES, Tak PP. Pro-atherogenic lipid changes and decreased hepatic LDL-receptor expression by tocilizumab in rheumatoid arthritis, Atherosclerosis 229 (1) (2013) 174–181. [PubMed: 23746537]

[66]. Maini RN, Taylor PC, Szechinski J, Pavelka K, Broll J, Balint G, Emery P, Raemen F, Petersen J, Smolen J, Thomson D, Kishimoto T, Group CS. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate, Arthritis Rheum. 54 (9) (2006) 2817–2829. [PubMed: 16947782]

[67]. Kawashiri SY, Kawakami A, Yamasaki S, Imazato T, Iwamoto N, Fujikawa K, Aramaki T, Tamai M, Nakamura H, Ida H, Origuchi T, Ueki Y, Eguchi K. Effects of the anti-interleukin-6 receptor antibody, tocilizumab, on serum lipid levels in patients with rheumatoid arthritis, Rheumatol. Int 31 (4) (2011) 451–456. [PubMed: 20024554]

[68]. Kim SC, Solomon DH, Rogers JR, Gale S, Klearman M, Sarsour K, Schneeweiss S. Cardiovascular safety of tocilizumab versus tumor necrosis factor inhibitors in patients with rheumatoid arthritis: a multi-database cohort study, Arthritis Rheumatol. 69 (6) (2017) 1154–1164. [PubMed: 28245350]

[69]. Generali E, Carrara G, Selmi C, Verstappen SMM, Zambon A, Bertolazzi A, Silvagni E, Scire CA. Comparison of the risks of hospitalisation for cardiovascular events in patients with rheumatoid arthritis treated with tocilizumab and etanercept, Clin. Exp. Rheumatol 36 (2) (2018) 310–313. [PubMed: 29303702]

[70]. Yamamoto K, Goto H, Hirao K, Nakajima A, Origasa H, Tanaka K, Tomobe M, Totsuka K. Long-term safety of tocilizumab: results from 3 years of followup postmarketing surveillance of 5573 patients with rheumatoid arthritis in Japan, J. Rheumatol 42 (8) (2015) 1368–1375. [PubMed: 26034149]

[71]. Ait-Oufella H, Libby P, Tedgui A. Anticytokine immune therapy and atherothrombotic cardiovascular risk, Arterioscler. Thromb. Vasc. Biol 39 (8) (2019) 1510–1519. [PubMed: 31294625]

[72]. Feingold KR, Grunfeld C. The Effect of Inflammation and Infection on Lipids and Lipoproteins. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dungan K, Grossman A, Hershman JM, Hofland J, Kalsas G, Koch C, Kopp P, Korbonits M, McLachlan R, Morley
[73]. Ueland T, Kleveland O, Michelsen AE, Wiseth R, Damas JK, Holven KB, Aukrust P, Gullesstad L, Yndestad A, Halvorsen B. Serum lipoprotein(a) is not modified by interleukin-6 receptor antagonism or associated with inflammation in non-ST-elevation myocardial infarction. Int. J. Cardiol 274 (2019) 348–350. [PubMed: 29961573]

[74]. Anstensrud AK, Woxholt S, Sharma K, Broch B, Aakhus S, Ueland T, Amundsen BH, Damas JK, Hopp E, Kleveland O, Stensaeth KH, Opdahl A, Klow NE, Seljeflot I, Andersen GO, Wiseth R, Aukrust P, Gullesstad L. Rationale for the ASSAIL-MI-trial: a randomised controlled trial designed to assess the effect of tocilizumab on myocardial salvage in patients with acute ST-elevation myocardial infarction (STEMI), Open Heart 6 (2) (2019) e001108. [PubMed: 31673391]

[75]. Schultz O, Oberhauser F, Saech J, Rubbert-Roth A, Hahn M, Krone W, Laudes M. Effects of inhibition of interleukin-6 signalling on insulin sensitivity and lipoprotein (a) levels in human subjects with rheumatoid diseases, PloS One 5 (12) (2010) e14328. [PubMed: 21179199]

[76]. Berthold HK, Laudes M, Krone W, Gouni-Berthold I. Association between the interleukin-6 promoter polymorphism −174G/C and serum lipoprotein(a) concentrations in humans, PloS One 6 (9) (2011) e24719. [PubMed: 21935443]

[77]. Muller N, Schulte DM, Turk K, Freitag-Wolf S, Hampe J, Zeuner R, Schroder JO, Gouni-Berthold I, Berthold HK, Krone W, Rose-John S, Schreiber S. Laudes M IL-6 blockade by monoclonal antibodies inhibits apolipoprotein (a) expression and lipoprotein (a) synthesis in humans, J. Lipid Res 56 (5) (2015) 1034–1042. [PubMed: 25713100]

[78]. Tsimikas S, Gords P, Nora C, Yeang C, Witztum JL. Statin therapy increases lipoprotein(a) levels, Eur. Heart J 41 (24) (2020) 2275–2284. [PubMed: 31111151]

[79]. Chennamsetty I, Claudel T, Kostner KM, Baghdasaryan A, Kratky D, Levak-Frank S, Frank S, Gonzalez FJ, Trauner M, Kostner GM. Farnesoid X receptor represses hepatic human APOA gene expression. J. Clin. Investig 121 (9) (2011) 3724–3734. [PubMed: 21804189]

[80]. Ghosh Laskar M, Eriksson M, Rudling M, Angelin B. Treatment with the natural FXR agonist chenodeoxycholic acid reduces clearance of plasma LDL whilst decreasing circulating PCSK9, lipoprotein(a) and apolipoprotein C-III, J. Intern. Med 281 (6) (2017) 575–585. [PubMed: 28145001]

[81]. Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, Franceschini F, Airo P, Bazzani C, Beindorf EA, Berlendis M, Bezzi M, Bossini N, Castellano M, Cattaneo S, Cavazzana I, Contessi GB, Crippa M, Delbarba A, De Peri E, Faletti A, Filippini F, Filippini M, Frassi M, Gaggiotti M, Gorla R, Lanspa M, Lorenzetti S, Marino R, Maroldi R, Metra M, Matteelli A, Modina D, Moioli G, Montani G, Muiesan ML, Odolini S, Peli E, Pesenti S, Pezzoli MC, Pirola I, Pozzi A, Proto A, Rasulo FA, Renisi G, Ricci C, Rizzoni D, Romanelli G, Rossi M, Salvetti M, Scolari F, Signorini L, Taglietti M, Tomasoni G, Tomasoni LR, Turla F, Valsecchi A, Zani D. Zucchetta F, Zunica F, Foca E, Andreoli L, Latronico N. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Brescia, Italy, Autoimmun. Rev 19 (7) (2020), 102568. [PubMed: 32376398]

[82]. Xu X, Han M, Li T, Sun W, Wang D, Fu B, Zhou Y, Zheng X, Yang Y, Li X, Zhang X, Pan A, Wei H. Effective treatment of severe COVID-19 patients with tocilizumab. Proc. Natl. Acad. Sci. USA 117 (20) (2020) 10970–10975. [PubMed: 32350134]

[83]. Perrone F, Piccirillo MC, Ascierio PA, Salvarani C, Parrella R, Marata AM, Popoli P, Ferraris L, Marocco-Trischitta MM, Ripamonti D, Binda F, Bonfant P, Squillace N, Castelli F, Muiesan ML, Lichtner M, Calzetti C, Salerno ND, Atipaldi L, Cascella M, Costantini M, Dolci G, Facciolongo NC, Fraganza F, Massari M, Montesarchio V, Mussini C, Negri EA, Botti G, Cardone C, Gargiulo P, Gravina A, Schettino C, Arenare L, Chiodini P, Gallo C, Tocivid-19 investigators I. Tocilizumab for patients with COVID-19 pneumonia. The single-arm TOCIVID-19 prospective trial, J. Transl. Med 18 (1) (2020) 405. [PubMed: 33087150]

[84]. Moriarty PM, Gorby LK, Stroes ES, Kastelein JP, Davidson M, Tsimikas S. Lipoprotein(a) and its potential association with thrombosis and inflammation in COVID-19: a testable hypothesis, Curr. Atheroscler. Rep 22 (9) (2020) 48. [PubMed: 32710255]
[85]. Scalsky RJ, Desai K, Chen YJ, O’Connell JR, Perry JA, Hong CC, Baseline cardiometabolic profiles and SARS-CoV-2 Risk in the UK Biobank, Prepr. Serv. Health Sci (2020).

[86]. Furlow B, COVACTA trial raises questions about tocilizumab’s benefit in COVID-19, Lancet Rheuma 2 (10) (2020), e592.

[87]. Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, Criner GJ, Kaplan-Lewis E, Baden R, Pandit L, Cameron ML, Garcia-Diaz J, Chavez V, Mekebeb-Reuter M, Lima de Menezes F, Shah R, Gonzalez-Lara MF, Assman B, Freedman J, Mohan SV, Tocilizumab in patients hospitalized with Covid-19 pneumonia, N. Engl. J. Med 384 (1) (2021) 20–30. [PubMed: 33332779]

[88]. Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, Horick NK, Healy BC, Shah R, Bensaci AM, Woolley AE, Nikiforow S, Lin N, Sagar M, Scharger H, Huckins DS, Axelrod M, Pincus MD, Fleisher J, Sacks CA, Dougan M, North CM, Halvorsen YD, Thurber TK, Dagher Z, Scherer A, Wallwork RS, Kim AT, Schoenfeld S, Sen P, Neilan TG, Peruginoc CA, Unizony SH, Collier DS, Matza MA, Yinh JM, Bowman KA, Meyerowitz E, Zafar A, Drobin MB, Kohler M, D’Silva KM, Dau J, Lockwood MM, Cubbin C, Weber BN, Mansour MK, B.B.T.T. Investigators, Efficacy of tocilizumab in patients hospitalized with Covid-19, N. Engl. J. Med 383 (24) (2020) 2333–2344. [PubMed: 33085857]

[89]. Tharmarajah E, Buazon A, Patel V, Hannah JR, Adas M, Allen VB, Bechman K, Clarke BD, Nagra D, Norton S, Russell MD, Rutherford AI, Yates M, Galloway JB, IL-6 inhibition in the treatment of COVID-19: a meta-analysis and meta-regression, J. Infect (2021).

[90]. Group RC, Horby P, Pessoa-Amorim G, Peto L, Brightling C, Sarkar A, Thomas K, Jeebun V, Ashish A, Tully R, Chadwick D, Sharafat M, Stewart R, Rudran B, Baillie J, Buch M, Chappell L, Day J, Hurst S, Jaki T, Jeffery K, Justszczak E, Shen Lim W, Montgomery A, Mumford A, Rowan K, Thwaites G, Matham M, Haynes R, Landray M, Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial, medRXiv (2021).

[91]. Horkko S, Bird DA, Miller E, Itabe H, Leitinger N, Subbanagounder G, Berliner JA, Friedman P, Dennis EA, Curtiss LK, Palinski W, Witztum JL, Monoclonal autoantibodies specific for oxidized phospholipids or oxidized phospholipid-protein adducts inhibit macrophage uptake of oxidized low-density lipoproteins, J. Clin. Investig 103 (1) (1999) 117–128. [PubMed: 9884341]

[92]. Que X, Hung MY, Yeang C, Prohaska TA, Sun X, Diehl C, Maatta A, Gaddis DE, Bowden K, Pattison J, MacDonald JG, Yla-Herttuala S, Mellon PL, Hedrick CC, Ley K, Miller YI, Glass CK, Peterson KL, Binder CJ, Tsimikas S, Witztum JL, Oxidized phospholipids are proinflammatory and proatherogenic in hypercholesterolaemic mice, Nature 558 (7709) (2018) 301–306. [PubMed: 29875409]

[93]. Taleb A, Witztum JL, Tsimikas S, Oxidized phospholipids on apoB-100-containing lipoproteins: a biomarker predicting cardiovascular disease and cardiovascular events, Biomark. Med 5 (5) (2011) 673–694. [PubMed: 22003918]

[94]. Tsimikas S, Bergmark C, Beyer RW, Patel R, Pattison J, Miller E, Juliano J, Witztum JL, Temporal increases in plasma markers of oxidized low-density lipoprotein strongly reflect the presence of acute coronary syndromes, J. Am. Coll. Cardiol 41 (3) (2003) 360–370. [PubMed: 12575961]

[95]. Tsimikas S, Brilakis ES, Miller ER, McConnell JP, Lennon RJ, Koonman KS, Witztum JL, Berger PB, Oxidized phospholipids, Lp(a) lipoprotein, and coronary artery disease, N. Engl. J. Med 353 (1) (2005) 46–57. [PubMed: 16000355]

[96]. Tsimikas S, Witztum JL, The role of oxidized phospholipids in mediating lipoprotein(a) atherogeneity, Curr. Opin. Lipidol 19 (4) (2008) 369–377. [PubMed: 18607184]

[97]. Leibundgut G, Scippione C, Yin H, Schneider M, Boffa MB, Green S, Yang X, Dennis E, Witztum JL, Koschinsky ML, Tsimikas S, Determinants of binding of oxidized phospholipids on apolipoprotein (a) and lipoprotein (a), J. Lipid Res 54 (10) (2013) 2815–2830. [PubMed: 23828779]

[98]. Edelstein C, Pfaffinger D, Hinman J, Miller E, Lipkind G, Tsimikas S, Bergmark C, Getz GS, Witztum JL, Scanu AM, Lysine-phosphatidylcholine adducts in kringle V impart unique immunological and potential pro-inflammatory properties to human apolipoprotein(a), J. Biol. Chem 278 (52) (2003) 52841–52847. [PubMed: 14557258]
[99]. Tsimikas S, Clopton P, Brilakis ES, Marcovina SM, Khera A, Miller ER, de Lemos JA, Witztum JL, Relationship of oxidized phospholipids on apolipoprotein B-100 particles to race/ethnicity, apolipoprotein(a) isoform size, and cardiovascular risk factors: results from the Dallas Heart Study, Circulation 119 (13) (2009) 1711–1719. [PubMed: 19307470]

[100]. Saleheen D, Haycock PC, Zhao W, Rasheed A, Taleb A, Imran A, Abbas S, Majeed F, Akhtar S, Qamar N, Zaman KS, Yaoqob Z, Saghir T, Rizvi SNH, Memon A, Mallick NH, Ishfaq M, Rasheed SZ, Memon FU, Mahmood K, Ahmed N, Frossard P, Tsimikas S, Witztum JL, Marcovina S, Sandhu M, Rader DJ, Danesh J, Apolipoprotein(a) isoform size, lipoprotein(a) concentration, and coronary artery disease: a mendelian randomisation analysis, Lancet Diabetes Endocrinol 5 (7) (2017) 524–533. [PubMed: 28408323]

[101]. Enkhmaa B, Anuurad E, Zhang W, Kim K, Berglund L, Heritability of apolipoprotein (a) traits in two-generation African-American and Caucasian families, J. Lipid Res 60 (9) (2019) 1603–1609. [PubMed: 31324652]

[102]. Steffen BT, Thanassoulis G, Duprez D, Stein JH, Karger AB, Tattersall MC, Kaufman JD, Guan W, Tsai MY, Race-based differences in lipoprotein(a)-associated risk of carotid atherosclerosis, Arterioscler. Thromb. Vasc. Biol (2019). [PubMed: 1297290]

[103]. Tsimikas S, Duff GW, Berger PB, Rogus J, Huttner K, Clopton P, Brilakis E, Kornman KS, Witztum JL, Pro-inflammatory interleukin-1 genotypes potentiate the risk of coronary artery disease and cardiovascular events mediated by oxidized phospholipids and lipoprotein(a), J. Am. Coll. Cardiol 63 (17) (2014) 1724–1734. [PubMed: 24530664]

[104]. Syrovets T, Thillet J, Chapman MJ, Simmet T, Lipoprotein(a) is a potent chemoattractant for human peripheral monocytes, Blood 90 (5) (1997) 2027–2036. [PubMed: 9292539]

[105]. Poon M, Zhang X, Dunsky KG, Taubman MB, Harpel PC, Apolipoprotein(a) induces monocyte chemotactic activity in human vascular endothelial cells, Circulation 96 (8) (1997) 2514–2519. [PubMed: 9355887]

[106]. Buechler C, Ullrich H, Aslanidis C, Bared SM, Lingenhel A, Ritter M, Schmitz G, Lipoprotein (a) downregulates lysosomal acid lipase and induces interleukin-6 in human blood monocytes, Biochim. Biophys. Acta 1642 (1–2) (2003) 25–31. [PubMed: 1297290]

[107]. Allen S, Khan S, Tam S, Koschinsky M, Taylor P, Yacoub M, Expression of adhesion molecules by lp(a): a potential novel mechanism for its atherogenicity, FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol 12 (15) (1998) 1765–1776.

[108]. Takami S, Yamashita S, Kihara S, Ishigami M, Takemura K, Kume N, Kitai T, Matsuzawa Y, Lipoprotein(a) enhances the expression of intercellular adhesion molecule-1 in cultured human umbilical vein endothelial cells, Circulation 97 (8) (1998) 721–728. [PubMed: 9498534]

[109]. Scipione CA, Sayegh SE, Romagnuolo R, Tsimikas S, Marcovina SM, Boffa MB, Koschinsky ML, Mechanistic insights into Lp(a)-induced IL-8 expression: a role for oxidized phospholipid modification of apo(a), J. Lipid Res 56 (12) (2015) 2273–2285. [PubMed: 26474593]

[110]. Schnitzler JG, Hoogeveen RM, Ali L, Prange KHM, Waissi F, van Weeghel M, Bachmann JC, Versloot M, Borrelli MJ, Yeang C, De Kleijn DPV, Houtkooper RH, Koschinsky ML, de Winther MPJ, Groen AK, Witztum JL, Tsimikas S, Stroes ESG, Kroon J, Atherogenic lipoprotein(a) increases vascular glycosylation, thereby facilitating inflammation and leukocyte extravasation, Circ. Res 126 (10) (2020) 1346–1359. [PubMed: 32160811]

[111]. van der Valk FM, Bekkering S, Kroon J, Yeang C, Van den Bossche J, van Buul JD, Ravandi A, Nederveen AJ, Verberne HJ, Scipione C, Nienwoudt M, Joosten LA, Netea MG, Koschinsky ML, Witztum JL, Tsimikas S, Riksen NP, Stroes ES, Oxidized phospholipids on lipoprotein(a) elicit arterial wall inflammation and an inflammatory monocyte response in humans, Circulation 134 (8) (2016) 611–624. [PubMed: 27496857]

[112]. Stiekema LCA, Prange KHM, Hoogeveen RM, Verweij SL, Kroon J, Schnitzler JG, Dzobo KE, Cupido AJ, Tsimikas S, Stroes ESG, de Winther MPJ, Bahijat M, Potent lipoprotein(a) lowering following apolipoprotein(a) antisense treatment reduces the pro-inflammatory activation of circulating monocytes in patients with elevated lipoprotein(a), Eur. Heart J 41 (24) (2020) 2262–2271. [PubMed: 32268367]

[113]. Stiekema LCA, Stroes ESG, Verweij SL, Kassahun H, Chen L, Wasserman SM, Sabatine MS, Mani V, Fayad ZA, Persistent arterial wall inflammation in patients with elevated lipoprotein(a)
despite strong low-density lipoprotein cholesterol reduction by proprotein convertase subtilisin/kexin type 9 antibody treatment, Eur. Heart J 40 (33) (2019) 2775–2781. [PubMed: 30561610]

[114]. Catapano AL, Pirillo A, Norata GD, Anti-PCSK9 antibodies for the treatment of heterozygous familial hypercholesterolemia: patient selection and perspectives, Vasc. Health Risk Manag 13 (2017) 343–351. [PubMed: 28919772]

[115]. Ridker PM, Rose LM, Kastelein JP, Santos RD, Wei C, Revkin J, Yunis C, Tardif JC, Shear CL, Studies of PI, the reduction of vascular events I. Cardiovascular event reduction with PCSK9 inhibition among 1578 patients with familial hypercholesterolemia: results from the SPIRE randomized trials of bococizumab, J. Clin. Lipidol 12 (4) (2018) 958–965. [PubMed: 29685591]

[116]. Santos RD, Stein EA, Hovingh GK, Blom DJ, Soran H, Watts GF, Lopez JAG, Bray S, Kurtz CE, Hamer AW, Raal FJ, Long-term evolocumab in patients with familial hypercholesterolemia, J. Am. Coll. Cardiol 75 (6) (2020) 565–574. [PubMed: 32057369]

[117]. Jong MC, Hofker MH, Havekes LM, Role of ApoCs in lipoprotein metabolism: functional differences between ApoC1, ApoC2, and ApoC3, Arterioscler. Thromb. Vasc. Biol 19 (3) (1999) 472–484. [PubMed: 10073946]

[118]. Berbee JF, van der Hoogt CC, Sundaramanan D, Havekes LM, Rensen PC, Severe hypertriglyceridemia in human APOC1 transgenic mice is caused by apoC-I-induced inhibition of LPL, J. Lipid Res 46 (2) (2005) 297–306. [PubMed: 15576844]

[119]. Gautier T, Masson D, de Barros JP, Athias A, Gambert P, Aunis D, Metz-Boutigue MH, Lagrost L, Human apolipoprotein C-II accounts for the ability of plasma high density lipoproteins to inhibit the cholesteryl ester transfer protein activity, J. Biol. Chem 275 (48) (2000) 37504–37509. [PubMed: 10978346]

[120]. Berbee JF, van der Hoogt CC, Kleemann R, Schippers EF, Kitchens RL, Bakker-Woudenberg IA, Havekes LM, Rensen PC, Apolipoprotein CI stimulates the response to lipopolysaccharide and reduces mortality in gram-negative sepsis, FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol 20 (12) (2006) 2162–2164.

[121]. Tall AR, Yvan-Charvet L, Cholesterol, inflammation and innate immunity, Nat. Rev. Immunol 15 (2) (2015) 104–116. [PubMed: 25614320]

[122]. Ueda M, Dunbar RL, Wolska A, Sikora TU, Escobar MDR, Seliktar N, deGoma E, DerOhannessian S, Morrell L, McIntyre AD, Burke F, Svirdov D, Amar M, Shamburek RD, Freeman L, Hegele RA, Remaley AT, Rader DJ, A Novel APOC2 missense mutation causing apolipoprotein C-II deficiency with severe triglyceridermia and pancreatitis, J. Clin. Endocrinol. Metab 102 (5) (2017) 1454–1457. [PubMed: 28201738]

[123]. Ramms B, Patel S, Nora C, Pessentheiner AR, Chang MW, Green CR, Golden GJ, Secrest P, Krauss RM, Metallo CM, Benner C, Alexander VJ, Witztum JL, Tsimikas S, Esko JD, Gords P, A.S.O. ApoC-III, promotes tissue LPL activity in the absence of apoE-mediated TRL clearance, J. Lipid Res 60 (8) (2019) 1379–1395. [PubMed: 31092690]

[124]. Gords PL, Nock R, Son NH, Ramms B, Lew I, Gonzales JC, Thacker BE, Basu D, Lee RG, Mullick AE, Graham MJ, Goldberg IJ, Crooke RM, Witztum JL, Esko JD, ApoC-III inhibits clearance of triglyceride-rich lipoproteins through LDL family receptors, J. Clin. Investig 126 (8) (2016) 2855–2866. [PubMed: 27400128]

[125]. Gong T, Zhou R, ApoC3: an ‘alarmin’ triggering sterile inflammation, Nat. Immunol 21 (1) (2020) 9–11. [PubMed: 31822868]

[126]. Ginsberg HN, Reyes-Soffer G, Is APOC3 the driver of cardiovascular disease in people with type I diabetes mellitus? J. Clin. Investig 129 (10) (2019) 4074–4076. [PubMed: 31449060]

[127]. Mahley RW, Apolipoprotein E: from cardiovascular disease to neurodegenerative disorders, J. Mol. Med 94 (7) (2016) 739–746. [PubMed: 27277824]

[128]. Van Oosten M, Rensen PC, Van Amersfoort ES, Van Eck M, Van Dam AM, Breve JJ, Vogel T, Panet A, Van Berkel TJ, Kuiper J, Apolipoprotein E protects against bacterial lipopolysaccharide-induced lethality. A new therapeutic approach to treat gram-negative sepsis, J. Biol. Chem 276 (12) (2001) 8820–8824. [PubMed: 11136731]

[129]. Morton RE, Liu Y, Izem L, ApoF knockdown increases cholesteryl ester transfer to LDL and impairs cholesterol clearance in fat-fed hamsters, J. Lipid Res 60 (11) (2019) 1868–1879. [PubMed: 31511396]
[130]. Weng W, Brandenburg NA, Zhong S, Halkias J, Wu L, Jiang XC, Tall A, Breslow JL. ApoA-II maintains HDL levels in part by inhibition of hepatic lipase. Studies in apoA-II and hepatic lipase double knockout mice, J. Lipid Res 40 (6) (1999) 1064–1070. [PubMed: 10357838]

[131]. Desmairais F, Bergeron KF, Lacaille M, Lemieux I, Bergeron J, Biron S, Rassart E, Joanisse DR, Mauriege P, Mounier C. High ApoD protein level in the round ligament fat depot of severely obese women is associated with an improved inflammatory profile, Endocrine 61 (2) (2018) 248–257. [PubMed: 29869155]

[132]. de Silva HV, Stuart WD, Duvic CR, Wetterau JR, Ray MJ, Ferguson DG, Albers HW, Smith WR, Harmony JA. A 70-kDa apolipoprotein designated ApoJ is a marker for subclasses of human plasma high density lipoproteins, J. Biol. Chem 265 (22) (1990) 13240–13247. [PubMed: 2376594]

[133]. Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, Pahwa JS, Moskina V, Dowzell K, Williams A, Jones N, Thomas C, Stretton A, Morgan AR, Lovestone S, Powell J, Poirier P, Lupton MK, Brayne C, Cruchaga C, Nowotny P, Morris JC, Mayo K, Sleezers J, Bettens K, Engelborghs S, De Deyn PP, van Broeckhoven C, Livingston G, Bass NJ, Gurling H, McQuillin A, Gwillym R, Deloukas P, A-Chalabi A, Shaw CE, Tsolaki M, Singleton AB, Guerreiro R, Hulihan MM, Carrasquillo MM, Pankratz VS, Yonk S, Holmans PA, O’Donovan M, Owen MJ, Williams J. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer’s disease, Nat. Genet 41 (10) (2009) 1088–1093. [PubMed: 19734902]

[134]. Christoffersen C, Ohnata H, Kumaraswamy SB, Galvani S, Ahnstrom J, Sevvana M, Egerer-Sieber C, Muller YA, Hla T, Nielsen LB, Dahlback B. Endothelium-protective sphingosine-1-phosphate provided by HDL-associated apolipoprotein M, Proc. Natl. Acad. Sci. USA 108 (23) (2011) 9613–9618. [PubMed: 21606363]

[135]. Kotite L, Zhang LH, Yu Z, Burlingame AL, Havel RJ. Human apoC-IV: isolation, characterization, and immunochemical quantification in plasma and plasma lipoproteins, J. Lipid Res 44 (7) (2003) 1387–1394. [PubMed: 12700345]

[136]. Allan CM, Taylor JM. Expression of a novel human apolipoprotein (apoC-IV) causes hypertriglyceridemia in transgenic mice, J. Lipid Res 37 (7) (1996) 1510–1518. [PubMed: 8827523]

[137]. Noto H, Hara M, Karasawa K, Iso ON, Satoh H, Togo M, Hashimoto Y, Yamada Y, Kosaka T, Kawamura M, Kimura S, Tsukamoto K. Human plasma platelet-activating factor acetylhydrolase binds to all the murine lipoproteins, conferring protection against oxidative stress, Arterioscler. Thromb. Vasc. Biol 23 (5) (2003) 829–835. [PubMed: 12649088]

[138]. Graner M, James RW, Kahri J, Nieminen MS, Syvanne M, Taskinen MR. Association of paraoxonase-1 activity and concentration with angiographic severity and extent of coronary artery disease, J. Am. Coll. Cardiol 47 (12) (2006) 2429–2435. [PubMed: 16781370]

[139]. Ridker PM, Devalaraja M, Baeres FMM, Engelmann MDM, Hovingh GK, Ikovic M, Lo L, Kling D, Pergola P, Raj D, Libby P, Davidson M, RESCUE Investigators. IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk (RESCUE): a double-blind, randomised, placebo-controlled phase 2 trial, Lancet (2021), 10.1016/S0140-6736(21)00520-1. In press.
Table 1
Proteins Present on Immunoprecipitated Lipoprotein (a) Particles.

| Detected Proteins (in addition to apo(a) and apoB100) | Details |
|-------------------------------------------------------|---------|
| ApoC1                                                 | Smallest apolipoprotein in plasma. ApoC1 is associated with VLDL and HDL and acts on lipoproteins by inhibiting binding mediated by apoE to the LDL receptor, VLDL receptor, and LRP [117], and inhibiting lipoprotein lipase (LPL) [118], and cholesteryl ester transfer protein (CETP) [119]. It also binds to lipopolysaccharide, which increases inflammation, and protects against sepsis [120]. |
| ApoA1                                                 | Is the main protein component of HDL. ApoA1 is involved in reverse cholesterol transport (RCT), i.e. the removal of cholesterol from macrophage foam cells in the arterial wall via ATP Binding Cassette Transporter A1 (ABCA1), transport in plasma, uptake by the liver and ultimate secretion into the bile. While mainly anti-inflammatory, pro-inflammatory effects of ApoA1 have also been reported [121]. |
| ApoC2                                                 | Co-factor for LPL activity [122] |
| ApoC3                                                 | Inhibitor of LPL [123] and apoE mediated binding to LDL receptor and LRP [124]. Newly suggested role as pro-inflammatory apolipoprotein [125,126]. |
| ApoE                                                  | Is associated with chylomicron remnants, VLDL, LDL, and HDL. Regulates VLDL and LDL clearance and contributes to HDL formation [127]. Binds lipopolysaccharide and protects against sepsis [128]. |
| ApoF                                                  | Small apolipoprotein associated with HDL, may have a role in lipid transfer between lipoproteins [129]. |
| ApoA2                                                 | Secondary apolipoprotein contained in HDL particles, inhibits hepatic lipase to maintain HDL levels [130]. |
| ApoD                                                  | ApoD is mainly associated with HDL and participates in lipid transport. It has a high affinity for arachidonic acid, and a diverse array of functions [131]. |
| ApoJ/Clusterin                                         | Associated with HDL [132]. Mainly role in Alzheimer’s Disease but crosses blood brain barrier [133]. |
| ApoM                                                  | Is primarily expressed and secreted from the liver and present on HDL. ApoM is the main chaperone of sphingosine-1-phosphate (S1P) on HDL [134]. |
| ApoC4                                                 | Mainly present on VLDL (80%) and also on HDL (20%) [135]. Linked to TG metabolism in mouse studies [136]. |
| PAF-AH                                                | Platelet activating factor – acetylhydrolase (PAF-AH) is present on LDL (70–83%) and HDL (11–30%) and hydrolyzes PAF-like oxidized phospholipids [137]. |
| PON – 1                                                | Paraoxonase-1 (PON-1) is mainly associated with apoA1 on HDL and inhibits LDL and HDL oxidation [138]. |