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# Lipoprotein apheresis: From familial hypercholesterolemia and elevated lipoprotein(a) to emerging roles in peripheral arterial and renal disease

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ABSTRACT

Lipoprotein apheresis (LA) achieves acute reductions of 60–80% in LDL cholesterol and lipoprotein(a) [Lp(a)] through extracorporeal removal of apolipoprotein B-containing particles, and remains the cornerstone of treatment for homozygous familial hypercholesterolemia and severe heterozygous FH refractory to pharmacotherapy. Registry data, including more than 11 years of follow-up from the German Lipoprotein Apheresis Registry, document consistent reductions in major adverse cardiovascular events across all principal indications, though randomized controlled trial evidence is absent. The introduction of PCSK9 inhibitors and inclisiran has progressively reduced apheresis utilization for LDL-centric management, while potent RNA-based Lp(a)-lowering agents (pelacarsen, olpasiran, lepodisiran) in late-stage development may further reshape the field. Beyond traditional cardiovascular indications, accumulating observational evidence supports LA in peripheral arterial disease through pleiotropic rheologic and anti-inflammatory mechanisms, and in steroid-resistant focal segmental glomerulosclerosis through oxidized LDL clearance and podocyte rescue. This review synthesizes current evidence across cardiovascular, peripheral vascular, and renal indications, compares apheresis modalities, examines integration with emerging pharmacotherapies, and proposes a three-part trajectory for LA: progressive contraction in LDL-centric use, a persisting role in Lp(a)-driven disease until RNA-based agents demonstrate outcome benefit, and a mechanistically grounded but evidence-limited niche in selected pleiotropic vascular and renal phenotypes.

## 1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of morbidity and mortality worldwide, driven fundamentally by the accumulation of atherogenic lipoproteins within the arterial wall [1,2]. While statin-based therapy has transformed cardiovascular prevention over the past three decades, a substantial proportion of patients with genetic dyslipidemias, particularly familial hypercholesterolemia (FH) and elevated lipoprotein(a) [Lp(a)], fail to achieve adequate lipid targets despite maximally tolerated pharmacotherapy [3,4]. For these individuals, lipoprotein apheresis (LA) provides a critical therapeutic option, achieving acute reductions of 60–80% in both LDL cholesterol (LDL-C) and Lp(a) through extracorporeal removal of apolipoprotein B (apoB)-containing particles [5,6].

Since the development of the first selective LDL-adsorption columns in the 1980s [7,8], LA has evolved from a niche procedure for homozygous FH (HoFH) into an established therapy with broadening indications. International registries encompassing thousands of patients have documented substantial reductions in major adverse cardiovascular events (MACE), improved survival, and regression of atherosclerotic burden in both HoFH and severe heterozygous FH (HeFH) [9–11]. More recently, the recognition of Lp(a) as an independent, genetically determined, causal risk factor for ASCVD has expanded the rationale for LA to patients with isolated hyperlipoproteinemia(a) and progressive vascular disease [2,12,13]. In many of these patients, Lp(a)-mediated residual risk persists despite optimal control of traditional risk factors, making LA the only available intervention that can meaningfully reduce circulating Lp(a) concentrations.

The therapeutic landscape for severe dyslipidemias is evolving rapidly. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and inclisiran have reduced LA utilization for LDL-C control in many patients [14,15], while potent RNA-based Lp(a)-lowering agents, including pelacarsen, olpasiran, and lepodisiran, are advancing through clinical trials with the potential to transform Lp(a)-driven apheresis practice [16–18]. Concurrently, accumulating evidence supports expanding LA indications beyond traditional ASCVD: in peripheral

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arterial disease (PAD), where pleiotropic rheologic and anti-inflammatory effects confer benefit beyond lipid lowering [19,20], and in renal disease, where LA shows promise in steroid-resistant focal segmental glomerulosclerosis (FSGS), post-transplant FSGS recurrence, and diabetic nephropathy [21–23]. These expanding indications highlight the unique multi-target profile of apheresis, an intervention that simultaneously removes not only atherogenic lipoproteins but also fibrinogen, inflammatory mediators, oxidized lipid species, and rheologically active proteins from the circulation [24].

This review argues that lipoprotein apheresis is evolving from a rescue intervention for refractory hypercholesterolemia into a selective, phenotype-driven extracorporeal therapy whose future role will be defined by the intersection of genetic indication, non-lipid pleiotropic effects, and competition with targeted molecular agents. We examine Lp(a) biology and the rationale for apheresis, outcomes in FH, available modalities and their comparative profiles, evidence in PAD and renal disease, integration with contemporary pharmacotherapies, and critical evidence gaps warranting future investigation.

## 2. Lp(a) biology and the rationale for apheresis

Lipoprotein(a) is a low-density lipoprotein; like particle in which apolipoprotein B100 is covalently linked to apolipoprotein(a) [apo(a)], a polymorphic glycoprotein with structural homology to plasminogen [2,25,26]. The apo(a) moiety contains a variable number of kringle IV type 2 (KIV−2) repeats, which determine particle size and inversely correlate with plasma Lp(a) concentration, smaller isoforms are associated with higher levels and greater cardiovascular risk [2,27]. Lp(a) concentration is predominantly determined by genetic variation at the *LPA* locus on chromosome 6q25–26, is highly heritable (approximately 70–90%), remains stable across the lifespan, and varies substantially by ancestry, with individuals of African descent exhibiting median levels approximately two- to threefold higher than those of European ancestry [2,27,28]. Importantly, plasma Lp(a) levels are largely resistant to modification by lifestyle interventions and most conventional lipid-lowering therapies, including statins, ezetimibe, and fibrates [2,12].

### 2.1. Pathogenic mechanisms

Lp(a) promotes atherothrombosis through three interconnected pathways. First, its LDL-like moiety mediates arterial wall retention through interaction with intimal proteoglycans, promoting subendothelial accumulation, macrophage uptake via scavenger receptors, foam-cell formation, and plaque destabilization through smooth muscle cell apoptosis and matrix metalloproteinase activation [2,25,26,29]. Second, Lp(a) is the principal carrier of oxidized phospholipids (OxPL) in plasma, conferring potent pro-inflammatory and pro-oxidative properties that amplify vascular injury, activate endothelial cells, recruit monocytes, and stimulate macrophage inflammatory signaling through Toll-like receptor pathways [2,29,30]. The OxPL content of Lp(a) particles is thought to be particularly relevant to its pathogenicity, as OxPL drive both the initiation and progression of atherosclerotic lesions while also promoting valvular calcification, a finding that provides a mechanistic link between elevated Lp(a) and calcific aortic valve stenosis [25,29]. Third, the apo(a) component, through its plasminogen-like kringle domains, exerts antifibrinolytic and prothrombotic effects by competitively inhibiting plasminogen binding to fibrin and cell surfaces, thereby impairing fibrinolysis, promoting clot stability, and enhancing the thrombotic potential of vulnerable plaques [25,26]. Additionally, Lp(a) has been shown to stimulate plasminogen activator inhibitor−1 (PAI−1) expression and tissue factor activity, further tipping the hemostatic balance toward thrombosis. This convergence of pro-atherogenic, pro-inflammatory, and prothrombotic activities makes Lp(a) a uniquely multifaceted cardiovascular risk factor that is mechanistically distinct from conventional LDL.

### 2.2. Epidemiology and risk thresholds

Epidemiologic studies and Mendelian randomization analyses have established a continuous, log-linear, causal association between Lp(a) concentration and ASCVD, PAD, and calcific aortic valve stenosis, independent of LDL-C levels and other conventional risk factors [1,3,28]. Risk increases continuously across the distribution, with a hazard ratio of approximately 1.11 per 50 nmol/L increment for coronary heart disease events [1,3]. Approximately 20% of the global population has Lp(a) levels above 50 mg/dL, making this one of the most prevalent genetically determined risk factors for cardiovascular disease [2,27]. The distribution of Lp(a) is markedly right-skewed in most populations, meaning that while most individuals have low levels, a significant minority carry concentrations that confer substantial excess risk. Mendelian randomization studies have been particularly important in establishing causality, as they circumvent the confounding and reverse causation that limit observational epidemiology, and they consistently demonstrate that genetically determined elevations in Lp(a) are associated with increased ASCVD risk proportional to the magnitude of the elevation [3,28]. Major societies now define elevated Lp(a) at $\geq$ 50 mg/dL ($\approx$125 nmol/L), with levels $\geq$ 150 nmol/L frequently considered the threshold for therapeutic intervention, although it should be noted that Lp(a) measurement remains non-standardized across assays, and the conversion between mass (mg/dL) and molar (nmol/L) units is only approximate due to isoform size heterogeneity [3,4,12,13].

### 2.3. Rationale for apheresis in elevated Lp(a)

Conventional lipid-lowering agents have limited effect on Lp(a): statins may paradoxically increase levels by 10–20% through upregulation of hepatic *LPA* gene expression, niacin provides modest reductions of 20–30% but was not shown to improve cardiovascular outcomes in recent trials, and PCSK9 inhibitors provide only modest 20–30% reductions, primarily by increasing Lp(a) catabolism rather than reducing its synthesis [2,12,14,31]. The potent RNA-targeted agents currently in development (pelacarsen, olpasiran, lepodisiran) can lower Lp(a) by 70–97% through hepatic inhibition of apo(a) synthesis but remain investigational pending cardiovascular outcome trials, with Lp(a)HORIZON (pelacarsen) expected to report results in the coming years [16–18]. In this context, LA remains the only widely available intervention capable of achieving acute Lp(a) reductions of 60–75% per session, although the characteristic rebound kinetics of Lp(a) between treatments mean that time-averaged reductions are typically 25–40%, depending on session frequency and individual rebound rate [5,6,32]. Cohort studies in patients with progressive ASCVD, near-normal LDL-C, and very high Lp(a), most notably the German Pro(a)LiFe study and its extensions, report substantial reductions in cardiovascular events with regular LA, supporting its use as a last-resort therapy when pharmacologic options are exhausted [6,32–34]. Additionally, apheresis has been shown to reduce the oxidative susceptibility of both LDL and Lp(a) fractions, a pleiotropic effect that may contribute to clinical benefit beyond the quantitative reduction in particle number [32].

## 3. Familial hypercholesterolemia: established outcomes

Familial hypercholesterolemia, whether heterozygous or homozygous, represents the archetypal indication for lipoprotein apheresis. In HoFH, where LDL receptor function is severely impaired or absent due to biallelic pathogenic variants in *LDLR*, *APOB*, *PCSK9*, or *LDLRAP1*, untreated LDL-C typically exceeds 500 mg/dL (13 mmol/L) and accelerated atherosclerosis begins in childhood, with coronary events and aortic valve disease frequently manifesting before age 20 in untreated patients [7–9]. LA has been a cornerstone of HoFH management since the 1980s, and multiple international cohorts have documented the long-term cardiovascular benefits of chronic LA in this population [9,10,

35].

### 3.1. HoFH, pediatric and long-term cohort data

The combined Homozygous FH International Clinical Collaborators (HICC) and CHildhood and Adolescent INternational (CHAIN) registries, encompassing childhood-onset HoFH across multiple continents, demonstrated that LA initiated during childhood was associated with a hazard ratio of 0.52 for ASCVD events and 0.30 for cardiovascular death compared with drug therapy alone [35]. These data are particularly striking given that the benefit of LA persisted after adjustment for background lipid-lowering therapy, suggesting an independent protective effect of extracorporeal lipid removal in this population. An expert consensus statement from ERKNet and ESPN has since recommended that LA be initiated early in children with HoFH who fail to achieve at least a 50% reduction in LDL-C with maximal pharmacotherapy, ideally before the age of 5 years in the most severe phenotypes [36]. The Sino-Roman Study, comparing HoFH management in China and Italy, revealed markedly better cardiovascular disease, free survival in the Italian cohort which had earlier access to LA and modern lipid-lowering therapy, highlighting the impact of treatment availability and health system infrastructure on outcomes in rare genetic diseases [37,38]. A pediatric LA registry of 50 children with HoFH confirmed that regular apheresis achieves large LDL-C reductions, although 12% had already developed cardiovascular disease before LA initiation, underscoring the importance of early diagnosis through cascade screening and prompt referral to specialized lipid centers [39].

### 3.2. Registry and systematic review data

The German Lipoprotein Apheresis Registry (GLAR), the largest ongoing national registry of its kind, has reported on 1125 patients followed over 11 years, documenting a 73% overall reduction in MACE, with phenotype-specific reductions ranging from 53% in patients treated primarily for elevated Lp(a) to 85% in patients with FH [11]. The GLAR also provides important procedural safety data: across more than 200,000 documented sessions, serious adverse events remain uncommon, with hypotension, circuit clotting, and vascular access complications representing the most frequently reported issues, all occurring at rates below 1% per session [11]. A systematic review of LDL-C apheresis for FH, encompassing 14 studies and more than 1000 patients, estimated per-session LDL-C reductions of 57–75% and long-term cardiovascular event reductions of 48–70% across multiple registries [40]. These data, while observational, are remarkably consistent in demonstrating that chronic LA substantially reduces cardiovascular morbidity in patients with FH refractory to pharmacotherapy, and the magnitude of benefit is comparable to or exceeds that seen with high-intensity pharmacologic intervention [9,10]. The absence of randomized controlled trials in this population reflects the ethical and practical challenges of randomizing patients with severely elevated LDL-C to a non-treatment arm, and registry data are therefore likely to remain the primary evidence base for the foreseeable future.

Complementing these European registries, a Japanese national survey of 201 patients with definite or probable HoFH provided important epidemiological context [41]. The cohort had a median age at diagnosis of 27 years, with 70% already manifesting coronary artery disease and 24% demonstrating valvular heart disease, predominantly aortic involvement. Only 21% were receiving lipoprotein apheresis, despite 74% being on high-intensity statins and 50% on PCSK9 inhibitors, with post-treatment LDL-C remaining at a mean of 3.9 mmol/L. Genetic testing was performed in only 32% of patients, revealing LDLR mutations in 52% and combined LDLR/PCSK9 variants in 26%. These data highlight persistent gaps in both the diagnosis and treatment intensity of HoFH in Japan, despite the relatively favorable accessibility of LA in the Japanese healthcare system, and underscore the global challenge of ensuring that patients with the most severe FH phenotypes receive early and sustained apheresis therapy. Notably, the Japan Atherosclerosis Society 2022 guidelines formally recommend LA for HoFH and drug-resistant severe HeFH, positioning it as a foundational treatment modality in the Japanese management algorithm [42].

### 3.3. Evolving management with novel agents

The treatment of HoFH is evolving with the introduction of lomitapide, an oral microsomal triglyceride transfer protein (MTP) inhibitor that reduces LDL-C by 40–50% independent of LDL receptor function; evinacumab, an anti-ANGPTL3 monoclonal antibody that lowers LDL-C by approximately 47% through upregulation of LDL receptor-independent clearance pathways; and evolving RNA-based therapies targeting ANGPTL3 and apoC-III [43–45]. Recent data suggest that evinacumab can substantially reduce LDL-C in HoFH patients including those with null-null receptor genotypes, and early cardiovascular outcome data appear encouraging [43]. Liver transplantation remains an option in selected cases of HoFH refractory to all medical and apheresis therapy, with long-term data from Australia and New Zealand demonstrating excellent normalization of LDL-C but with the well-known risks of transplant surgery and lifelong immunosuppression [46]. However, access to these newer agents is variable globally, long-term outcome data remain limited compared with LA, hepatotoxicity and gastrointestinal side effects with lomitapide require careful monitoring, and expert consensus from the European Atherosclerosis Society, HEART UK, and international working groups continues to recommend LA as a guideline-recommended therapy, particularly when initiated early in childhood [9,35,44,47,48]. In practice, most lipid centers now employ a multimodal approach that combines maximally tolerated statin and ezetimibe therapy with one or more adjunctive agents and LA, titrating the frequency and intensity of apheresis sessions to achieve individualized LDL-C targets.

## 4. Apheresis modalities

Four principal LA modalities are currently in clinical use, each employing a distinct mechanism for selective removal of atherogenic lipoproteins (Table 1). While all achieve broadly comparable acute LDL-C and Lp(a) reductions, important differences in selectivity, co-removal profiles, procedural characteristics, and ancillary effects guide modality

**Table 1**
Comparison of Lipoprotein Apheresis Modalities.

| Modality | Mechanism | Lipid Removal | Key Features |
|---|---|---|---|
| DSA / Liposorber | Plasma over dextran sulfate cellulose binding apoB | LDL-C ↓60–75%; Lp(a) ↓60–70%; modest HDL loss | Widely available; strong LDL/Lp(a) lowering; removes coagulation factors; affected by high TGs [7,8,49–52] |
| H.E.L.P. | Heparin-induced acidic precipitation of LDL/Lp(a) | LDL-C ↓60–70%; strong fibrinogen reduction (~60%) | Preferred for PAD/CKD; marked rheologic benefits; reduces viscosity [19,53,54] |
| DALI | Whole-blood adsorption on polyacrylate | LDL-C ↓70–77%; Lp(a) ↓~60% | No plasma separation needed; shorter sessions (~135 min); broadest protein adsorption [49,55,56] |
| Immunoadsorption | Anti-apoB antibody columns | LDL-C ↓75–82%; greatest % reduction | Reusable columns; less coagulation factor loss; greater HDL loss (~20%) [49,53,57] |

selection in clinical practice.

Dextran sulfate adsorption (DSA), pioneered in Japan in the early 1980s, remains the most widely used modality globally [7,8]. DSA systems separate plasma from whole blood and pass it over columns of dextran sulfate cellulose beads, which bind apoB-containing lipoproteins through electrostatic interactions. This approach achieves robust LDL-C and Lp(a) reductions but also co-removes coagulation factors, particularly fibrinogen and antithrombin III, which necessitates monitoring in patients on concurrent anticoagulation [50–52]. High serum triglyceride concentrations attenuate DSA efficacy by competing for binding sites, a consideration in patients with mixed dyslipidemias [54].

The H.E.L.P. system exploits the differential solubility of lipoproteins at low pH in the presence of heparin, precipitating LDL, Lp(a), and fibrinogen from plasma while allowing most other plasma proteins to remain in solution [53]. This method achieves substantial fibrinogen reduction (approximately 60% per session) and marked improvements in whole-blood viscosity, plasma viscosity, and erythrocyte aggregation, which are particularly relevant in patients with PAD and chronic kidney disease where rheologic abnormalities contribute to microvascular ischemia [19,20,53]. The rheologic benefits of H.E.L.P. apheresis are among the most distinctive advantages of this modality and provide a mechanistic rationale for its preferential use in PAD populations.

DALI is unique among apheresis modalities in that it operates on whole blood without prior plasma separation, adsorbing apoB-containing lipoproteins directly from blood as it passes through polyacrylate bead columns [55,56]. This simplifies the circuit, shortens treatment times to approximately 90–135 min, and broadens the spectrum of adsorbed proteins, including complement components and C-reactive protein. DALI may be preferred in patients with poor venous access or those who prefer shorter treatment sessions, though the broader protein removal profile requires awareness of potential immunomodulatory effects.

Immunoadsorption employs columns containing sheep anti-human apoB polyclonal antibodies, providing the highest specificity among available modalities [49,57]. The columns are regenerable and reusable over multiple sessions, potentially reducing long-term costs. Immunoadsorption achieves the greatest percentage LDL-C reduction per session (75–82%) but is associated with more substantial HDL loss (approximately 20%), which may be a consideration in patients with low baseline HDL-C levels [49,53].

A prospective randomized cross-over trial in statin-treated FH patients demonstrated that dextran sulfate adsorption and immunoadsorption reduced LDL-C more effectively than DALI (84% and 82% vs. 77%, respectively), with similar Lp(a) reductions of approximately 63% across all three systems [49]. In practice, modality selection is determined by patient-specific factors, including triglyceride levels, the desire for fibrinogen and viscosity reduction, procedural convenience, venous access quality, anticoagulation status, and institutional availability, rather than by differences in hard clinical outcomes, which remain undemonstrated in head-to-head studies [5,6,40,49]. Notably, these modality-specific differences in fibrinogen removal, protein adsorption breadth, and rheologic effects may become especially relevant as LA is evaluated not only for lipid lowering but also for its pleiotropic vascular and renal applications.

## 5. Peripheral arterial disease: emerging evidence

The application of LA in peripheral arterial disease represents a biologically plausible and clinically promising emerging indication, supported by a growing body of observational evidence from Germany and Japan demonstrating benefits that extend well beyond lipid lowering [19,20]. PAD affects over 200 million individuals worldwide and is associated with substantial morbidity, limb loss, and cardiovascular mortality, yet it remains under-recognized and undertreated relative to coronary and cerebrovascular disease. Elevated Lp(a) has been identified as an independent risk factor for PAD in multiple epidemiologic studies, and the prothrombotic and rheologic derangements associated with advanced PAD provide a particularly compelling mechanistic rationale for an intervention that targets not only lipoproteins but also fibrinogen, viscosity, and inflammatory mediators [19,58].

### 5.1. Clinical evidence

Observational German cohorts of PAD patients with elevated Lp(a) on maximally tolerated statins, including the Pro(a)LiFe registry (170 CVD patients, 65 with PAD), have documented approximately 68% chronic Lp(a) reduction and 80–85% reductions in annual MACE and adverse limb events over 5 years of regular LA [19]. Smaller PAD registries (e.g., Poller et al., 10 patients with Lp(a) $>$ 60 mg/dL) have reported improvements in ankle-brachial index (ABI) from $0.5 \pm 0.2$–$0.9 \pm 0.1$, with revascularizations decreasing from 35 to 1 in the year after initiating weekly LA, sustained over 2 years [19,20]. These improvements in ABI, a surrogate for macrovascular patency, were accompanied by subjective improvements in claudication distance and quality of life, although formal quality-of-life assessment instruments were not employed in most of these studies. In patients with concurrent chronic kidney disease and PAD, H.E.L.P. apheresis improved pain, walking distance, and tissue lesion healing despite normal baseline LDL-C, indicating benefits that are not limited to patients with uncontrolled lipids and suggesting a dominant role for the non-lipid, rheologic mechanisms of LA in this population [20]. Long-term revascularization outcomes data from the German and Japanese registries further support that LA may reduce both the frequency and complexity of peripheral interventions, with the potential to modify the clinical course of PAD-related limb ischemia.

A large Japanese clinical database analysis of 924,238 patients with CKD identified 147 with concurrent PAD who received LDL apheresis, providing real-world insight into current practice patterns [59]. The cohort was heavily comorbid: 86% had diabetes mellitus, 48% had prior stroke, 34% had ischemic heart disease, and 86% were on maintenance hemodialysis, reflecting the selection of the most severely affected patients for LA. Over a median observation period of 812 days, mortality reached 41%, and multivariate analysis showed that LA did not independently improve prognosis, likely reflecting profound selection bias toward end-stage vascular disease rather than treatment futility. Importantly, only 2.7% received bypass surgery despite severe PAD, and statin use was limited to 40%, suggesting that LA was deployed as a last-resort intervention in patients with few remaining therapeutic options. These data reinforce the need for earlier initiation of LA in PAD and highlight the limitations of retrospective database analyses in evaluating apheresis efficacy in this population.

### 5.2. Mechanisms beyond lipid lowering

LA acutely removes multiple atherothrombotic mediators beyond LDL-C and Lp(a). A comprehensive review of the systemic pleiotropic effects of LA has characterized five interconnected domains of non-lipid benefit: anti-inflammatory activity, endothelial function restoration, hemorheologic improvement, coagulation modulation, and immune modulation [24]. Reductions in fibrinogen, blood viscosity, and platelet aggregation improve microcirculation and tissue perfusion in the ischemic limb [19,20,24,60]. The reduction in whole-blood viscosity is particularly relevant in critical limb ischemia, where the rheologic properties of blood at low shear rates determine perfusion through stenotic and collateral vessels. Serial sessions lower adhesion molecules (E-selectin, VCAM−1, ICAM−1) and inflammatory cytokines (IL−6, TNF-α), while decreases in oxidized LDL and reactive oxygen species reduce oxidative vascular injury and may promote endothelial recovery [20,60]. In hemodialysis patients with PAD, LDL apheresis has been shown to reduce reactive oxygen species production from circulating leukocytes, providing direct evidence that the procedure modulates

systemic oxidative stress [60]. Positron emission tomography (PET) studies using fluorodeoxyglucose (FDG) and sodium fluoride tracers demonstrate that LA, unlike the modest Lp(a) reductions achieved with PCSK9 inhibitors alone, can acutely reduce arterial wall inflammation and possibly slow vascular calcification [61,62], raising the possibility of clinical benefit in PAD even when serum lipoproteins are adequately controlled. Collectively, these pleiotropic effects suggest that LA may function as a multi-modal intervention in PAD, addressing lipid-dependent and lipid-independent mechanisms of disease progression.

Current evidence, while encouraging, is based on small, predominantly German and Japanese observational cohorts with inherent selection bias and limited generalizability. Large randomized PAD-specific trials, including the LETS-PAD initiative, are needed to establish LA as an evidence-based intervention in this population and to identify which patient subgroups derive the greatest benefit [19,20,58].

## 6. Renal indications

The use of LA in renal disease is supported by a distinct mechanistic rationale, clearance of oxidized LDL, Lp(a), and associated inflammatory mediators from the circulation, and by clinical experience that is strongest in Japan, where LDL apheresis for steroid-resistant FSGS has been approved since 1992 [21–23]. The pathogenic role of dyslipidemia in glomerular diseases has been recognized for decades, with nephrotic-range proteinuria itself driving secondary hyperlipidemia through hepatic lipoprotein overproduction, creating a vicious cycle of lipid-mediated renal injury [63]. LA interrupts this cycle by directly removing the injurious lipid species from the circulation. A comprehensive mechanistic review of the Japanese experience has identified several distinct pathways by which LA may exert renal benefit: reduction of macrophage infiltration via clearance of oxidized LDL, adsorption of circulating permeability factors and inflammatory mediators, restoration of sensitivity to immunosuppressive agents, and upregulation of the anti-inflammatory cytokine IL−10, an effect observed specifically in nephrotic syndrome (FSGS, minimal change disease, and diabetic nephropathy) but not in atherosclerosis obliterans, suggesting a disease-specific immunomodulatory mechanism [64].

Among renal applications, the strongest clinical evidence supports LA in steroid-resistant FSGS, where prospective data and regulatory approval in Japan have established clinical precedent. Evidence for post-transplant FSGS recurrence is more limited and largely based on single-center series, while the rationale for LA in diabetic nephropathy and cholesterol crystal embolism remains primarily mechanistic, supported by case reports and small cohorts rather than controlled studies. The following subsections are organized to reflect this evidentiary hierarchy.

### 6.1. Steroid-resistant focal segmental glomerulosclerosis

In a Japanese prospective trial of 11 children with steroid-resistant and cyclosporine-resistant primary FSGS, intensive LDL apheresis (12 sessions over 3 months) combined with high-dose prednisone achieved remission in 7 of 11 patients (5 complete, 2 partial), with complete responders maintaining preserved renal function over a median of 4.4 years of follow-up [21]. The study suggested that the benefit of LA was greatest in patients who retained some degree of steroid responsiveness, implying a synergistic mechanism between immunosuppression and lipid clearance. A U.S. multicenter single-arm study using the Liposorber LA−15 system in drug-resistant primary FSGS and post-transplant recurrence demonstrated partial or complete remission in 25–100% of early enrollees, with stable or improved estimated glomerular filtration rate (eGFR) in short-term follow-up [23]. The variability in response rates across these studies likely reflects heterogeneity in the underlying podocyte injury mechanism, disease duration, and the degree of irreversible tubulointerstitial fibrosis at the time of treatment initiation. These data support LA as an adjunct to immunosuppression rather than a standalone therapy, with the greatest benefit observed when some degree of residual steroid responsiveness persists and when treatment is initiated before advanced sclerotic changes have become established [21,23].

A post-hoc analysis of the Japanese POLARIS study extended these findings by evaluating LDL apheresis efficacy across the spectrum of baseline renal function [65]. Among 64 episodes of LDL-A in 58 patients with drug-resistant nephrotic syndrome, outcomes were stratified by eGFR: normal ($\geq$60 mL/min/1.73 m$^2$), moderately impaired (30−60), and severely impaired (<30). Significant reductions in proteinuria were observed in the normal and moderately impaired groups, with a favorable trend in the severely impaired group. Critically, most patients across all strata did not progress to end-stage renal disease at 2-year follow-up, challenging the prior assumption that LDL apheresis loses efficacy once renal function is substantially compromised. These data support a broader therapeutic window for LA in nephrotic syndrome than previously recognized and suggest that treatment should not be withheld solely on the basis of reduced eGFR [65].

### 6.2. Post-transplant recurrent FSGS and podocyte rescue

Recurrence of FSGS in the transplanted kidney occurs in 20–40% of patients and is a major cause of allograft failure. Among pediatric FSGS patients undergoing kidney transplantation, LDL apheresis reduced oxidized LDL and lipoprotein-associated phospholipase A2 (Lp-PLA2), halving proteinuria without GFR loss [22]. The mechanistic basis for this benefit involves direct podocyte injury by oxidized LDL, which causes apoptosis, disruption of the slit diaphragm protein nephrin, and detachment from the glomerular basement membrane; lipid-modulating therapies, including statins, protect podocytes via activation of the phosphatidylinositol 3-kinase (PI3K)/Akt survival signaling pathway [66]. LA extends this principle by directly removing the injurious ligand from the circulation, providing a more immediate and quantitatively greater reduction in oxidized LDL exposure than pharmacotherapy alone. The combination of LA with plasmapheresis and rituximab has become an increasingly common approach to post-transplant FSGS recurrence at many transplant centers, although the relative contribution of each modality remains difficult to disentangle in the absence of controlled trials.

### 6.3. Diabetic nephropathy and Lp(a)-mediated renal vascular injury

In diabetic kidney disease (DKD), renal deposition of oxidized LDL on podocytes drives progressive injury and proteinuria through mechanisms involving the oxidized LDL receptor LOX−1, downregulation of the cytoprotective factor Klotho, and activation of the RAC1/OLR1 signaling pathway [67]. LA rapidly removes LDL, Lp(a), oxidized LDL, and inflammatory mediators, potentially interrupting this pathogenic cascade at the level of the circulating injurious ligand. However, evidence in DKD remains limited to case reports and mechanistic extrapolation from other settings, and no prospective clinical trials have evaluated LA specifically for diabetic nephropathy [20]. Japanese series in cholesterol crystal embolism (15 patients) suggest that LA combined with steroids can stabilize or transiently improve eGFR, providing proof-of-concept that extracorporeal lipid removal can modify renal outcomes in cholesterol-mediated vascular injury [68]. The geographic heterogeneity in practice, with Japan maintaining an established role for LA in renal indications including FSGS, cholesterol embolism, and selected cases of DKD, while Europe and the United States rely primarily on trial-based or case-based use, reflects the absence of robust randomized evidence and the influence of different regulatory frameworks and reimbursement structures on clinical practice [20–23].

### 6.4. Expanding indications beyond FSGS: evidence from Japan

Although Japanese National Health Insurance coverage for LDL

apheresis in renal disease has been limited to FSGS since its approval in 1992, accumulating clinical evidence supports therapeutic benefit across a broader range of nephropathies [64,65]. Muso et al. have systematically reviewed the evidence for LA in drug-resistant nephrotic syndrome due to non-FSGS etiologies, including minimal change nephrotic syndrome (MCNS), membranous nephropathy, and diabetic nephropathy, with data demonstrating favorable proteinuria responses in each category [64]. The proposed mechanisms of benefit differ from those operative in FSGS and involve not only direct removal of nephrotoxic lipid species but also adsorption of circulating permeability factors, modulation of macrophage-mediated glomerular inflammation, and a distinctive anti-inflammatory response characterized by upregulation of IL−10 [64]. This IL−10 response was observed specifically in patients with nephrotic syndrome, regardless of histological subtype, but not in patients undergoing LDL apheresis for atherosclerosis obliterans, suggesting that the immunomodulatory effect is mediated by the renal disease process itself rather than being a generic consequence of extracorporeal lipid removal. The POLARIS study and its post-hoc analyses have provided prospective evidence that LA is effective across the continuum of renal function impairment, with proteinuria reduction and prevention of progression to end-stage renal disease even in patients with eGFR below 30 mL/min/1.73 $m^2$ [65]. Collectively, these Japanese data provide a rationale for further evaluation of LA in nephrotic syndrome beyond FSGS and for reconsideration of existing indication boundaries, and for conducting international multicenter trials to validate these findings in diverse populations [64,65].

## 7. Integration with pharmacologic therapies

The introduction of PCSK9 inhibitors marked a paradigm shift in LA utilization. In patients with HeFH receiving chronic apheresis, the addition of alirocumab to background statin therapy reduced the frequency of sessions by 75%, and approximately 64% of patients were able to discontinue apheresis entirely while maintaining LDL-C below target [14]. These findings have transformed the treatment algorithm for HeFH, with current consensus statements positioning PCSK9 monoclonal antibodies as enabling less frequent or discontinued apheresis for LDL-C control, and reserving LA for patients who remain above target despite maximally tolerated pharmacotherapy including a PCSK9 inhibitor [14–16,31,69]. The important caveat is that the modest 20–25% Lp(a) reduction achieved by PCSK9 inhibitors is often insufficient for patients with Lp(a)-driven residual risk, meaning that a substantial proportion of patients who can discontinue LDL-focused apheresis will still require ongoing treatment for elevated Lp(a) [14,31,69].

### 7.1. Inclisiran

Inclisiran, a small interfering RNA (siRNA) conjugated to N-acetylgalactosamine for hepatocyte-specific uptake, targets PCSK9 synthesis at the mRNA level and lowers LDL-C by approximately 50–60% with convenient twice-yearly subcutaneous dosing [16–18,70,71]. By silencing PCSK9 production intracellularly, inclisiran achieves sustained LDL-C reduction without the need for frequent injections, which may improve adherence in populations with documented poor compliance to monthly monoclonal antibody regimens. Inclisiran reduces Lp(a) by 15–25%, a magnitude comparable to PCSK9 monoclonal antibodies and insufficient to meaningfully address Lp(a)-driven risk in most patients [16–18,70]. While inclisiran can substitute for PCSK9 monoclonal antibodies in the LDL-centric treatment algorithm and further reduce apheresis utilization for LDL-C management, particularly in health systems where the logistic burden of biweekly or monthly injections is a barrier, it does not address the substantial Lp(a)-related risk that necessitates apheresis in many patients [14,16]. The positioning of inclisiran relative to monoclonal antibodies and LA in practice guidelines continues to evolve as post-marketing cardiovascular outcome data from ORION−4 mature.

### 7.2. RNA-based Lp(a)-lowering agents

Antisense and siRNA agents targeting hepatic *LPA* expression represent a potentially transformative development in Lp(a) therapeutics that may substantially alter the role of LA in clinical practice (Table 2). Pelacarsen, an antisense oligonucleotide (ASO) targeting apo(a) mRNA, achieved 70–80% Lp(a) reductions in early-phase trials, with the phase 3 cardiovascular outcome trial Lp(a)HORIZON enrolling over 8000 patients with established ASCVD and Lp(a) $\geq$ 70 mg/dL [16–18,33]. Olpasiran, a siRNA targeting apo(a) synthesis, demonstrated 71–97% Lp(a) reductions lasting several months after a single dose in phase 1, with confirmatory dose-ranging results in phase 2 confirming potent, durable, and dose-dependent Lp(a) lowering [16–18,72]. Lepodisiran, another siRNA employing a distinct conjugation chemistry, has shown similarly potent and durable Lp(a) lowering in early clinical studies, with some dosing regimens achieving near-complete suppression of Lp(a) for up to six months. If ongoing cardiovascular outcome trials demonstrate that these agents reduce hard ASCVD endpoints in proportion to the magnitude of Lp(a) lowering, as predicted by Mendelian randomization data, most patients currently receiving Lp(a)-driven apheresis could be transitioned to pharmacotherapy, with LA reserved for nonresponders, patients with contraindications to RNA-based agents, or exceptional clinical scenarios requiring immediate and maximal Lp(a) reduction [14,16–18].

Notably, PET imaging has demonstrated persistent arterial wall inflammation in patients receiving PCSK9 inhibitors with residual elevated Lp(a), even when LDL-C is well controlled below 70 mg/dL [61,62]. This finding underscores that LDL-C reduction alone does not fully mitigate Lp(a)-mediated vascular risk and supports the unique multi-target profile of LA, which simultaneously removes LDL, Lp(a), fibrinogen, and inflammatory mediators in a single treatment session [14,24,61,62]. Until the RNA-based Lp(a) therapies demonstrate cardiovascular outcome benefit and achieve widespread availability and reimbursement, LA will continue to occupy a critical niche for Lp(a)-driven risk management. Taken together, the pharmacotherapy landscape suggests a three-part trajectory for LA: progressive contraction in LDL-centric indications as PCSK9 inhibitors and inclisiran become standard of care; a persisting and potentially expanding role in Lp(a)-driven disease until RNA-based agents demonstrate outcome benefit and achieve broad access; and a distinct, mechanistically grounded but evidence-limited rationale for non-lipid indications in PAD and renal disease that pharmacologic Lp(a) lowering alone may not address.

## 8. Gaps in evidence and future directions

Despite decades of clinical use and consistent observational evidence supporting LA efficacy, several critical evidence gaps persist and limit the strength of current guideline recommendations.

**Table 2**
Impact of Emerging Therapies on Apheresis Utilization.

| Therapy Class | Typical Lp(a) Reduction | Impact on LA Need | Key Considerations |
|---|---|---|---|
| PCSK9 mAbs | ~20–25% | Often reduce/stop LDL apheresis; Lp(a) apheresis often still needed | 64% of HeFH patients discontinued LA; Lp(a) reduction insufficient [14,31,69] |
| Inclisiran | ~15–25% | Similar to PCSK9 mAbs; no direct LA comparison data | Twice-yearly dosing; convenient but limited Lp(a) effect [16–18,70,71] |
| Lp(a) ASO/siRNA | 70-> 97% | Expected to largely replace Lp(a) apheresis if outcome trials positive | Pelacarsen, olpasiran, lepodisiran in phase 2–3; outcome data pending [16–18,72] |

### 8.1. Absence of randomized controlled trials

No large randomized controlled trials have demonstrated that adding LA to optimal modern pharmacotherapy reduces hard ASCVD endpoints in HoFH, HeFH, or isolated elevated Lp(a) [5,14,73,74]. All outcome evidence derives from registries, cohort studies, and before-after comparisons, which, while remarkably consistent in direction and magnitude, cannot exclude residual confounding, selection bias, or regression to the mean. The ethical challenges of randomizing patients with severely elevated lipid levels to a non-treatment arm have been a longstanding barrier, but adaptive trial designs, waitlist controls, and comparison of high- versus low-frequency apheresis schedules could provide randomized evidence while maintaining ethical standards. Priority trials should test "apheresis plus best medical therapy versus best therapy alone" in three populations: HoFH with LDL-C above target despite maximal pharmacotherapy, high-risk HeFH with residual LDL-C elevation, and very high Lp(a) with progressive ASCVD despite optimal management of conventional risk factors [5,14,73,74].

### 8.2. Integration with novel agents

The optimal integration of LA with PCSK9 inhibitors, lomitapide, evinacumab, and emerging RNA-based Lp(a) therapies remains undefined. Questions of clinical importance include: at what Lp(a) threshold can apheresis be safely discontinued in patients responding to RNA-based agents? What is the appropriate monitoring interval after de-escalation? Are there patients who benefit from combination therapy with both pharmacologic Lp(a) lowering and continued apheresis? A trial of pelacarsen in German patients receiving weekly apheresis is directly testing whether potent Lp(a) lowering permits apheresis down-titration without loss of clinical benefit [29]. Comparative studies examining long-term outcomes of continued apheresis versus switching to or combining with RNA-based therapies are urgently needed, as is pharmacoeconomic modeling to guide health system decision-making during the transition period [14,16–18].

### 8.3. Standardization and global harmonization

Regulatory and guideline heterogeneity across regions, with Germany, Japan, and the United States each employing different indication criteria, reimbursement thresholds, and approved modalities, reflects the absence of high-quality evidence and creates significant disparities in patient access [5,14,73,74]. In Germany, where the Federal Joint Committee (G-BA) approved LA for isolated elevated Lp(a) in 2008, more than 2000 patients receive regular treatment, whereas in many other countries, LA for Lp(a) is unavailable or requires individual insurance authorization. International registries, as advocated by the International Atherosclerosis Society and the European Atherosclerosis Society, are needed to standardize indications, collect longitudinal outcomes including quality-of-life metrics, and inform future evidence-based thresholds for LA initiation and continuation [73–75]. Cost-effectiveness analyses are also lacking and essential for health-system decision-making: while LA is resource-intensive (estimated at $50,000-$100,000 per patient per year depending on modality and session frequency), the cost of recurrent cardiovascular events, revascularizations, and disability in untreated patients may offset treatment costs in appropriately selected high-risk populations [5,14]. Patient-reported outcome measures, including treatment burden, vascular access complications, and the psychological impact of chronic extracorporeal therapy, should be systematically incorporated into registries and trials to provide a comprehensive assessment of LA value.

## 9. Conclusion

Lipoprotein apheresis remains an indispensable therapy for patients with severe genetic dyslipidemias refractory to pharmacotherapy, supported by decades of registry data documenting consistent reductions in major adverse cardiovascular events across diverse populations and treatment settings. Yet the clinical identity of LA is shifting. The arrival of PCSK9 inhibitors, inclisiran, and potent RNA-based Lp(a)-lowering agents is progressively narrowing its role in routine LDL-C management, while simultaneously, emerging evidence from PAD and renal disease cohorts suggests that the non-lipid effects of extracorporeal lipoprotein removal, including rheologic improvement, anti-inflammatory modulation, and clearance of oxidized LDL, may carry independent clinical relevance in selected phenotypes. In this evolving landscape, LA should no longer be viewed simply as a legacy rescue therapy for refractory LDL-C elevation, but as a highly selective intervention whose future will be defined by phenotype: enduring in severe inherited dyslipidemias and Lp(a)-driven cardiovascular disease, potentially relevant in some pleiotropic vascular and renal settings, and increasingly shaped by competition and complementarity with targeted molecular therapies. Realizing this future will require randomized trial evidence in prioritized populations, international registry harmonization, systematic pharmacoeconomic evaluation, and greater attention to patient-reported outcomes including treatment burden and vascular access complications. Until the ongoing cardiovascular outcome trials of RNA-based Lp(a)-lowering agents mature and these therapies achieve broad global availability, LA will continue to occupy a critical niche for the highest-risk patients whom pharmacotherapy alone cannot adequately protect.

## Declaration of Generative AI and AI-assisted technologies in the writing process

Generative artificial intelligence tools (Claude, Anthropic) were used to assist with literature synthesis, manuscript drafting, and reference formatting during preparation of this manuscript. All content was reviewed, verified, and edited by the authors, who take full responsibility for the accuracy and integrity of the work.

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