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Successful Lipid Lowering With Alirocumab and Bempedoic Acid in a Statin-Intolerant Heterozygous Familial Hypercholesterolemia With Markedly Elevated Lipoprotein(a): A Case Report

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Abstract

Intensive lipid lowering is essential in the management of heterozygous familial hypercholesterolaemia (HeFH). Statin intolerance necessitates consideration of alternative lipid-lowering therapies, while concomitantly elevated lipoprotein(a) (Lp(a)) further increases cardiovascular risk and the importance of adequate lipid reduction. We report the case of a 66-year-old woman with severe statin intolerance and dyslipidaemia. Following assessment in the lipid clinic, she was identified to have genetically confirmed HeFH with severely elevated Lp(a) at 617 nmol/L. Her computerized tomography coronary angiogram (CTCA) demonstrated unobstructed coronary arteries with no lesions seen, and her coronary artery calcium (CAC) score was 0. Despite a baseline low-density lipoprotein cholesterol (LDL-C) of 8.4 mmol/L and non-high-density lipoprotein cholesterol (non-HDL-C) of 9.1 mmol/L in July 2025, her lipid parameters improved substantially with alirocumab and bempedoic acid. LDL-C improved by 69.0% to 2.6 mmol/L, and non-HDL-C decreased by 64.8% from baseline to a level of 3.2 mmol/L. As non-HDL-C remained above the target of <2.5 mmol/L, ezetimibe was subsequently added.

Categories: Cardiology, Internal Medicine, Endocrinology/Diabetes/Metabolism
Keywords: alirocumab, atherosclerotic cardiovascular disease, bempedoic acid, heterozygous familial hypercholesterolaemia, ldl cholesterol, lipoprotein (a), statin intolerance

Introduction

Familial hypercholesterolaemia (FH) is an inherited disorder characterized by lifelong elevation of low-density lipoprotein cholesterol (LDL-C), resulting in increased risk of atherosclerosis and premature coronary heart disease. The majority of cases are heterozygous, with the likelihood increasing when total cholesterol exceeds 7.5 mmol/L [1]. FH is caused by a pathogenic variant in the *LDLR*, *APOB*, or *PCSK9* genes. Affected individuals may first present with early-onset atherosclerotic cardiovascular disease (ASCVD) [2]. Management focuses on modifiable cardiovascular risk factors, such as obesity or hypertension, secondary causes of hyperlipidaemia, and lipid-modification therapy. National Institute for Health and Care Excellence (NICE) recommends a target reduction in LDL-C of greater than 50% from baseline in these patients [1].

Lipoprotein(a) (Lp(a)) is a cholesterol-rich lipoprotein structurally similar to LDL-C, with apolipoprotein(a) covalently linked to apolipoprotein B. Circulating levels are predominantly genetically determined by variants in the *LPA* gene and, like FH, elevated levels can cluster within families. Increased Lp(a) concentrations are independently associated with a higher risk of ASCVD and calcific aortic valve disease [3]. Evidence for the clinical benefit of directly lowering Lp(a) remains limited due to the lack of established Lp(a)-specific therapies and cardiovascular outcome data. There is a need for more targeted therapeutic strategies, and currently, tighter goals for lipid-lowering are suggested in these patients [4,5].

In the management of familial hypercholesterolaemia (HeFH), it is recommended that Lp(a) levels be measured at least once to identify those at higher risk of ASCVD [4]. An Lp(a) level above 250 nmol/L is associated with an observed 10-year ASCVD risk of 28.7% in FH, compared to 11% with Lp(a) <250 nmol/L [6], reiterating the need for tight risk factor control.

The HEART UK consensus statement on Lp(a) recommends that in individuals with Lp(a) > 90 nmol/L, management should focus on reducing overall atherosclerotic cardiovascular risk and recommends a reduction in non-HDL-C of >50%. Alternatively, a non-HDL-C target of <2.5 mmol/L may be used (broadly equivalent to LDL-C <1.8 mmol/L). In patients with progressive cardiovascular disease and recurrent events despite maximum lipid-lowering therapy (including PCSK9 inhibitor treatment), lipoprotein apheresis may be considered when Lp(a) >150 nmol/L [4].

Statins are the cornerstone of lipid-lowering therapy, with high-intensity treatment reducing LDL-C by ~50%. Statin intolerance primarily manifests as SAMS (statin-associated muscle symptoms) with myalgia, myopathy, and rhabdomyolysis. The prevalence of statin intolerance differs substantially between clinical trials and routine practice, partly owing to the influence of the nocebo effect. Where statin therapy is insufficient or not tolerated, ezetimibe can be considered in conjunction or as monotherapy; this functions by lowering cholesterol absorption in the intestine [2]. Bempedoic acid is a further novel oral lipid-lowering agent which inhibits adenosine triphosphate (ATP)-citrate lyase, an enzyme upstream of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase pathway. For the same amount of LDL-C reduction, bempedoic acid appears to provide a similar cardiovascular benefit to statins [7]. The proprotein convertase subtilisin/kexin type 9 (PCSK9) plays a key role in regulating LDL-C receptor expression. Genetic evidence linking PCSK9 loss of function with lower LDL-C and ASCVD risk validated PCSK9 as a therapeutic target. PCSK9 inhibitor therapies are particularly useful when there is failure to meet LDL-C targets with maximum statin and ezetimibe, statin intolerance, or in FH [8].

This case report demonstrates the challenges of lipid management in a patient with genetically confirmed heterozygous familial hypercholesterolaemia, markedly elevated Lp(a), and reported statin intolerance. It also highlights the potential discordance between inherited cardiovascular risk and coronary imaging findings, and the importance of continued intensive risk-factor modification despite apparently reassuring imaging.

Case Presentation

We present a case of a 66-year-old woman of Iranian descent with confirmed HeFH and severely elevated Lp(a). The patient was referred to the lipid clinic (January 2024) for specialist management following suboptimal control of her dyslipidaemia.

In primary care, she had previously been treated with atorvastatin and simvastatin; however, adequate lipid control had not been achieved. Subsequent dose escalation was associated with reported worsening myalgia and insomnia, prompting discontinuation of statin therapy and referral for specialist assessment.

Historical primary care records were unavailable for review, preventing verification of the exact details of prior statin therapy, including dosing and duration, and any subsequent rechallenge. Information regarding prior rhabdomyolysis and the patient's age at diagnosis of hypercholesterolaemia was also unavailable. Ezetimibe had not previously been trialled.

Following her initial specialist review in January 2024, she was lost to follow-up and was re-referred to the lipid clinic in July 2025. At the time of this subsequent specialist assessment, she was not receiving statin therapy.

Her past medical history was notable for hypothyroidism, premature ovarian insufficiency, migraine, anxiety, and asthma. Regular medications included levothyroxine 25 micrograms once daily, calcium carbonate 1500 mg/colecalciferol 10 micrograms one tablet twice daily, beclometasone dipropionate/formoterol fumarate (100/6 micrograms) inhaler, salbutamol inhalers as required, and amitriptyline 10 mg once daily. Thyroid function was within the normal range.

There was no previous history of coronary artery disease, cerebrovascular or peripheral arterial disease, diabetes, metabolic dysfunction-associated steatotic liver disease (MASLD), hypertension, or pancreatitis.

Her family history was notable for hypercholesterolaemia on the maternal side, although it was unclear whether genetic testing had been performed. Her mother also had coronary artery disease and pre-diabetes. Additional maternal relatives had coronary artery disease, although these events occurred after 60 years of age. Her son was reported to have hypercholesterolaemia, but we are not aware of any formal genetic testing.

A computerized tomography coronary angiogram performed in May 2024 showed unobstructed coronary arteries with no lesions seen, and a CAC score of 0 [9], despite severe hypercholesterolaemia and markedly elevated Lp(a).

Her BMI was 30.1 kg/m^2. She was an ex-smoker, having ceased smoking 21 years before presentation. Corneal arcus was noted on examination. Blood pressure in the specialty clinic was 155/81 mmHg, although the patient reported that her home readings were typically lower. Glycated haemoglobin (HbA1c) was 39 mmol/mol. Liver and renal function tests were within normal limits.

Her age-adjusted Welsh Familial Hypercholesterolaemia score was 7, meeting the criteria for genetic testing [10]. Genetic analysis identified a heterozygous pathogenic *LDLR* c.1285G>A (p.Val429Met) variant, confirming a diagnosis of heterozygous familial hypercholesterolaemia IIa.

Lipid panel results on re-referral to specialty clinic, and further historical results from 2023 can be seen in

Table 1. LDL-C was measured directly by the laboratory rather than calculated.

Date	Total Cholesterol (mmol/L)	Cholesterol HDL Ratio	HDL (mmol/L)	Triglycerides (mmol/L)	Non-HDL Cholesterol (mmol/L)	LDL (mmol/L)
Reference ranges	Not reported,* 2.3-4.9†	< 5.0,* 0.0-4.0†	>1.2,* 1.2-1.7†	<1.7,* 0.0-2.3†	Not reported,* 0.0-3.8†	Not reported
01/2023	11.8*	8.19*	1.44*	1.85*	10.4*	9.52
06/2023	10.2*	7.3*	1.4*	1.4*	8.8*	8.2
01/2024 (Results in specialty clinic)	10.8†	7.2†	1.5†	2.8†	9.3†	8
08/2024	11.1*	8.5*	1.3*	1.7*	9.8*	9
05/2025	10.4*	7.4*	1.4*	3*	9.0*	7.5
07/2025 (Results in specialty clinic)	10.6†	7.1†	1.5†	1.5†	9.1†	8.4

TABLE 1: Lipid panel results in specialty clinic, as well as further historical results.

Reference ranges are reported as provided by the respective laboratories. Where a reference range was unavailable, this is indicated as 'Not reported'.

* Reference range reported by the community laboratory.

† Reference range reported by the hospital laboratory.

HDL: high-density lipoprotein; LDL: low-density lipoprotein

In January 2024, testing demonstrated significantly elevated Lp(a) results at 617 nmol/L, apolipoprotein B at 2.2 g/L, and apolipoprotein A1 at 1.64 g/L. Apolipoprotein B to A1 Ratio was 1.3, further indicating an increased atherogenic risk.

PCSK9 inhibitor therapy was commenced in July 2025 with alirocumab 75 mg subcutaneously every two weeks. This was continued throughout follow-up.

On review in December 2025, non-HDL-C decreased from 9.1 mmol/L to 5.6 mmol/L (38.5%), while LDL-C decreased from 8.4 mmol/L to 4.8 mmol/L (42.0%). Neither parameter had fallen by >50% from the July 2025 baseline, and non-HDL-C remained above the target of <2.5 mmol/L for individuals with elevated Lp(a) [4]. Therefore, bempedoic acid 180 mg once daily was commenced. Given the patient's reported statin intolerance, bempedoic acid was selected as an alternative non-statin lipid-lowering therapy.

Follow-up blood tests in June 2026 demonstrated further improvement, with non-HDL-C decreasing to 2.2 mmol/L and LDL-C to 1.7 mmol/L. Repeat lipid measurements were arranged for three months' time.

On review in September 2026, LDL-C had increased to 2.6 mmol/L. Non-HDL-C levels had increased to 3.2 mmol/L, exceeding the target of <2.5 mmol/L. Consequently, ezetimibe 10 mg once daily was commenced. Repeat blood tests are planned for December 2026.

The therapeutic interventions and subsequent lipid profile results are shown in Figure 1, while the timeline of key clinical events and changes in lipid-lowering therapy is summarised in Table 2.

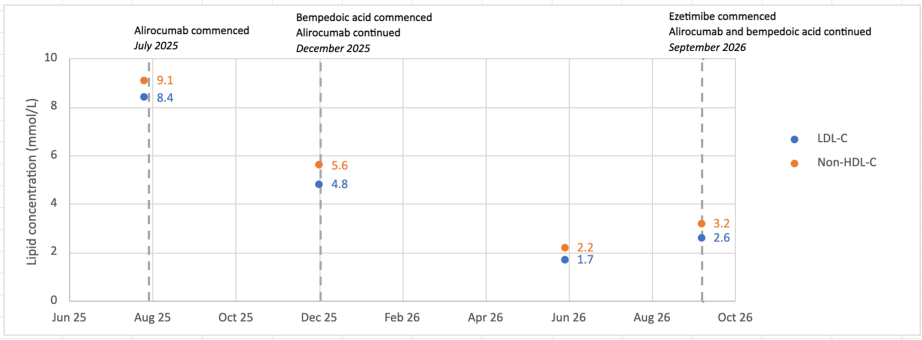


FIGURE 1: Serial changes in LDL-C and non-HDL-C following sequential lipid-lowering therapy.

The vertical dashed lines indicate the initiation of alirocumab in July 2025, bempedoic acid in December 2025, and ezetimibe in September 2026. Non-HDL-C decreased from 9.1 mmol/L at baseline to 5.6 mmol/L following initiation of alirocumab, and to 2.2 mmol/L following the addition of bempedoic acid. By September 2026, non-HDL-C had increased to 3.2 mmol/L, and LDL-C was 2.6 mmol/L, prompting the addition of ezetimibe.

LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol

Date	Event
January 2024	Initial lipid clinic assessment
May 2024	CTCA showed unobstructed coronary arteries, CAC score = 0
July 2025	Re-referral to specialty clinic for assessment and management; alirocumab commenced
December 2025	Partial response to alirocumab; bempedoic acid added
June 2026	Further improvement in lipid profile on combination therapy
September 2026	Subsequent increase in non-HDL-C; ezetimibe added

TABLE 2: Timeline of key clinical events and changes in lipid-lowering therapy in relation to the patient's lipid response.

CTCA: computerized tomography coronary angiogram; CAC: coronary artery calcium score; HDL-C: high-density lipoprotein cholesterol

Overall, substantial lipid reduction was achieved following sequential therapy with alirocumab and bempedoic acid. Compared with the July 2025 pre-treatment values, LDL-C decreased from 8.4 mmol/L to 2.6 mmol/L (69.0%) and non-HDL-C from 9.1 mmol/L to 3.2 mmol/L (64.8%) by September 2026. Although LDL-C and non-HDL-C reached their lowest values of 1.7 mmol/L and 2.2 mmol/L in June 2026, respectively, subsequent increases in lipid levels prompted the addition of ezetimibe 10 mg once daily. Repeat Lp(a) measurement was not performed.

Discussion

This case highlights two important clinical considerations: the challenges of achieving intensive lipid lowering in a patient with HeFH, marked Lp(a) elevation and statin intolerance, and the heterogeneity of coronary atherosclerotic burden despite substantial inherited lipid risk.

Current recommendations advocate for intensive LDL-C reduction in patients with FH and elevated Lp(a), particularly where additional risk factors are present. The HEART UK Consensus recommends a reduction in non-HDL-C of >50% or a non-HDL-C target of <2.5 mmol/L [4]. The 2025 European Society of Cardiology/Eurpoean Atherosclerosis Society (ESC/EAS) Focused Update retains the risk-based approach of the 2019 ESC/EAS Guidelines. Under this risk-based framework, the combination of FH with an additional major risk factor (extreme Lp(a) elevation (>430 nmol/L)) places this patient within the very-high-risk category, for which an LDL-C target of <1.4 mmol/L and a ⩾50% reduction from baseline are recommended [7].

Statin intolerance represented a significant therapeutic challenge. Nevertheless, sequential treatment with alirocumab and bempedoic acid achieved substantial reductions in atherogenic lipoproteins. Following the addition of bempedoic acid, non-HDL-C fell to 2.2 mmol/L in June 2026, achieving the recommended target of <2.5 mmol/L for individuals with elevated Lp(a). However, this target was subsequently exceeded at follow-up in September 2026, necessitating further treatment escalation with ezetimibe. In contrast, the LDL-C target of <1.4 mmol/L was not achieved at either follow-up assessment despite the substantial percentage reduction observed. Importantly, residual cardiovascular risk is likely to persist owing to lifelong exposure to atherogenic lipoproteins, markedly elevated Lp(a), and incomplete attainment of recommended LDL-C targets. Ongoing optimisation of atherogenic lipid burden remains a key management objective.

Currently, specific pharmacological therapies targeting Lp(a) are not routinely available. Management therefore focuses on optimization of dyslipidaemia and other cardiovascular risk factors [4]. Lipoprotein apheresis is currently the only licensed treatment for an elevated Lp(a), a procedure that selectively filters out apoB-containing lipoproteins from the blood. Although a time-intensive and expensive procedure, it has shown substantial reductions in LDL-C and Lp(a) levels and major adverse cardiovascular events [11]. It is indicated in patients with a lipid profile as described in our case but with progressive ASCVD and recurrent events [4].

PCSK9 inhibitors reduce Lp(a) levels by approximately 27% on average; however, further evidence is awaited on the impact of this reduction on cardiovascular outcomes [12]. Furthermore, their LDL-C-lowering efficacy is dependent on residual LDL receptor activity, resulting in varying treatment response according to the underlying FH genotype and degree of residual receptor function. PCSK9 inhibitors are also associated with practical considerations, including injection-site reactions, treatment costs, and eligibility criteria for prescribing [13]. The use of both injectable and oral lipid-lowering therapies may increase overall treatment burden and potentially affect long-term adherence.

These limitations have contributed to interest in emerging therapies such as oral PCSK9 inhibitors and cholesteryl transfer protein (CETP) inhibitors. Enlicitide decanoate is an oral PCSK9 inhibitor that has demonstrated substantial LDL-C reductions in Phase 2 trials and may offer a more convenient alternative to injectable PCSK9 inhibitor therapy [14]. Obicetrapib, a CETP inhibitor, has also emerged as a further add-on therapy, working by enhancing reverse cholesterol transport and remodelling apolipoprotein B-containing lipoproteins. The current data available, however, are only based on lipid endpoints [15].

Several novel Lp(a)-lowering therapies are currently in clinical development. The small interfering RNA (siRNA) agents olpasiran and lepodisiran have demonstrated reductions in Lp(a) of >90%, while the oral small-molecule inhibitor muvalaplin has achieved reductions of approximately 70-86% in phase 2 studies. Pelacarsen, an antisense oligonucleotide, has demonstrated reductions of approximately 80%. These agents are now being evaluated in phase 3 cardiovascular outcomes trials, including OCEAN(a)-Outcomes, ACCLAIM-Lp(a), MOVE-Lp(a), and Lp(a) HORIZON, respectively. The focus of these trials is whether substantial pharmacological lowering of Lp(a) translates into reduced cardiovascular events [11].

A limitation of this case is the inability to fully characterise the patient's previous statin exposure and degree of statin intolerance, as historical primary care records were unavailable for review. We also do not know if other potential confounders of her myalgia and insomnia had been addressed in primary care. The age at initial diagnosis of hypercholesterolaemia was also unavailable, limiting assessment of cumulative lifetime lipid exposure. In addition, medication adherence and tolerability, weight and diet changes, or any other concomitant interventions during follow-up were not systematically documented and therefore could not be reliably assessed retrospectively, although no treatment interruptions were recorded in the available records.

A further consideration is the interpretation of LDL-C measurements in patients with markedly elevated Lp(a), as a proportion of measured cholesterol is carried within Lp(a) particles and may therefore contribute to the overall apparent LDL-C burden [16]. As Lp(a)-targeted therapies continue to emerge, biomarker standardisation will become increasingly important. Variability in apo(a) isoform size can affect Lp(a) measurement, and the use of assays calibrated to WHO/International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference standards with reporting in nmol/L may improve consistency in cardiovascular risk assessment and treatment selection [4].

Secondly, this case highlights the variability in coronary atherosclerotic burden among patients with inherited lipid risk, showing a low burden of detectable coronary atherosclerosis despite substantial lipid exposure.

The findings of a CAC score of 0 and unobstructed coronary arteries with no lesions seen on CTCA were notable given the patient's adverse lipid phenotype, age, and suboptimal treatment. In a large cross-sectional study of 1,011 patients with HeFH, 42% had a CAC score of 0 and 33% had no detectable coronary plaque on CTCA. The mean age of this multinational cohort was 48 years. Of interest, approximately 89% of participants were receiving statin therapy, limiting extrapolation of these findings to untreated HeFH [17]. A meta-analysis by Qiu et al. investigating the association between Lp(a) and coronary artery calcification

found that elevated Lp(a) was associated with 31% higher odds of coronary artery calcification (OR 1.31, 95% CI 1.06-1.61; p=0.01). When Lp(a) was analysed as a continuous variable, each 1 mg/dL increase in Lp(a) was associated with a 5% increase in the odds of coronary artery calcification (OR 1.05, 95% CI 1.02-1.08; p=0.003) [18]. However, these data were not specific to patients with HeFH, and the prevalence of a CAC score of 0 in patients with HeFH and markedly elevated Lp(a) remains poorly characterised.

Taken together, these findings suggest that inherited lipid risk alone does not invariably translate into detectable coronary atherosclerosis on coronary imaging, despite the established association between HeFH, elevated Lp(a), and ASCVD.

The risk of ASCVD is influenced by multiple factors. Variants in genes associated with other dyslipidaemias may act as phenotype modifiers, while the cumulative effect of multiple common lipid-associated variants, captured by polygenic risk scores (PRS), may further influence the lipid phenotype and risk of ASCVD. These genetic factors may therefore contribute to the marked inter-individual variability observed in HeFH [19]. Traditional cardiovascular risk factors, including cigarette smoking, male sex, hypertension, high BMI, chronic kidney disease (CKD), diabetes, elevated Lp(a), and a personal or family history of premature ASCVD, further modify risk. The SAFEHEART and Familial Hypercholesterolaemia Risk Scores incorporate many of these factors, although their derivation predominantly in statin-treated patients with genetically confirmed FH and the need for validation across diverse populations are recognised limitations [20]. These observations highlight the importance of a precision medicine approach that integrates genetic findings, lipid phenotype, imaging characteristics, and additional cardiovascular risk factors when assessing risk and guiding treatment in patients with HeFH.

Coronary artery calcification scoring provides prognostic information beyond traditional risk factors and established FH risk equations. The absence of coronary artery calcification is associated with a very low observed risk of ASCVD events, while the presence of coronary artery calcification enhances the prediction of ASCVD. The additional prognostic value of detecting non-calcified plaque by CTCA remains uncertain. It is important to note that a normal CAC score or absence of coronary plaques should not be a reason to forgo LDL-C-lowering therapies [20].

Conclusions

This case highlights the challenges of managing severe dyslipidaemia in a patient with genetically confirmed heterozygous FH, markedly elevated Lp(a), and statin intolerance. Sequential treatment with alirocumab and bempedoic acid achieved substantial reductions in LDL-C and non-HDL-C, demonstrating the potential value of combining non-statin lipid-lowering therapies when conventional treatment is not tolerated. Despite these improvements, continued monitoring and treatment escalation were required to maintain lipid control and optimise cardiovascular risk reduction.

The absence of detectable coronary atherosclerosis on CTCA and CAC score of 0, despite longstanding severe dyslipidaemia and markedly elevated Lp(a), illustrates the variability in the observed coronary atherosclerotic burden among individuals with substantial inherited lipid risk. However, such findings should not be interpreted as elimination of future cardiovascular risk nor diminish the importance of intensive lipid lowering. This case reinforces the need for a personalised, sustained approach to cardiovascular risk reduction in patients with complex inherited lipid disorders and highlights the importance of further research into the factors influencing the relationship between inherited lipid risk, Lp(a) concentrations, and coronary atherosclerosis.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Madhura S. Nootigattu, Preet Mukesh Shah

Acquisition, analysis, or interpretation of data: Madhura S. Nootigattu, Preet Mukesh Shah

Drafting of the manuscript: Madhura S. Nootigattu

Critical review of the manuscript for important intellectual content: Preet Mukesh Shah

Supervision: Preet Mukesh Shah

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