Cardiovascular outcomes in patients with homozygous familial hypercholesterolaemia on lipoprotein apheresis initiated during childhood: long-term follow-up of an international cohort from two registries

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Summary

Background Homozygous familial hypercholesterolaemia (HoFH) is a rare genetic disease characterised by extremely high plasma LDL cholesterol from birth, causing atherosclerotic cardiovascular disease at a young age. Lipoprotein apheresis in combination with lipid-lowering drugs effectively reduce LDL cholesterol, but long-term health outcomes of such treatment are unknown. We aimed to investigate the long-term cardiovascular outcomes associated with lipoprotein apheresis initiated in childhood or adolescence.

Methods In this cohort study, data were drawn from the HoFH International Clinical Collaboration (HICC) and the international registry for Children with Homozygous Hypercholesterolemia on Lipoprotein Apheresis (CHAIN). An overall cohort included patients diagnosed with HoFH aged 0–18 years who were alive and in follow-up between Jan 1, 2010, and Nov 8, 2021, and whose high plasma LDL cholesterol concentrations made them eligible for lipoprotein apheresis. To compare cardiovascular outcomes, patients who initiated lipoprotein apheresis in childhood (lipoprotein apheresis group) and patients who only received lipid-lowering drugs (pharmacotherapy-only group) were matched by sex and untreated plasma LDL cholesterol concentrations. The primary outcome was a composite of cardiovascular death, myocardial infarction, ischaemic stroke, percutaneous coronary intervention, coronary artery bypass grafting, aortic valve replacement, peripheral artery disease, carotid endarterectomy, angina pectoris, and supra-aortic or aortic stenosis (collectively referred to as atherosclerotic cardiovascular disease), for which survival analyses were performed in the matched cohort. Cox regression analyses were used to compare disease-free survival between cohorts and to calculate hazard ratio (HR) and 95% CI adjusted for sex, age at diagnosis, untreated plasma LDL cholesterol concentration, and number of lipid-lowering therapies other than lipoprotein apheresis.

Findings The overall cohort included 404 patients with a median age at diagnosis of 6·0 years (IQR 3·0–9·5) and median untreated plasma LDL cholesterol of 17·8 mmol/L (14·7–20·8). The matched cohorts included 250 patients (125 patients per group), with a median untreated LDL cholesterol of 17·2 mmol/L (14·8–19·7). Mean reduction in plasma LDL cholesterol concentrations between baseline and final follow-up was greater in the lipoprotein apheresis group (–55% [95% CI –60 to –51] *vs* –31% [–36 to –25]; p<0·0001). Patients in the lipoprotein apheresis group had longer atherosclerotic cardiovascular disease-free survival (adjusted HR 0·52 [95% CI 0·32–0·85]) and longer cardiovascular death-free survival (0·0301 [0·0021–0·4295]). Cardiovascular death was more common in the pharmacotherapy-only group than in the lipoprotein apheresis group (ten [8%] *vs* one [1%]; p=0·010), whereas median age at coronary artery bypass grafting was lower in the lipoprotein apheresis group than in the pharmacotherapy-only group (15·0 years [IQR 12·0–24·0] *vs* 30·5 years [19·0–33·8]; p=0·037).

Interpretation Among patients with HoFH, lipoprotein apheresis initiated during childhood and adolescence is associated with reduced long-term risk of atherosclerotic cardiovascular disease and death, and clear benefits of early initiation of high-frequency treatment on reducing plasma cholesterol were found. Consensus recommendations are now needed to guide more widespread and timely use of lipoprotein apheresis for children with HoFH, and research is required to further optimise treatment and ensure benefits of early and aggressive treatment delivery are balanced against effects on quality of life.

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See Online for appendix

Introduction

Homozygous familial hypercholesterolaemia (HoFH) is a rare life-threatening disease with an estimated worldwide prevalence of one in 300 000–400 000.[1,2] Physiologically characterised by extremely high plasma LDL cholesterol, HoFH is caused by biallelic variants in genes encoding key proteins involved in LDL catabolism (*LDLR*, *APOB*, *PCSK9*, and *LDLRAP1*). HoFH can be diagnosed using clinical criteria or by identification of biallelic pathogenic variants in these genes.[3]

Left untreated, patients with HoFH typically develop premature atherosclerosis in childhood and adolescence, which can result in supra-aortic or aortic stenosis, angina pectoris, myocardial infarction, or even death.[2] Children with HoFH have been known to show extremely rapid progression of atherosclerotic cardiovascular disease, leading to their death at as young as 4 years. Mean age at death before the availability of statins was 18 years.[4,5]

LDL cholesterol must be lowered as early and aggressively as possible to prevent premature atherosclerotic cardiovascular disease and death. The cornerstone of lipid-lowering therapy includes a cholesterol-lowering diet and pharmacological therapy with high-intensity statins and ezetimibe. Although safe, these interventions often fail to lower plasma LDL cholesterol to target concentrations.[6] Novel lipid-lowering therapies such as PCSK9 inhibitors, lomitapide, and evinacumab show promise, but insufficient efficacy (PCSK9 inhibitors), costs (particularly lomitapide and evinacumab), lack of paediatric registration for HoFH (PCSK9 inhibitors and lomitapide), and toxicity concerns (lomitapide) might preclude routine use.[7] Lipoprotein apheresis has been used in children with HoFH for decades and is regarded as crucial adjunctive treatment when plasma LDL cholesterol cannot be sufficiently reduced with lipid-lowering therapy, especially in children for whom new drug-based therapies are inaccessible.[8] Lipoprotein apheresis is an extracorporeal treatment whereby lipoproteins are selectively removed from plasma or whole blood, resulting in an acute LDL cholesterol reduction of 60–80% depending on the treatment modality and treated blood volume.[8,9] Following the acute reduction, a rapid rise in LDL cholesterol occurs, and the resulting need for regular sessions makes lipoprotein apheresis a time-consuming treatment modality associated with a reduced quality of life.[10] Importantly, lipoprotein apheresis is not widely accessible because it requires expensive and specialist technology, although it is less costly than some novel lipid-lowering drug therapies.[11,12]

Guidelines recommend lipoprotein apheresis for patients with HoFH.[3,13–15] However, evidence on its effectiveness on long-term cardiovascular endpoints is scarce, particularly for patients who begin treatment as children and adolescents.[16] We aimed to compare the treatment outcomes of patients with HoFH receiving lipoprotein apheresis from childhood to those managed with pharmacotherapy only.

Research in context

Evidence before this study

PubMed was searched on Jan 31, 2024, for articles published in English with the terms "homozygous familial hypercholesterolaemia" and "lipoprotein apheresis" (and related terms). Retrieved articles were supplemented from reference lists of relevant publications. Lipoprotein apheresis has been used since 1975 to lower plasma LDL cholesterol in patients with the most severe form of homozygous familial hypercholesterolaemia (HoFH), with the aim of reducing their risk of cardiovascular disease. Guidance for the optimal age of treatment initiation, duration, and frequency has relied on expert opinion. Several studies have indirectly shown benefit of lipoprotein apheresis in patients with HoFH, but only five studies with small sample sizes (n≤62) have evaluated cardiovascular disease-free survival in patients who initiated lipoprotein apheresis in childhood.

Added value of this study

This study leverages comprehensive patient data collated by the two largest patient registries for HoFH and contributes to our understanding of how lipoprotein apheresis initiated in childhood to reduce plasma LDL cholesterol affects long-term risk of atherosclerotic cardiovascular disease. Compared with management by pharmacotherapy only, we confirm with robust evidence that lipoprotein apheresis improves control of plasma LDL cholesterol in patients with HoFH who do not respond adequately to lipid-lowering therapy, and that initiation of lipoprotein apheresis in childhood reduces the risk of atherosclerotic cardiovascular disease and cardiovascular death.

Implications of all the available evidence

The advanced understanding of long-term cardiovascular outcomes associated with use of lipoprotein apheresis to treat children with severe HoFH will aid the development of treatment strategies and inform next steps to achieve improved cardiovascular outcomes. Further research is required to assess other aspects of lipoprotein apheresis, including cost-effectiveness and its effect on quality of life.

Methods

Study population and design

Data for this cohort study were collected from two patient registries, the HoFH International Clinical Collaboration (HICC) and the international registry for Children with Homozygous Hypercholesterolemia on Lipoprotein

Apheresis (CHAIN). The HICC registry includes patients who were either clinically or genetically diagnosed with HoFH, regardless of age and treatment modality.[2,3] CHAIN included patients with clinically or genetically confirmed HoFH who had started lipoprotein apheresis by age 19 years.[3,17] Individual contributors to this study were responsible for meeting local standards set by their respective institutional review board or ethics committee and for obtaining approvals. This study was conducted according to International Standards of Good Clinical Practice.

Study design, patient selection, and data collection have been described previously.[2,17] To capture contemporary information, only data for patients with HoFH who were alive and in clinical follow-up between Jan 1, 2010, and Nov 8, 2021, were selected. We considered patients diagnosed with HoFH aged 0–18 years who met the LDL cholesterol criterion for HoFH proposed by the European Atherosclerosis Society (untreated plasma LDL cholesterol >13 mmol/L or total plasma cholesterol >15 mmol/L, or on-treatment plasma LDL cholesterol ≥8 mmol/L or total plasma cholesterol ≥10 mmol/L, when untreated concentrations were unavailable).[3] This criterion was also used to exclude patients with mild phenotypes who would probably not be considered for lipoprotein apheresis in clinical practice. We also excluded patients for whom data on lipid-lowering therapy were not available. The resulting overall cohort was analysed for patient characteristics treatment and cardiovascular outcomes of patients with HoFH considered to be eligible for lipoprotein apheresis.

The comparison of cardiovascular outcomes among patients who received lipoprotein apheresis with those who did not is strongly subject to confounding by indication. To reduce differences between the groups and facilitate a fairer comparison, we created a matched cohort in which patients who started lipoprotein apheresis in childhood (lipoprotein apheresis group) and patients who never started lipoprotein apheresis (pharmacotherapy-only group) were matched by sex and untreated plasma LDL cholesterol (within a 1 mmol/L range). Patients who already had evidence of atherosclerotic cardiovascular disease before lipoprotein apheresis was initiated were excluded from the matched cohort.

Data collection

Age at diagnosis, age at last follow-up, sex, country of treatment, molecular diagnosis, untreated and on-treatment lipid profile, types of lipid-lowering therapy, physical signs of HoFH (xanthomas, xanthelasma, or corneal arcus) and other cardiovascular risk factors (hypertension, diabetes, smoking status, and BMI) were retrieved. Genetic data, when available, were assessed by molecular geneticists, as previously described.[2] Duration of lipoprotein apheresis was derived from the difference between age at time of lipoprotein apheresis initiation and age at the most recent follow-up or, if applicable, age at time of lipoprotein apheresis discontinuation.

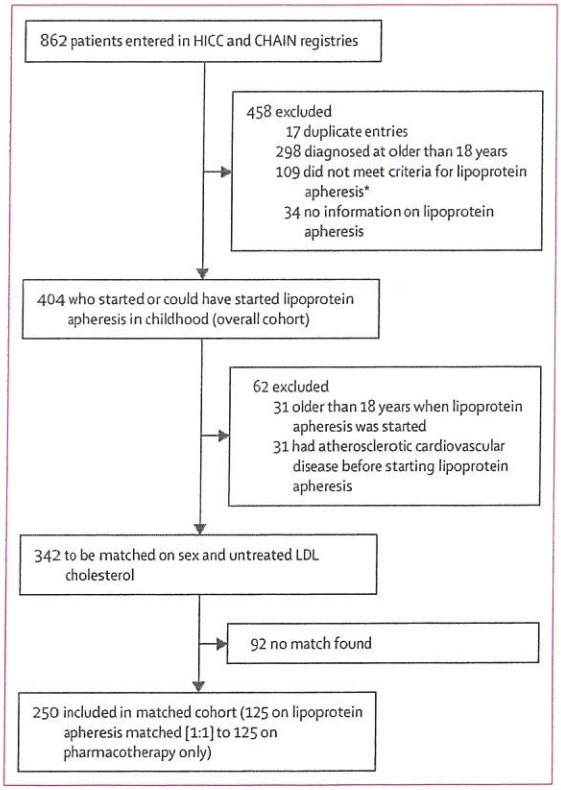

Figure 1: **Study design**
CHAIN=Children with Homozygous Hypercholesterolemia on Lipoprotein Apheresis. HICC=HoFH International Clinical Collaboration. HoFH=homozygous familial hypercholesterolaemia. *Based on lipid concentration: untreated LDL cholesterol of less than 13 mmol/L or untreated total cholesterol of less than 15 mmol/L.

The most recent plasma lipid concentrations at time of entry in the registry were used as on-treatment plasma lipid concentrations. For patients undergoing lipoprotein apheresis, lipid concentrations in blood drawn both immediately before and immediately after an apheresis session were used to estimate the mean plasma LDL cholesterol concentration, as described by Kroon and colleagues[18] and as adjusted by Thompson and colleagues.[19]

Mean LDL cholesterol=LDL cholesterol post-apheresis+ 0·65×(LDL cholesterol pre-apheresis−LDL cholesterol post-apheresis)

To compensate for missing data, we assumed that lipoprotein apheresis reduces plasma LDL cholesterol by 70%[17,20,21] and therefore that any patient for whom post-apheresis plasma LDL cholesterol had not been recorded had 30% pre-apheresis plasma LDL cholesterol. Untreated plasma lipid concentrations were derived from blood sampled at the time of diagnosis and before lipid-lowering therapy was initiated. Missing untreated plasma LDL cholesterol

	Matched cohort (n=250)	Pharmacotherapy-only group (n=125)	Lipoprotein apheresis group (n=125)	p value
Age at HoFH diagnosis, years	6·0 (3·0–9·0)	6·0 (3·0–10·0)	6·0 (2·0–9·0)	0·47
Age at last follow-up, years	16·0 (10·0–26·0)	17·0 (10·0–27·0)	15·0 (10·0–24·0)	0·33
Sex	..	..	..	>0·999
Male	114 (46%)	57 (46%)	57 (46%)	..
Female	136 (54%)	68 (54%)	68 (54%)	..
Xanthomas at diagnosis	187/221 (85%)	97/115 (84%)	90/106 (85%)	0·21
BMI, kg/m²*	21·9 (18·8–25·4)	21·5 (18·3–25·3)	22·6 (19·9–25·4)	0·38
Diabetes	1 (<1%)	1 (1%)	0	>0·999
Hypertension	20/243 (8%)	7/120 (6%)	13/123 (11%)	0·24
Chronic kidney disease	3/175 (2%)	0	3/78 (4%)	0·25
Smoking (ever)	20/198 (10%)	11/114 (10%)	9/84 (11%)	0·82
Plasma lipid, mmol/L				
Untreated				
Total cholesterol	19·0 (16·6–21·8)	19·3 (16·4–21·4)	18·6 (16·9–22·0)	0·66
LDL cholesterol	17·2 (14·8–19·7)	17·2 (14·8–19·7)	17·2 (14·7–19·4)	0·95
HDL cholesterol	0·92 (0·75–1·21)	0·91 (0·75–1·20)	0·92 (0·76–1·21)	0·69
Triglycerides	1·25 (0·90–1·75)	1·28 (0·91–1·73)	1·21 (0·87–1·70)	0·27
Most recent				
Total cholesterol†	11·2 (7·5–14·9)	13·1 (9·5–15·9)	9·1 (6·0–13·1)	0·0001
LDL cholesterol‡	9·9 (6·7–13·3)	11·4 (7·7–14·0)	9·3 (5·5–12·6)	0·0067
LDL cholesterol (Kroon)	NA	NA	7·4 (4·3–10·0)	<0·0001
LDL cholesterol goal reached§	16/230 (7%)	4/108 (4%)	12/122 (10%)	0·075
LDL receptor functionality available	162 (65%)	92 (74%)	70 (56%)	..
LDL receptor functionality	..	..	..	0·0009
Defective/defective	85/162 (52%)	60/92 (65%)	25/70 (36%)	..
Defective/null	23/162 (14%)	14/92 (15%)	9/70 (13%)	..
Null/null	51/162 (31%)	17/92 (18%)	34/70 (49%)	..
Uncertain	3/162 (2%)	1/92 (1%)	2/70 (3%)	
LDLRAP1/LDLRAP1	7 (3%)	4 (3%)	3 (2%)	>0·999
Lipid-lowering therapy				
Lipoprotein apheresis	125 (50%)	0	125 (100%)	..
Starting age apheresis, years	10·0 (7·0–13·0)	NA	10·0 (7·0–13·0)	..
Apheresis duration, years	7·0 (4·0–17·5)	NA	7·0 (4·0–17·5)	..

(Table 1 continues on next page)

concentrations were calculated as the difference between the reported total plasma cholesterol and the median difference in concentrations of total plasma cholesterol and plasma LDL cholesterol across the entire cohort (2·0 mmol/L; appendix pp 3–4).

Plasma LDL cholesterol treatment targets was considered attained if the most recent plasma LDL cholesterol concentration did not exceed 3·4 mmol/L in children, 2·6 mmol/L in adults without cardiovascular disease, and 1·8 mmol/L in adults with cardiovascular disease, which align with the treatment targets at the time of data collection.[3]

Statistical analysis

All endpoints were physician reported. The primary atherosclerotic cardiovascular disease endpoint was a composite of reported cardiovascular events and symptoms: cardiovascular death, myocardial infarction, ischaemic stroke, percutaneous coronary intervention, coronary artery bypass grafting, aortic valve replacement, peripheral artery disease, carotid endarterectomy, angina pectoris, and supra-aortic or aortic stenosis. Specifications or severity of these atherosclerotic cardiovascular disease endpoints were not collected.

Differences in continuous data between the lipoprotein apheresis group and pharmacotherapy-only group in the overall and matched cohorts were tested using independent samples *t* test or Mann–Whitney *U* test, as appropriate. Categorical data were compared using the χ^2 test or Fisher's exact test for small groups (fewer than ten individuals). The differences between untreated and on-treatment lipid results between groups were analysed using the paired *t* test.

Cumulative Kaplan–Meier curves were constructed to explore the differences in time to first atherosclerotic cardiovascular disease event and time to cardiovascular death between the lipoprotein apheresis and pharmacotherapy-only groups of the matched cohort. Follow-up time was the time between birth and year of first event (cardiovascular event or cardiovascular death) or the last follow-up, whichever happened first. Patients who underwent liver transplantation were censored at time of liver transplantation because this intervention eliminates the need for most lipid-lowering therapy. Cox regression analyses were used to compare disease-free survival between the lipoprotein apheresis and pharmacotherapy-only groups of the matched cohort, and to calculate hazard ratio (HR) with 95% CI adjusted for sex, age at diagnosis, untreated plasma LDL cholesterol concentration, and number of lipid-lowering therapies other than lipoprotein apheresis.

Multiple imputation by chained equations was used (100 iterations) to impute missing values for untreated total plasma cholesterol and LDL cholesterol, age at diagnosis, and age at the start of lipoprotein apheresis, just before matching patients.[22] This multiple imputation resulted in five datasets; the first of which was used for the analysis, and the remaining used for sensitivity analysis.

A two-sided p value of less than 0·05 was considered significant. R software (version 4.0.3) was used for all statistical analyses.

Role of the funding source

The funders had no role in the design and conduct of the study; collection, analysis, and interpretation of the data; writing of the report; and in the decision to submit the manuscript for publication.

Results

Of 862 patients in the HICC and CHAIN registries, 404 eligible patients from 37 countries (appendix p 2)

were included in the overall cohort (figure 1) with a median age at diagnosis of 6·0 years (IQR 3·0–9·5) and median untreated plasma LDL cholesterol of 17·8 mmol/L (14·7–20·8). We excluded 298 patients older than 18 years at time of diagnosis, 109 patients with mild phenotypes, 34 patients with missing data, and 17 patients who appeared in both registries.

Demographic, clinical, and genetic patient characteristics of the overall cohort are summarised in the appendix (p 3). Disease severity differed between the lipoprotein apheresis and pharmacotherapy-only groups (median untreated plasma LDL cholesterol 18·6 mmol/L [IQR 15·5–22·6] *vs* 16·6 mmol/L [13·6–19·3]; p<0·0001). Among the 240 (59%) of 404 patients who received lipoprotein apheresis, the median age at time of initiation was 11·0 years (IQR 7·0–16·0), and the median duration of lipoprotein apheresis was 15·0 years (IQR 6·0–21·0). The frequency of lipoprotein apheresis varied from twice per week to once per month, with once per week (40 [34%] of 177 patients) and once per 2 weeks (59 [50%] patients) being the most common schedules. The most common type of treatments in 87 patients with known type of lipoprotein apheresis were dextran-sulphate plasma separation or full-blood adsorption (37 [43%] patients) and double filtration plasma apheresis (20 [23%] patients). Ten (2%) patients underwent liver transplantation at a median age of 13·5 years (IQR 8·5–17·5).

Disease characteristics for the 203 (50%) patients in the overall cohort who developed atherosclerotic cardiovascular disease are summarised in the appendix (p 5). The most common diseases were aortic stenosis (148 [37%] patients), coronary artery bypass grafting (59 [15%] patients), and angina pectoris (54 [13%] patients; appendix p 5).

Demographic, clinical, and genetic characteristics and plasma lipid data for 31 patients who developed atherosclerotic cardiovascular disease before the start of lipoprotein apheresis at a median age of 12·0 years (IQR 7·5–18·0) and for 25 patients who died of cardiovascular causes at a median age of 26·0 years (17·0–38·0) are summarised in the appendix (p 6).

31 patients in the overall cohort who initiated lipoprotein apheresis after the age of 18 years, and 31 patients with atherosclerotic cardiovascular disease before starting lipoprotein apheresis were excluded from the matching cohort. 250 patients were successfully matched (125 patients in lipoprotein apheresis group; 125 patients in the pharmacotherapy-only group), with patient characteristics resembling those of the overall cohort (table 1). The median untreated plasma LDL cholesterol concentration was 17·2 mmol/L (IQR 14·8–19·7) and, given the matching design, did not differ between lipoprotein apheresis and pharmacotherapy-only groups. Lipoprotein apheresis therapy was initiated at a median age of 10·0 years (IQR 7·0–13·0). Patients with *LDLR* null/null variants were more common in the lipoprotein apheresis group than in the pharmacotherapy-only group (a complete list of genetic variants is shown in the appendix pp 7–14). Statin treatment was equally prevalent among the groups, whereas ezetimibe treatment was most prevalent in the pharmacotherapy-only group.

	Matched cohort (n=250)	Pharmacotherapy-only group (n=125)	Lipoprotein apheresis group (n=125)	p value
(Continued from previous page)				
Medication				
Statin	180/215 (84%)	106 (85%)	74/90 (82%)	0·75
Ezetimibe	145/215 (67%)	92 (74%)	53/90 (59%)	0·034
PCSK9 inhibitor	43/215 (20%)	29 (23%)	14/90 (16%)	0·23
Lomitapide	17/215 (8%)	5 (4%)	12/90 (13%)	0·13
Evinacumab	4/215 (2%)	1 (1%)	3/90 (3%)	0·62
Resins	14/215 (7%)	6 (5%)	8/90 (9%)	0·78
Fibrate	1/215 (<1%)	1 (1%)	0	>0·999

Data are median (IQR), n (%), or n/N (%). HoFH=homozygous familial hypercholesterolaemia. NA=not applicable. *BMI data were available for 94 patients in the pharmacotherapy-only group and 55 in the lipoprotein apheresis group. †Most recent total plasma cholesterol data were available for 105 patients in the pharmacotherapy-only group and 90 in the lipoprotein apheresis group. ‡Most recent plasma LDL cholesterol data were available for 108 patients in the pharmacotherapy-only group and 122 in the lipoprotein apheresis group. §Plasma LDL cholesterol treatment targets (using the Kroon equation) were defined as no more than 3·4 mmol/L for children, no more than 1·8 mmol/L or less for adults with cardiovascular disease, and no more than 2·6 mmol/L for adults without cardiovascular disease.

Table 1: **Demographic, clinical and genetic characteristics, and plasma lipid levels in the matched cohort**

Mean reduction in plasma LDL cholesterol concentrations between baseline and the most recent plasma sampling was more pronounced in the lipoprotein apheresis group of the matched cohort (figure 2). Guideline-recommended plasma LDL cholesterol targets were reached by 12 (10%) of 122 patients in the lipoprotein apheresis group and four (4%) of 108 patients in the pharmacotherapy-only group. Subanalysis by frequency of lipoprotein apheresis showed significantly lower on-treatment plasma LDL cholesterol among patients treated at least once per week than among patients treated less than once per week (appendix pp 15–16).

The matched cohort had a median age of 16·0 years (IQR 10·0–26·0) at final follow-up. Their atherosclerotic cardiovascular disease characteristics during the follow-up period are summarised in table 2. 52 (42%) of 123 patients in the lipoprotein apheresis group and 59 (49%) of 120 patients in the pharmacotherapy-only group developed atherosclerotic cardiovascular disease, with similar median age of disease onset between groups. Aortic stenosis was the most common disease in both groups. The youngest age at which aortic stenosis occurred was 2 years, and the youngest age at which myocardial infarction occurred was 4 years. Cardiovascular death was more common in the pharmacotherapy-only group, whereas median age at coronary artery bypass grafting was lower in the lipoprotein apheresis group.

When adjusting for possible confounders consisting of sex, age at diagnosis, untreated plasma LDL cholesterol concentration, and number of lipid-lowering therapies other than lipoprotein apheresis, median atherosclerotic cardiovascular disease-free survival was significantly longer in the lipoprotein apheresis group than in the

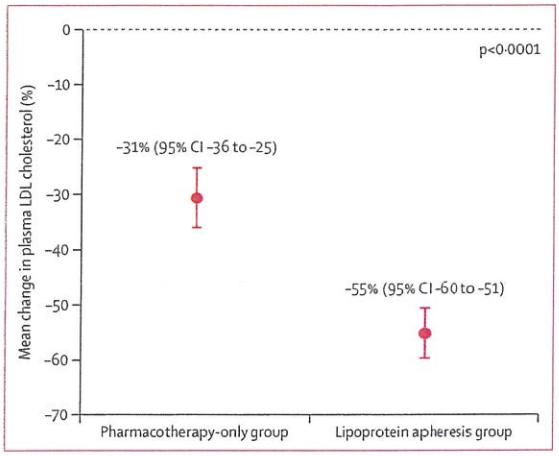

Figure 2: **Mean percentage reduction in LDL cholesterol between baseline and final follow-up**
Two patients in the pharmacotherapy-only group and four in the lipoprotein apheresis group who had undergone liver transplantation were excluded from this analysis. Error bars indicate 95% CIs.

	Pharmacotherapy-only group (n=120)	Lipoprotein apheresis group (n=123)	p value
Any atherosclerotic cardiovascular disease	59 (49%)	52 (42%)	0·45
Age at any atherosclerotic cardiovascular disease*, years	16·0 (9·0–25·0)	15·5 (12·3–27·0)	0·67
Myocardial infarction	4 (3%)	8 (7%)	0·38
Percutaneous coronary intervention	11 (9%)	8 (7%)	0·63
Coronary artery bypass grafting	14 (12%)	11 (9%)	0·40
Aortic valve replacement	7 (6%)	5 (4%)	0·77
Angina pectoris	15 (13%)	6 (5%)	0·066
Aortic stenosis	47 (39%)	38 (31%)	0·21
Peripheral artery disease	4 (3%)	7 (6%)	0·54
Stroke, carotid stent, or endarterectomy	1 (1%)	1 (1%)	>0·999
Cardiovascular death	10/125 (8%)	1/125 (1%)	0·010
Age at myocardial infarction, years	19·5 (11·8–27·3)	27·0 (24·0–29·5)	0·64
Age at percutaneous coronary intervention, years	21·0 (15·0–34·0)	25·0 (14·8–30·8)	0·84
Age at coronary artery bypass grafting, years	30·5 (19·0–33·8)	15·0 (12·0–24·0)	0·037
Age at aortic valve replacement, years	33·0 (21·5–37·0)	30·0 (27·0–31·0)	0·51
Age at angina pectoris, years	27·5 (19·0–32·8)	23·5 (13·3–30·8)	0·36
Age at aortic stenosis, years	15·0 (9·0–23·0)	15·5 (9·8–27·8)	0·51
Age of peripheral artery disease, years	19 (17–46)	18·5 (13·5–31·5)	0·57
Age at stroke, carotid stent, or endarterectomy, years	26·0†	NA	NA
Age at cardiovascular death, years	24·0 (14·0–33·8)	32·0†	0·53

Data are n (%), median (IQR), or n/N (%). NA=not applicable. *Derived from data for 57 of 59 patients in the pharmacotherapy-only group and for 30 of 52 patients in the lipoprotein apheresis group. †One event.

Table 2: **Atherosclerotic cardiovascular disease characteristics in matched cohort**

pharmacotherapy-only group (30 years [95% CI 27–not estimable] *vs* 23 years [20–32]; adjusted HR 0·52 [95% CI 0·32–0·85]; figure 3). Cardiovascular death-free survival was also longer in the lipoprotein apheresis group than in the pharmacotherapy-only group (adjusted HR 0·0301 [95% CI 0·0021–0·4295]).

Discussion

To our knowledge, this is the largest study to investigate the efficacy of lipoprotein apheresis in patients with HoFH who started lipoprotein apheresis before age 19 years and the first comparison with matched patients with HoFH who never received lipoprotein apheresis. Starting lipoprotein apheresis in childhood before onset of clinically evident atherosclerotic cardiovascular disease is associated with a significant and clinically relevant lower risk of atherosclerotic cardiovascular disease and cardiovascular death compared with treatment without lipoprotein apheresis. This provides crucial support for the recommendation that lipoprotein apheresis should be started at a young age in patients with HoFH.

We show that in real-world clinical practice, lipoprotein apheresis is not initiated in a timely manner. Most patients captured in two patient registries start this therapy modality in their second decade of life and a considerable proportion of patients only start therapy after atherosclerotic cardiovascular disease has already been established. We found that plasma LDL cholesterol reduction was greater among patients receiving lipoprotein apheresis than among matched patients who never received lipoprotein apheresis, yet fewer than 10% of the lipoprotein apheresis group achieved guideline-recommended plasma LDL cholesterol targets, which suggests under-treatment of many patients on lipoprotein apheresis.

Several small observational studies have investigated the effect of lipoprotein apheresis on atherosclerotic cardiovascular disease outcomes.[23–26] Our findings are in line with the results of one such retrospective study that compared atherosclerotic cardiovascular disease outcomes between patients from a centre in Rome, Italy, who were treated with lipoprotein apheresis from childhood with patients from a centre in Beijing, China, who were not treated with lipoprotein apheresis.[27] The investigators found a non-significant difference in the number of patients with atherosclerotic cardiovascular disease and age at first atherosclerotic cardiovascular disease event in favour of patients with HoFH treated with lipoprotein apheresis, and a significant difference in atherosclerotic cardiovascular disease-free survival (adjusted HR 6·6 [95% CI 1·08–41·0]). Such retrospective studies are important investigations of the effect of lipoprotein apheresis on atherosclerotic cardiovascular disease outcomes given that randomised controlled trials are not feasible, because of ethical reasons and the rarity of HoFH.

Despite the benefits of lipoprotein apheresis observed in our study, its potential has possibly been underestimated because lipoprotein apheresis regimens can be optimised according to patient's age at initiation and on-treatment plasma LDL cholesterol. The latter is exemplified by the lower on-treatment plasma LDL cholesterol among children undergoing lipoprotein apheresis sessions at least

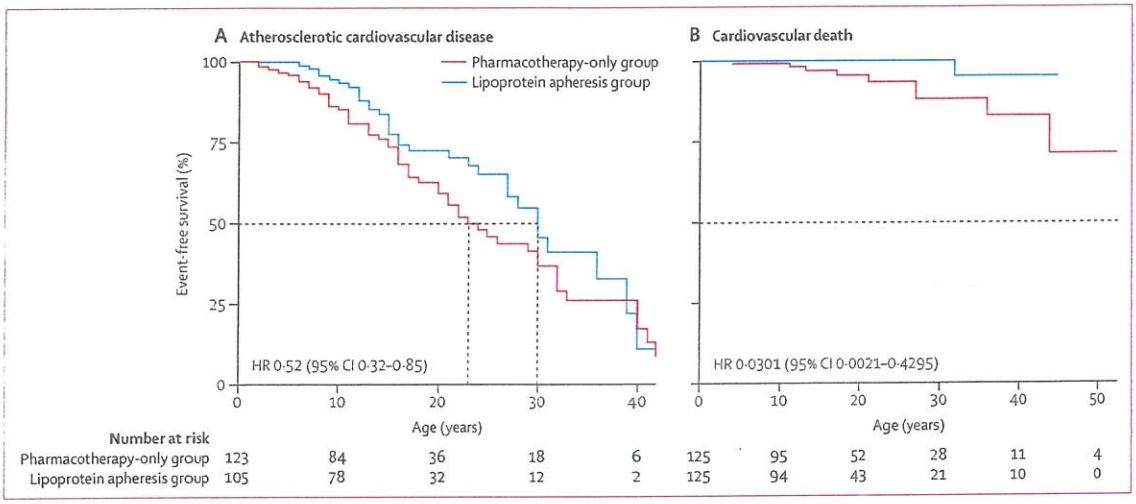

Figure 3: **Event-free survival from atherosclerotic cardiovascular disease (A) and cardiovascular death (B)**
HR=hazard ratio. The HR was adjusted for sex, age at diagnosis, untreated LDL cholesterol concentration, and number of lipid-lowering treatments other than lipid apheresis.

weekly compared with those with less frequent sessions. Further room for optimisation of standard and novel lipid-lowering therapies in both groups could help achieve treatment targets and reduce the risk of atherosclerotic cardiovascular disease.

Exposure to high plasma LDL cholesterol has a cumulative effect and is considered a causal factor for atherosclerotic cardiovascular disease, whereas lower plasma LDL cholesterol is associated with longer survival.[28,29] As such, the treatment concept for patients with HoFH is focused on reducing plasma LDL cholesterol as much and as soon as possible by starting multimodal lipid-lowering therapy at diagnosis to reduce the exposure to high plasma LDL cholesterol throughout life.

We found lipoprotein apheresis was initiated at a median age of 10 years; however, lipoprotein apheresis can be started as young as 2 years, depending on several factors, including vascular access, achieved blood flow, blood volume of the child, and the experience of the medical team.[30–32] Undoubtedly, plasma LDL cholesterol is reduced far more in patients undergoing lipoprotein apheresis than in those who are not, yet more than 90% of patients do not reach guideline-recommended treatment targets. That patients present with atherosclerotic cardiovascular disease before lipoprotein apheresis could be initiated stresses the urgency of timely HoFH diagnosis and treatment initiation.

Besides starting lipoprotein apheresis early, the regimen must be optimised for each patient. In our study, the median treated plasma LDL cholesterol concentrations were far from the recommended treatment targets, yet two-thirds of patients undergoing lipoprotein apheresis were treated at intervals of more than 1 week. We found the mean on-treatment plasma LDL cholesterol concentrations in the lipoprotein apheresis group higher than reported elsewhere.[17] This might be due to suboptimal frequency of lipoprotein apheresis sessions or to insufficient blood volumes filtered per session, which could render the treatment less effective and less likely to prevent development of atherosclerotic cardiovascular disease. Several centres have shown that plasma LDL cholesterol treatment targets can be achieved even without new lipid-lowering therapy if lipoprotein apheresis is optimally applied.[17] However, a guideline on the application of lipoprotein apheresis in children with HoFH in terms of methodology and technology, lipoprotein apheresis frequency, treated blood volume, plasma LDL cholesterol targets, and expected adverse events was published very recently and was not available during this study.[33] Data on travel distance to hospital, tolerability of sessions, or overall quality of life in patients on lipoprotein apheresis are also not available; these factors should be balanced against the expected benefits of intensifying lipoprotein apheresis.[34]

Our results fit the paradigm that reducing cumulative exposure to elevated concentrations of plasma LDL cholesterol by early and aggressive therapy improves atherosclerotic cardiovascular disease-free survival. However, our results do not support the interpretation that lipoprotein apheresis is superior to other lipid-lowering therapies; rather, they lend support for the use of lipoprotein apheresis in addition to other therapies when those therapies do not achieve the plasma LDL cholesterol target. New lipid-lowering therapies that act independently of the LDL receptor (eg, evinacumab, which inhibits angiopoietin-like 3, or the microsomal triglyceride transfer protein inhibitor lomitapide) have also shown clinically meaningful reductions in plasma LDL cholesterol and will probably have an important part in the standard treatment of patients with HoFH in the future.[7] The additional reduction of plasma LDL cholesterol with use of these drugs has allowed some patients to reduce the frequency of or even discontinue lipoprotein apheresis.[35]

Some methodological limitations of our study merit discussion. Inherent to the retrospective design is selection bias, resulting in the inclusion of patients with more severe disease in the lipoprotein apheresis group and thereby a lack of exchangeability of the treatment groups. Backed by our large sample size, we mitigated this problem by carefully matching patients from both treatment groups by untreated plasma LDL cholesterol concentrations. Importantly, despite similar untreated plasma LDL cholesterol concentrations, homozygous *LDLR*-null variants were more common among the lipoprotein apheresis group than the pharmacotherapy-only group. *LDLR*-null variants are associated with an increased risk of premature atherosclerotic cardiovascular disease and therefore might underestimate the reduction of atherosclerotic cardiovascular disease risk in the lipoprotein apheresis group. Furthermore, frequent hospital visits and potentially more intensive follow-up for patients treated with lipoprotein apheresis could induce reporting bias. The earlier detection of atherosclerotic cardiovascular disease possibly explains the lower age at coronary artery bypass grafting in the lipoprotein apheresis group, which could in turn have led to us underestimating the effect of lipoprotein apheresis on atherosclerotic cardiovascular disease events. However, the potentially earlier interventions might save these patients from a fatal myocardial infarction and, therefore, could contribute to the reduced mortality compared with the pharmacotherapy-only group.

Although we adjusted for major confounding factors, the observational nature of our study ultimately meant that the possibility of unmeasured and residual confounding cannot be fully excluded. For example, survival analyses were corrected for the overall number of lipid-lowering therapy used other than lipoprotein apheresis. Such correction might not fully capture nuances between groups at the level of individual drugs such as lomitapide and evinacumab. Furthermore, patients with an unknown year of atherosclerotic cardiovascular disease onset were excluded from the survival analysis, leading to underestimation of atherosclerotic cardiovascular disease in the study cohort. Another cause for underestimation of atherosclerotic cardiovascular disease in this cohort is that patients with the most severe phenotype of HoFH who died at a young age were not included in the registry. Finally, granularity of atherosclerotic cardiovascular disease data, such as the severity of observed aortic stenosis or whether coronary artery bypass grafting or percutaneous coronary intervention involved single-vessel or multivessel disease, was often missing.

Our study also has important strengths. Leveraging data from two global registries with the largest sample size of patients with this rare disease allowed us to carefully match patients undergoing lipoprotein apheresis with patients who did not, while retaining adequate power to investigate the effect of lipoprotein apheresis therapy. Our population includes a diverse group of patients from 37 countries with a large number of patients-years, reflecting the diversity of the real-world patient population and treatment options, thus improving generalisability and limiting the influence of unmeasured or measured confounding from a single health-care setting.

Further progress is needed in determining the effect of lipoprotein apheresis started in childhood on the development and progress of atherosclerotic cardiovascular disease in patients with HoFH. Registries can be used to follow up patients over a longer period of time. To create a complete picture of the directionality and proportionality of the effect of lipoprotein apheresis, future research should assess cost-effectiveness and the effect of lipoprotein apheresis on quality of life in paediatric patients with HoFH. Adults with HoFH receiving lipoprotein apheresis have a reduced quality of life, although this tends to be less severe among patients diagnosed earlier.[10] Topics for future research are the influence of elevated plasma lipoprotein (a) concentrations on atherosclerotic cardiovascular disease outcomes in this population, and the effect of therapies that reduce lipoprotein (a) concentrations, including lipoprotein apheresis.

Contributors

MDR drafted the article. TRT and MDR made the figures. MDR, TRT, BAH, and DMK had access to the data and verified and analysed the data. MDR, TRT, BAH, DMK, and JWG contributed to data interpretation and reviewed and editing the original draft. GKH, DJB, MC, ALC, EJD, AG, LCH, FJR, KKR, FS, and HS provided critical interpretation and revision. With all authors' approval, MDR and DMK were responsible for the decision to submit the manuscript.

Declaration of interests

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competing interests. The declaration of interests of individual collaborators are listed in the appendix (p 27).

Data sharing

Ownership of the data shared with the HICC registry remains the property of the individual contributors. Hence, the HICC Registry cannot share data with third parties without the respective contributors' approval.

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