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

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**Summary**

Background: Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disease characterised by extremely high LDL-C levels from birth onwards, causing atherosclerotic cardiovascular disease (ASCVD) at a young age. Lipoprotein apheresis (LA) is often required in addition to lipid-lowering drugs to lower LDL-C levels sufficiently, but is only available in specialised centres. We compare cardiovascular outcomes of HoFH patients who received LA from childhood with those who did not.

Methods: We combined data from two HoFH registries and identified 404 patients diagnosed before the age of 19 eligible for LA based on LDL-C levels. Matching 125 patients treated with LA (LA+ group) with 125 patients not treated with LA (LA- group) by sex and untreated LDL-C levels. The primary outcome was ASCVD for which survival analyses were performed.

Results: In the overall cohort (n=404), median (IQR) age at diagnosis was 6·0 (3·0-9·5) years and median untreated LDL-C level was 17·8 (14·7-20·8) mmol/L. When comparing the matched groups, (median follow-up time 16·0 [10·0-26·0] years), mean (SD) on-treatment LDL-C levels were lower in the LA+ group compared with the LA- group (7·2±3·4 versus 11·3±4·4 mmol/L, p<0·001) despite similar (matched) untreated LDL-C levels. Cardiovascular death was more common in the LA- group compared to the LA+ group (10 [8·0%] versus 1 [0·8%], p=0·013), while age at coronary artery bypass grafting was younger in the LA+ group (15·0 [12·0-24·0] versus 30·5 [19·0-33·8] years, p=0·037). Survival analysis demonstrated longer ASCVD-free survival for patients on LA (adjusted HR 0·52 [95% CI 0·32-0·85]), as well as longer survival from cardiovascular death (adjusted HR 0·03 [95% CI 0·002-0·4295].

Interpretation: This first large study evaluating the efficacy of LA in HoFH demonstrates that LA is associated with a reduced risk of ASCVD and death in patients with HoFH. In children with HoFH LA should be started as early as possible without delay.

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**Keywords:** Homozygous familial hypercholesterolaemia; lipoprotein apheresis; atherosclerotic cardiovascular disease; aortic valve stenosis

## Research in context

### Evidence before this study

Articles were identified through PubMed using search terms (related to) “homozygous familial hypercholesterolaemia” and “lipoprotein apheresis”. Searches were supplemented by checking reference lists of relevant publications. Articles published in English up to and including January 2024 were included.

In the most severe cases of homozygous familial hypercholesterolemia (HoFH), patients have minimal or no residual low-density lipoprotein receptor (LDLR) activity and therefore either require removal of circulating LDL-C via methods independent of the LDLR or inhibition of LDL production. Lipoprotein apheresis (LA), which involves extracorporeal removal of lipoproteins and thereby works independently of the LDLR, has been used for decades to lower LDL-C in patients with HoFH, with the aim of preventing cardiovascular disease. However, given the rarity of the condition and paucity of evidence, guidance for the optimal age of its initiation, as well as duration and interval between sessions, has relied on expert opinion. Although some lipid-lowering therapies that act independently of the LDLR (lomitapide and evinacumab) show great promise as add-on therapies to lower LDL-C levels to guideline recommended targets, these are not registered (yet) for use in children of all ages and are not available or affordable in many countries. Several studies have indirectly shown benefit of LA in HoFH, but only a limited number of studies with a small sample size evaluated cardiovascular disease-free survival in patients undergoing LA initiated in childhood.

### Added value of this study

We leveraged the largest databases of HoFH patients available worldwide, to investigate the effects of initiating LA in childhood on atherosclerotic cardiovascular disease (ASCVD), in order to better guide clinical decision-making concerning initiation of LA. We show that LDL-C levels were significantly lower in patients treated with LA from childhood compared with those who were never treated with LA, though they frequently remained above guideline-recommended LDL-C targets. Using matched groups and adjusting for potential confounders, we show that ASCVD-free survival is longer in patients treated with LA compared to patients not receiving this therapy, even though LA was not always optimally applied.

### Implications

Our findings show that LA improves control of LDL-C levels, and its initiation in childhood reduces the risk for ASCVD and cardiovascular death in HoFH patients who do not respond adequately to lipid-lowering therapy. This provides the robust evidence to date for current recommendations to start LA therapy in patients with HoFH at a young age, particularly if existing lipid-lowering drug therapies fail to lower LDL-C levels adequately.

## Introduction

Homozygous familial hypercholesterolemia (HoFH) is a rare, life-threatening disease with an estimated worldwide prevalence of one in 300 000 - 400 000.[1, 2] It is characterised by extremely high low-density lipoprotein cholesterol (LDL-C) levels, and is caused by bi-allelic variants in genes encoding key proteins involved in LDL catabolism (LDLR, APOB, PCSK9 and LDLRAP1). The diagnosis of HoFH can be suspected clinically and confirmed based on identification of bi-allelic pathogenic variants in these genes.[3]

If left untreated, patients with HoFH typically develop premature atherosclerosis in childhood and adolescence, which can result in (supra)aortic stenosis, angina pectoris, myocardial infarction or even death.[2] Studies show that some children with HoFH experience extremely rapid progression of atherosclerotic cardiovascular disease (ASCVD) leading to death in children as young as four years old. Mean age of death prior to the availability of statins, was 18 years.[4, 5]

To prevent premature ASCVD and death, it is crucial to lower LDL-C levels as early and aggressively as possible. The cornerstone of lipid-lowering treatment (LLT) includes a cholesterol-lowering diet and pharmacological therapy consisting of high-intensity statins and ezetimibe. Although safe, these interventions often fail to lower LDL-C to target levels.[6] Novel lipid-lowering therapies such as PCSK9 inhibitors (PCSK9-i), lomitapide and evinacumab are additional therapeutic options, but multiple factors including lack of efficacy in HoFH (PCSK9-i), costs (particularly lomitapide, and evinacumab), lack of paediatric registration for HoFH (PCSK9-i, lomitapide) and toxicity concerns (lomitapide) may preclude routine use.[7] Therefore, lipoprotein apheresis (LA), which has been used in children with HoFH for decades, is regarded as a critical adjunctive treatment when LDL-C levels cannot be sufficiently reduced with available LLT, especially in children for whom novel LLTs may not be available or approved.[8] With this extracorporeal treatment, lipoproteins are selectively removed from plasma or whole blood, resulting in an acute LDL-C reduction of 60-80% depending on the treatment modality and treated blood volume.[8, 9] Following the acute reduction, a rapid LDL-C rise occurs and therefore, regular LA sessions are required, making it a time-consuming treatment that has been associated with reduced quality of life.[10] LA is not available for all HoFH patients since it is only performed in specialized centers and costs are high, although less costly than some novel LLTs.[11, 12]

Based on the substantial LDL-C reduction, guidelines recommend LA for patients with HoFH[3, 13-15], however strong evidence on the effectiveness on cardiovascular endpoints is lacking, particularly in children and adolescents.[16] The aim of this study is to evaluate and compare the treatment outcomes of patients with HoFH receiving LA from childhood to those managed with pharmacotherapy only. Our hypothesis is that LA therapy results in a more marked reduction in plasma LDL-C levels and, consequently, in risk of ASCVD.

## Methods

Study population and design

The data for this cohort study was collected from two registries: HICC (HoFH, the International Clinical Collaborators; NCT04815005) and CHAIN (Children with Homozygous hypercholesterolemia on lipoprotein Apheresis: an INternational registry). Information concerning study design, patient selection and data collection is available in previous publications.[2, 17] To reflect contemporary rather than historic information, only data of patients with HoFH who were alive and being followed up in, or after 2010, were used. Individual contributors were responsible for meeting local standards set by their institutional review board or ethics committee and obtaining required approvals. The study was conducted according to International Standards of Good Clinical Practice.

In brief, the HICC registry included patients who were either clinically or genetically diagnosed with HoFH, regardless of age and treatment modality.[2, 3] CHAIN specifically included patients with clinically or genetically confirmed HoFH who had started LA therapy before the age of 19 years.[3, 17]

Cohort definition

For the present study, we considered patients who were diagnosed with HoFH up to the age of 18 years and met the cholesterol criteria proposed for HoFH by the European Atherosclerosis Society consensus statement (untreated LDL-C or total cholesterol levels >13 and >15 mmol/L, respectively, or on-treatment levels ≥8 or ≥10 mmol/L, respectively, when untreated levels were unavailable).[3] This criterion was used to exclude patients with 'milder' phenotypes who would likely not be considered for LA in clinical practice. We excluded patients for whom no data on LLT was available. This yielded 'the overall cohort' (figure 1). This cohort was used to describe the patient characteristics and real-word data on treatment and cardiovascular outcomes of HoFH patients who could be considered eligible for LA therapy.

Comparing cardiovascular outcomes of patients who started LA therapy with those who did not, is strongly subject to confounding by indication. To reduce differences between the groups and allow for a fairer comparison between groups, patients who started LA therapy in childhood (LA+ group; n=125) were matched with patients who never started LA therapy (LA- group; n=125) based on sex and untreated LDL-C levels (within a 1 mmol/L range), 'the matched cohort'). Patients who already had evidence of ASCVD before starting LA were excluded from this matching (figure 1).

Data collection

Data on age at diagnosis, age at last follow-up, sex, country, molecular diagnosis, untreated an on-treatment lipid profile, LLT, physical signs of HoFH (xanthomas, xanthelasma, corneal arcus) and other cardiovascular risk factors (hypertension, diabetes mellitus, smoking status, body mass index) were retrieved. Genetic data, when available, was assessed by molecular genetics experts as previously described.[2] Duration of LA therapy was defined as the difference between age at which LA therapy was started and age of latest follow-up or, if applicable, age at which LA therapy was discontinued.

Lipid levels

The most recent lipid levels at time of entry in the registry were used as on-treatment lipid levels. For patients undergoing LA therapy, we used lipid levels obtained from blood drawn both immediately before as well as immediately after an apheresis session. Using both these values, we estimated the mean LDL-C levels with the formula of Kroon et al.[18] as adjusted by Thompson et al.[19] as follows:

**Mean LDL-C = LDL-C post-apheresis + 0.65 × (LDL-C pre-apheresis – LDL-C post-apheresis)**

Missing post-apheresis LDL-C levels were estimated to be 0.3 * LDL-C pre-apheresis, reflecting an estimated 70% LDL-C reduction with the apheresis session.[17, 20, 21] Untreated lipid levels were defined as values obtained in the absence of LLT at the time of HoFH diagnosis. Missing untreated LDL-C levels were estimated by subtracting 2.0 mmol/L from the reported total cholesterol value, reflecting the median difference between total cholesterol and LDL-C in the entire cohort (supplementary table 2).

Attainment of the LDL-C treatment targets was defined as most recent LDL-levels ≤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 according to the used treatment targets at time of data collection.[3]

### Cardiovascular disease

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

### Statistical analysis

Differences in continuous data between the LA+ and LA- groups in the overall and matched cohort were tested using independent samples t-test or Mann-Whitney U test, as appropriate. Categorical data were compared using the Chi-square test or Fisher's exact test for small groups (<10). The differences between untreated and on-treatment lipid results between groups were analysed using the paired t-test.

In the matched cohort, cumulative Kaplan-Meier curves were constructed to explore the differences in time to first ASCVD event and time to cardiovascular death between patients that received LA since childhood and those who never received LA. Follow-up was defined as the time between birth and year of the first cardiovascular event/death or the last follow-up, whichever came first. Patients who underwent liver transplantation (n=10) were censored at time of liver transplantation because this intervention eliminates the need for most LLT, making the patient no longer comparable with either subgroup. In the matched cohort, Cox regression analyses were used to compare disease-free survival between patients who started LA and those who did not, and to calculate hazard ratios with 95% confidence intervals (CIs) adjusted for sex, age at diagnosis, untreated LDL-C level and number of LLTs other than LA.

Multiple imputation by chained equations was used (100 iterations) to impute missing values for untreated total cholesterol and LDL-C, age at diagnosis and age at the start of LA, just prior to matching patients.[22] This multiple imputation resulted in five datasets. The first dataset was used for the analysis. As a sensitivity analysis we performed the analysis in the four other datasets which showed similar results.

A two-sided p-value <0·05 was considered statistically significant. Statistical analyses were performed using R, version 4.0.3.

### 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

### Selection of the study population

Figure 1 shows the patient selection. Of 862 patients included in the HICC and CHAIN registry, we identified 404 eligible patients from 37 countries that comprised our 'overall cohort' (supplementary table 1 and figure 1). These patients were diagnosed with HoFH in childhood and met the criteria to start LA. Patients diagnosed after the age of 18 years old (n=298), with milder phenotypes and

therefore not meeting criteria to start LA (n=109), or with missing data regarding receiving LA (n=34) were excluded. If patients were included in both registries, one of the data entries was excluded (n=17). From the overall cohort, 31 patients started LA after the age of 18 years old and 31 patients had clinically evident ASCVD prior to starting LA and all were excluded from matching (supplementary table 4). Of the remaining 342 patients, 250 patients were successfully matched, consisting of 125 patients in the LA+ group and 125 patients in the LA- group (figure 1).

Description of the overall cohort

Patient characteristics of the overall cohort can be found in supplementary table 2. Comparison in the overall cohort highlights significant differences in disease severity between patients receiving LA therapy versus those who did not, as reflected by their untreated LDL-C levels (18·6 [15·5-22·6] versus 16·6 [13·6-19·3] mmol/L respectively, p<0·001). Overall, 240 (59·4%) patients were treated with LA therapy which was initiated at a median age of 11·0 (7·0-16·0) years. The median duration of LA therapy was 15·0 (6·0-21·0) years. The frequency of LA varied between twice a week to once a month, with once per week (n=40 [34·2%]) and once every two weeks (n=59 [50·4%]) being the most common regimens. Of 82 patients for whom details on type of LA were known, 37 (42·5%) were treated by dextran-sulphate plasma separation or full blood adsorption (Kaneka) and 20 (23·0%) by double filtration plasma apheresis, as most common treatment modalities. Ten (2·5%) patients underwent liver transplantation at a median age of 13·5 (8·5-17·5) years, after which point data from these patients were no longer used in analyses. ASCVD outcomes of the overall cohort are summarized in supplementary table 3. ASCVD was present in 203 (51·9%) patients, with aortic stenosis (37·9%), coronary artery bypass grafting (CABG) (15·1%) and angina pectoris (13·8%) being the most prevalent.

In supplementary table 4, data from two subgroups are of special interest. The first group comprised of 31 patients who had developed ASCVD (at a median age of 12·0 (7·5-18·0) years) already before starting LA. The second group consisted of 25 patients who died of cardiovascular causes at a median age of 26·0 (17·0-38·0) years of which 9 (36%) had started LA therapy at a median age of 13·0 (11·0-14·0) years.

Description of the matched cohort

Patient characteristics of the matched cohort resemble the overall cohort from which it was derived. Characteristics of the 125 patients who started LA therapy in childhood and the 125 patients who never received LA therapy, are described in table 1. Of this cohort, 45·6% were male and the median age at diagnosis was 6·0 (3·0-9·0) years. Untreated LDL-C levels were 17·2 (14·8-19·7) mmol/L. As per matching design, these variables did not differ between the LA+ and LA- group. Patients treated with LA therapy started at a median age of 10·0 (7·0-13·0) years and continued with this therapy for a median of 7·0 (4·0-17·5) years. Regarding LDLR functionality, for those whom genetic testing was conducted, a greater proportion carried LDLR null/null variants in the LA+ than in LA- group (34 [48·6%] vs 17 [18·5%], respectively, p<0·001). All genetic variants are listed in supplementary table 5. A similar number of patients were taking statins, whereas more LA- patients were receiving ezetimibe than LA+ patients (92 [73·6%] vs 53 [58·9%], respectively, p=0·034). Although not statistically significant, more LA+ patients were receiving lomitapide and evinacumab than LA- patients (12 [13·3%] vs 5 [4·0%] and 3 [3·3%] vs 1 [0·8%], respectively.

LDL-C reduction – matched cohort

The mean reduction between baseline LDL-C and the most recent LDL-C level is shown in figure 2. Mean LDL-C was significantly more reduced in LA+ patients (55·2% ± 26·3% [17·2±3·9 to 7·2±3·4

mmol/L]) compared to LA- patients (30·8% ± 31·2% [17·1±3·7 to 11·3±4·4 mmol/L], p<0·001). Overall, 16 patients (7·0%) reached guideline-recommended LDL-C targets. Sub-analysis by frequency of LA shows significantly lower on-treatment LDL-C levels in patients (n=46) treated weekly or more often of 5·5 mmol/L compared to 9·9 mmol/L in patients (n=71) treated less than once a week (p<0·001) (supplementary table 6).

Cardiovascular disease and association with lipoprotein apheresis – matched cohort

Table 2 describes ASCVD observed in the matched cohorts during the follow-up period (median age at follow-up: 16·0 years [10·0-26·0]). Across the matched groups, 52 (42·3%) of the LA+ and 59 (49·2%) of the LA- patients developed ASCVD, with aortic stenosis being the most common (30·9 and 39·2%, respectively). The median age of ASCVD onset was 16·0 (11·0-24·0) years and did not differ between both groups. Cardiovascular death was significantly more present in the LA- group compared to the LA+ group (10 [8·0%] versus 1 [0·8%], p=0·013), while age at CABG was younger in the LA+ versus the LA- group (15·0 [12·0-24·0] versus 30·5 [19·0-33·8] years respectively, p=0·037). The prevalence of other ASCVD and age of onset were comparable between the LA+ and LA- groups. The youngest age at which aortic stenosis and myocardial infarction occurred was two and four years respectively.

When adjusting for possible confounders consisting of sex, age at diagnosis, untreated LDL-C level and number of LLTs other than LA, median ASCVD-free survival-time was significantly longer in the LA+ group compared to the LA- group (30 years [95% CI 27-NA] versus 23 years [95% CI 20-32], respectively, with an adjusted hazard ratio of 0·52 [95% CI 0·32-0·85]) (figure 3). In addition, a significant longer cardiovascular death free survival was found in the LA+ group compared to the LA- group (adjusted hazard ratio 0.03 [95% CI 0·002-0·4295]).

## Discussion

This is the largest study to investigate the efficacy of LA in patients with HoFH, started before the age of 19 years, compared to matched HoFH patients who never received LA. Starting LA therapy in childhood before onset of clinically evident ASCVD is associated with a significant and clinically relevant lower risk of ASCVD and cardiovascular death compared to treatment without LA. This provides critical support for the recommendation that LA should be started at a young age in patients with HoFH. We show that in real-world clinical practice, LA therapy is not initiated timely enough, with most patients starting this therapy in the second decade of life and, in a considerable proportion, only after ASCVD has already been established. We found that patients on LA therapy achieved greater LDL-C reductions compared with matched patients who never received LA therapy, yet fewer than 10% of the patients reached guideline-recommended LDL-C levels which suggests unnecessary undertreatment of many patients on LA.

Several smaller observational studies have investigated the effect of LA on ASCVD outcomes.23-26 One smaller retrospective study compared ASCVD outcomes in patients treated with LA to the ASCVD outcomes in patients treated without LA in a similar way.[27] The results of this study, comparing HoFH patients from a center in Rome treated with LA from childhood to patients from a center in Beijing not treated with LA, are in line with the results of our study.[27] The study showed a non-significant difference in the number of patients experiencing ASCVD and age at first ASCVD event in favour of HoFH patients treated with LA, and a significant difference in ASCVD-free survival (adjusted hazard ratio of 6·6 [95% CI 1·08–41·0]). Retrospective studies like these are important to investigate the effect of LA on ASCVD outcomes given the impossibility to perform randomized controlled trials, both for ethical reasons and because of the limited number of patients with this rare disease.

Moreover, it is possible that the benefits of LA observed in our study underestimate its true potential, because there appears room for optimisation of LA treatment regimens both with regard to age of initiation and to on-treatment LDL-C levels. The latter is exemplified by the lower on-treatment LDL-C levels in children undergoing LA sessions at least weekly, compared with those with longer intervals between sessions. There is also room for optimisation of standard and novel LLT therapies in both groups in order to better achieve treatment targets and reduce rates of ASCVD. Exposure to high LDL-C levels has been shown to have a cumulative effect and to be a causal factor for ASCVD, and lower LDL-C levels are associated with longer survival.[28, 29] As such, the treatment concept for patients with HoFH is focussed on reducing LDL-C levels as much and as soon as possible by starting multimodal LLT at diagnosis to reduce the exposure to high LDL-C levels throughout life. The median start age of LA was 10 years, while LA can already be started in children as young as two years old, dependent on several factors including vascular access, achieved blood flow, blood volume of the child and the experience of the medical team.[30-32] Undoubtedly, LDL-C levels are reduced far more in patients on LA compared to those who are not, yet more than 90% of the patients fail to reach guideline-recommended treatment targets. The patients who presented with ASCVD before LA could be started exemplify the urgency of timely HoFH diagnosis and initiation of treatment. Besides starting LA early, it is important that the LA regimen is optimized for each patient. In our cohort, the median treated LDL-C levels were far from the recommended treatment targets, yet two thirds of patients were treated with intervals of more than one week between LA sessions. The mean on-treatment LDL-C levels in the LA+ group were also higher compared with other reports.[17] This might be due to either suboptimal frequency of LA sessions or to insufficient blood volumes filtered per session, which could render the treatment less effective and less likely to prevent development of ASCVD. Several centers have shown that LDL-C treatment targets can be achieved even without new LLT, if LA is optimally applied.[17] However, guidelines on performing LA in children with HoFH, giving guidance in which methods to use, LA frequency, treated blood volume, LDL-C targets, adverse events, etcetera, are still lacking. That said, data on travel distance to hospital, tolerability of sessions or overall quality of life among patients on LA were unavailable; factors that should be balanced against the expected benefits of intensifying LA therapy.[33]

Our results fit the paradigm that reducing cumulative exposure to elevated levels of LDL-C, by lowering it early and aggressively, improves ASCVD-free survival. However, our results should not be misinterpreted as LA therapy being preferred over other LLTs, but rather to justify the use of LA in addition to other therapies when these therapies do not achieve the LDL-C target. New LLTs that act independently of the LDLR, such as evinacumab, which inhibits Angiopoietin-like 3, or the microsomal triglyceride transfer protein inhibitor lomitapide, have shown clinically meaningful additional LDL-C reductions and will likely play an important role in the standard treatment of HoFH patients in the future.[7] It has been shown that the use of added LDL-C lowering of these drugs allowed some patients to reduce the frequency of LA or even to discontinue this therapy.[34]

Strengths and limitations

Some methodological aspects of our study merit discussion. Inherent to the retrospective design is selection bias, resulting in the inclusion of more severe patients in the LA+ 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 on untreated LDL-C levels. Despite similar untreated LDL-C levels as a result of this matching, the LA+ group had a larger proportion of patients with homozygous LDLR-null variants as compared to the LA- group, which increases the risk of premature ASCVD and therefore may underestimate the reduction of ASCVD risk in the LA+ group. Furthermore, frequent hospital visits and potentially more intensive follow-up for

patients treated with LA could induce reporting bias. This may lead to earlier detection of ASCVD, possibly explaining the lower age at CABG in the LA+ group and may result in an underestimation of the effect of LA on ASCVD events. However, the potentially earlier interventions might save these patients from fatal MI and therefore, could contribute to the reduced mortality compared to the LA- group. Although we adjusted for major confounding factors, due to the observational nature of our study we cannot exclude the possibility of unmeasured and residual confounding. For example, survival analyses were corrected for the overall number of LLT used other than LA, but this may not fully capture nuances between groups at the level of individual drugs such as lomitapide and evinacumab, which were used more frequently in the LA+ group, although rarely used and therefore not significantly different. Furthermore, patients with an unknown year of ASCVD onset were excluded from the survival analysis, leading to an underestimation of ASCVD in the study cohort. Another cause for underestimation of ASCVD in this cohort is that HoFH patients with the most severe phenotype, who died at a young age, were not included in the registry, because only patients with data available in 2010 or later were eligible for inclusion. Lastly, granularity of ASCVD data, such as the severity of observed aortic stenosis or whether coronary artery bypass grafting or percutaneous coronary intervention involved single- or multivessel disease, was often missing.

Our study also has important strengths. Leveraging data from two global registries with the largest sample size of data on patients with this rare disease, allowed us to carefully match patients undergoing LA with patients who did not, while retaining adequate power to investigate the effect of LA therapy. Our population comprises a diverse group of patients from 37 countries with a large number of patients-years, reflecting the diversity of the patient population and treatment options, improving generalizability of our results and limiting the possibility that findings were influenced by (un)measured confounding from a single healthcare setting.

There is room for further progress in determining the effect of LA started in childhood on the development and progress of ASCVD in HoFH patients. Registries can be used to perform a follow-up over a longer period of time including subclinical and clinical ASCVD. To create a complete picture of the directionality and proportionality of the effect of LA, future research should be performed to assess cost-effectiveness and the effect of LA on quality of life in patients with HoFH. In adults with HoFH receiving LA, quality of life shows to be reduced. Although, quality of life is less reduced in patients diagnosed earlier.[10] Studies specifically on quality of life in children with HoFH (receiving LA) have not been performed yet. Another topic for future research is the influence of elevated lipoprotein(a) levels on ASCVD outcomes in this cohort, and potentially the relation with some LLT, including LA, which reduce lipoprotein(a) levels.

In conclusion, using the largest cohort of patients with HoFH eligible for LA to date, we demonstrated that LA is associated with greater LDL-C reductions and, more importantly, a reduction in the risk of ASCVD and cardiovascular death in patients with HoFH. However, this study also shows that most HoFH patients do not meet the LDL-C treatment targets despite initiating LLT and LA at a young age, and individuals continue to manifest early onset ASCVD in childhood. This emphasizes there is still room for improvement in developing strategies in order to optimise access and availability of intensive combination LLT, including LA from diagnosis onwards, to reduce the LDL-C burden and protect children with HoFH from premature ASCVD and death.

## Declaration of interests

BAH received a research grant of Silence Therapeutics. GKH reports research grants from the Klinkerpad fonds, and part-time employment at Novo Nordisk A/S, Denmark since April 2019. GKH is shareholder of Novo Nordisk. DJB reports clinical trial fees paid to the institution from LIB Therapeutics, Novartis, Silence Therapeutics and IONIS. Speaker fees from Amgen, Sanofi, Organon, MSD, Amryt and Novartis. Consulting fees from Amryt. ALC has received research grants/support from Amarin, Amgen, Menarini, Mylan, Sanofi, and Sanofi Regeneron, and has served as a consultant for or received honoraria from Akcea, Amarin, Amgen, Daiichi Sankyo, Esperion Therapeutics, Inc., Ionis, Kowa, Medco, Menarini, MSD, Mylan, Novartis, Recordati, Regeneron, Sanofi, and The Corpus. MC reports institutional support for the conduction of clinical trials from Regeneron Pharmaceuticals, and Regenxbio; consulting fees from Amryt Pharma. AG received grants and personal fees from Amgen, Sanofi and Regeneron, Mylan Viatris, MSD, Akcea Therapeutics, Amryt, Servier, Novartis and Ultragenyx. FJR reports receiving advisory board fees and lecture fees from Amgen, Sanofi-Aventis, Regeneron Pharmaceuticals, Novartis, and LIB Therapeutics. KKR grants from Amgen, Sanofi–Regeneron, Pfizer, Merck Sharp & Dohme, and Daiichi Sankyo, Ultragenyx, Consulting fees AstraZeneca, Kowa, Novartis, Sanofi, Amgen, Eli Lilly, Algorithm, Boehringer Ingelheim, Novo Nordisk, Silence Therapeutics, Bayer, Esperion, Daiichi Sankyo, Abbott, New Amsterdam, SCRIBE, CRISPR, VAXXINITY, EMENDOBIO, Cargene, Viatris, Amarin, Nodthera and Resverlogix, honoraria for lectures AstraZeneca, Novartis, Sanofi, Amgen, Algorithm, Boehringer Ingelheim, Novo Nordisk, Esperion, Daiichi Sankyo, Amarin, Stock options New Amsterdam, PEMI 31 and SCRIBE. HS reports research grants from Amgen, MSD, Synageva, Amryt, Alexion and Akcea; consulting fees from Amgen, Alexion, Daiichi-Sankyo, Novartis, Pfizer, Akcea; speaker fees from Amgen, Daiichi-Sankyo, Sanofi and Akcea. AW reports research grants from Amgen, Esperion, Novartis, Regeneron, Sanofi, Silence Therapeutics, and Ultragenyx; consulting fees from Amryt, and Novartis; speaker fees from Algorithm, Sanofi, and Ultragenyx. MDR, TRT, EJD, LCH, FS, JWG and DMK have nothing to disclose. The declaration of interests of individual collaborators are listed in the appendix.

## Author's contributions

MDR drafted the article. TRT and MDR made the figures. MDR, TRT, BAH and DMK had access to the data, verified the data and performed data analysis. Together with AW and JWG, they worked on data interpretation, reviewing and editing of the original draft. GKH, DJB, MC, ALC, EJD, AG, LCH, FJR, KKR, FS and HS provided critical interpretation and revision of the article. All authors gave approval for submitting the final version. MDR and DMK were responsible for the decision to submit the manuscript.

## Data sharing agreement

Data ownership for 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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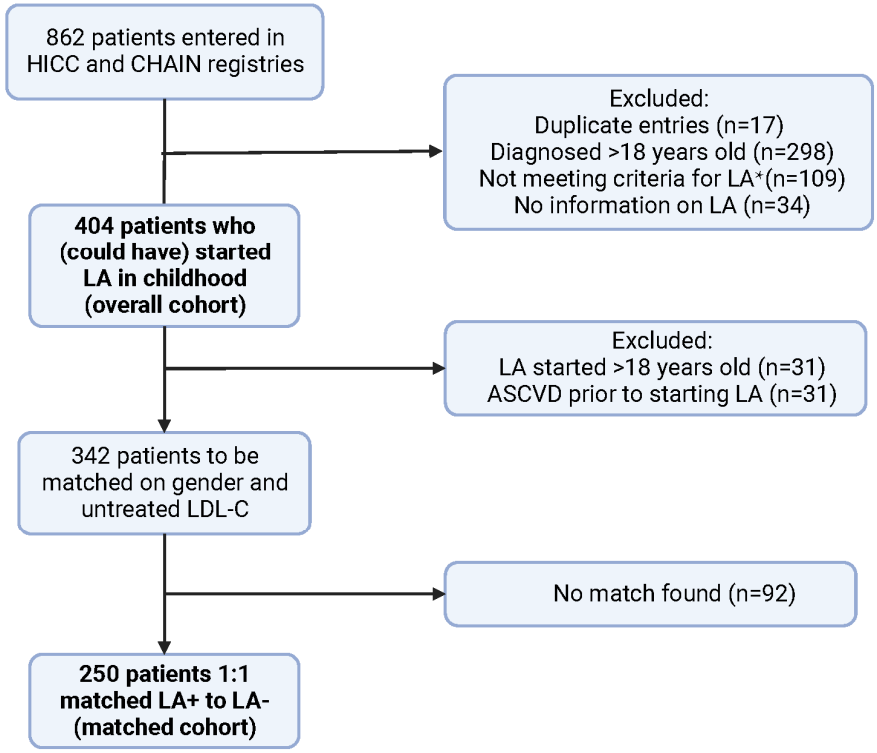
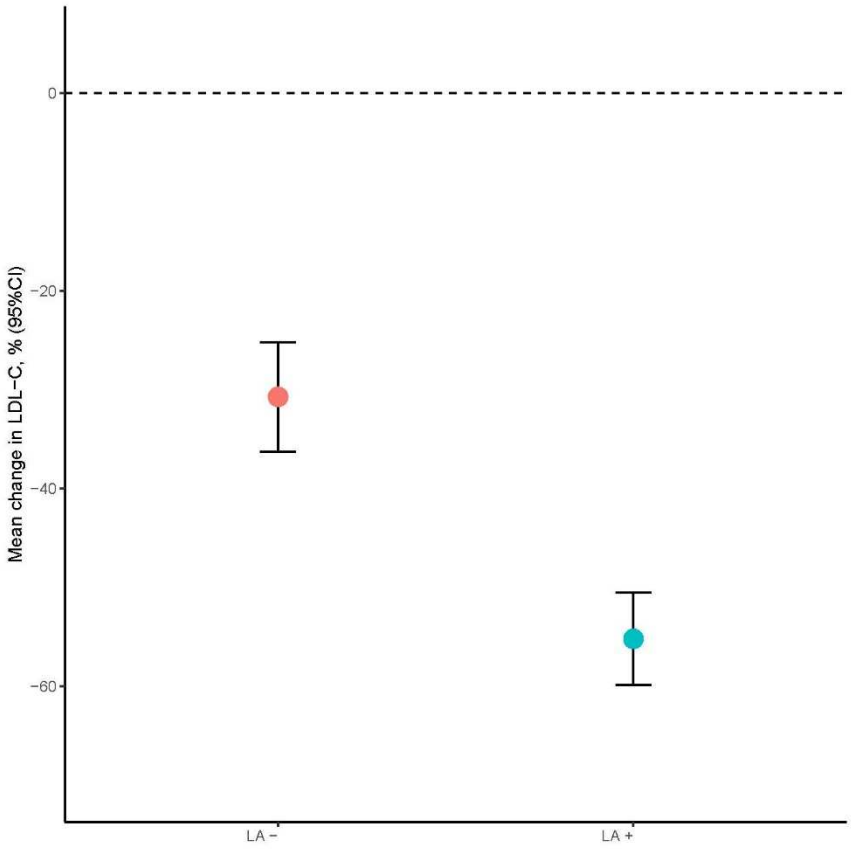
**Figure 1 – Flowchart of selection of the study population**




*Based on lipid levels: untreated LDL-C <13 mmol/L or untreated TC <15 mmol/L (see methods section)

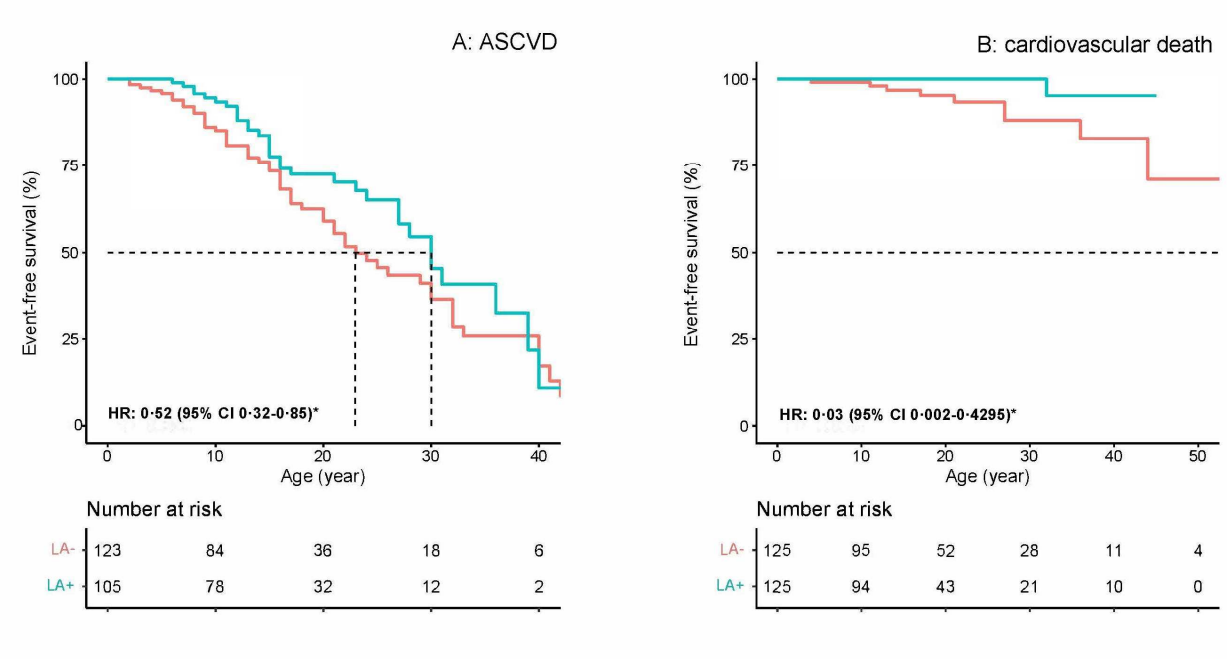
ASCVD, atherosclerotic cardiovascular disease; CHAIN, Children with Homozygous hypercholesterolemia on lipoprotein Apheresis: an INternational registry; HICC, HoFH, the International Clinical Collaborators; LA, lipoprotein apheresis; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy.

**Figure 2 – Mean percentage LDL-C reduction between baseline LDL-C levels and most recent LDL-C levels**




The mean (±95%CI) percentage LDL-C reduction was larger in patients in the LA+, using the Kroon equation, compared with the LA- group (-55·2, 95%CI -36 to -25 versus -30·8, 95%CI -60 to -51, *p<0·001). Six patients who had undergone liver transplantation were excluded from this analysis.

**Figure 3 – Event-free survival from ASCVD and cardiovascular death**




1A: Median survival-time was 23 [95% CI 20-32] years in the LA- group versus 30 [95% CI 27-NA] years in the LA+ group. *Hazard ratio was adjusted for sex, age at diagnosis, untreated LDL-C level and number of LLTs other than LA.

ASCVD, atherosclerotic cardiovascular disease; HR, hazard ratio; LA, lipoprotein apheresis.

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

| | **Overall** | **LA-** | **LA+** | |
|---|---|---|---|---|
| | N = 250 | N = 125 | N = 125 | **p-value** |
| Age of FH diagnosis (years) | 6·0 [3·0-9·0] | 6·0 [3·0-10·0] | 6·0 [2·0-9·0] | 0·472 |
| Age at last follow-up (years) | 16·0 [10·0-26·0] | 17·0 [10·0-27·0] | 15·0 [10·0-24·0] | 0·334 |
| Male | 114 (45·6%) | 57 (45·6%) | 57 (45·6%) | >0·999 |
| Xanthomas at diagnosis | 187 (84·6%) | 97 (84·3%) | 90 (84·9%) | 0·205 |
| Body mass index (kg/m$^2$)[#] | 21·9 [18·8-25·4] | 21·5 (18·3-25·3) | 22·6 (19·9-25·4) | 0·380 |
| Diabetes mellitus | 1 (0·4%) | 1 (0·8%) | 0 (0·0%) | >0·999 |
| Hypertension | 20 (8·4%) | 7 (6·0%) | 13 (10·7%) | 0·243 |
| Chronic kidney disease | 3 (1·7%) | 0 (0·0%) | 3 (3·8%) | 0·247 |
| Smoking (ever) | 20 (10·1%) | 11 (9·6%) | 9 (10·7%) | 0.816 |
| **Lipids (mmol/L) – median [IQR]** | | | | |
| *Untreated* | | | | |
| Total cholesterol | 19·0 [16·6-21·8] | 19·3 [16·4-21·4] | 18·6 [16·9-22·0] | 0·661 |
| LDL-C | 17·2 [14·8-19·7] | 17·2 [14·8-19·7] | 17·2 [14·7-19·4] | 0·954 |
| HDL-C | 0·92 [0·75-1·21] | 0·91 [0·75-1·20] | 0·92 [0·76-1·21] | 0·685 |
| Triglycerides | 1·25 [0·90-1·75] | 1·28 [0·91-1·73] | 1·21 [0·87-1·70] | 0·266 |
| *Most recent* | | | | |
| Total cholesterol[#] | 11·2 [7·5-14·9] | 13·1 [9·5-15·9] | 9·1 [6·0-13·1] | <0·001 |
| LDL-C[#] | 9·9 [6·7-13·3] | 11·4 [7·7-14·0] | 9·3 [5·5-12·6] | 0·007 |
| LDL-C (Kroon) | NA | NA | 7·4 [4·3-10·0] | <0·001 |
| LDL-C goal* reached | 16 (7·0%) | 4 (3·7%) | 12 (9·8%) | 0·075 |
| **LDLR functionality available** | 162 (64·8%) | 92 (73·6%) | 70 (56·0%) | |
| *LDLR functionality* | | | | |
| Defective/defective | 85 (52·5%) | 60 (65·2%) | 25 (35·7%) | <0·001 |
| Defective/null | 23 (14·2%) | 14 (15·2%) | 9 (12·9%) | |

| | | | | |
|---|---|---|---|---|
| Null/null | 51 (31·5%) | 17 (18·5%) | 34 (48·6%) | |
| Uncertain | 3 (1·9%) | 1 (1·1%) | 2 (2·9%) | |
| *LDLRAP1/LDLRAP1* | 7 (2·8%) | 4 (3·2%) | 3 (2·4%) | >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] | |
| *Medication – information available* | 215 (86·0%) | 125 (100·0%) | 90 (72·0%) | |
| Statin | 180 (83·7%) | 106 (84·8%) | 74 (82·2%) | 0·751 |
| Ezetimibe | 145 (67·4%) | 92 (73·6%) | 53 (58·9%) | 0·034 |
| PCSK9-inhibitor | 43 (20·0%) | 29 (23·2%) | 14 (15·6%) | 0·226 |
| Lomitapide | 17 (7·9%) | 5 (4·0%) | 12 (13·3%) | 0·130 |
| Evinacumab | 4 (1·9%) | 1 (0·8%) | 3 (3·3%) | 0·621 |
| Resins | 14 (6·5%) | 6 (4·8%) | 8 (8·9%) | 0·784 |
| Fibrate | 1 (0·5%) | 1 (0·8%) | 0 (0·0%) | >0·999 |

Data are shown as n (%) for categorical variables or as median [IQR]. ~matched; #Body mass index, most recent total cholesterol and LDL-C, were available for 149, 195, and 230 patients, respectively. *LDL-C treatment targets (mmol/L, using the Kroon equation) were defined as ≤3.4 in children and ≤1.8 and ≤2.6 in adults with and without cardiovascular disease, respectively.

FH=familial hypercholesterolaemia. HDL-C=high-density lipoprotein cholesterol. IQR=interquartile range. LA=lipoprotein apheresis. LDL-C=low-density lipoprotein cholesterol. LDLRAP1=low-density lipoprotein receptor adapter protein 1. LLT= lipid-lowering therapy. NA=not applicable. PCSK9=proprotein convertase subtilisin/kexin type 9.

**Table 2 – ASCVD in matched cohort**

| | LA- N = 125 | LA+ N = 125 | p-value |
|---|---|---|---|
| Any ASCVD[#] | 59 (49·2%) | 52 (42·3%) | 0·445 |
| Age of any ASCVD[^] | 16·0 [9·0-25·0] | 15·5 [12·3-27·0] | 0·674 |
| MI | 4 (3·3%) | 8 (6·5%) | 0·376 |
| PCI | 11 (9·2%) | 8 (6·5%) | 0·634 |
| CABG | 14 (11·7%) | 11 (8·9%) | 0·404 |
| AVR | 7 (5·8%) | 5 (4·1%) | 0·769 |
| Angina pectoris | 15 (12·5%) | 6 (4·9%) | 0·066 |
| Aortic stenosis | 47 (39·2%) | 38 (30·9%) | 0·207 |
| PAD | 4 (3·3%) | 7 (5·7%) | 0·540 |
| Stroke/carotid stent/endarterectomy | 1 (0·8%) | 1 (0·8%) | >0·999 |
| Cardiovascular death | 10 (8·0%) | 1 (0·8%) | 0·010 |
| Age at MI – median [IQR] | 19·5 [11·8-27·3] | 27·0 [24·0-29·5] | 0·639 |
| Age at PCI | 21·0 [15·0-34·0] | 25·0 [14·8-30·8] | 0·836 |
| Age at CABG | 30·5 [19·0-33·8] | 15·0 [12·0-24·0] | 0·037 |
| Age at AVR | 33·0 [21·5-37·0] | 30·0 [27·0-31·0] | 0·514 |
| Age at angina pectoris | 27·5 [19·0-32·8] | 23·5 [13·3-30·8] | 0·364 |
| Age at aortic stenosis | 15·0 [9·0-23·0] | 15·5 [9·8-27·8] | 0·510 |
| Age of PAD | 19 [17-46] | 18·5 [13·5-31·5] | 0·569 |
| Age at stroke/carotid stent/endarterectomy | 26·0 (only 1 event) | NA | NA |
| Age at cardiovascular death | 24·0 [14·0-33·8] | 32·0 (only 1 event) | 0·526 |

Data are shown as n (%) for categorical variables or as median [IQR]. [#]Available for 120 LA- patients and 123 LA+ patients; [^]Available for 57/59 LA- patients and 30/52 LA+ patients

ASCVD=atherosclerotic cardiovascular disease. AVR=aortic valve replacement. CABG=coronary artery bypass grafting. LA=lipoprotein apheresis. MI=myocardial infarction. NA=not applicable. PAD=peripheral artery disease. PCI=percutaneous coronary intervention.