



Clinical practice recommendations on lipoprotein apheresis for children with homozygous familial hypercholesterolaemia: An expert consensus statement from ERKNet and ESPN

M. Doortje Reijman^a, D. Meeike Kusters^a, Jaap W. Groothoff^a, Klaus Arbeiter^b, Eldad J. Dann^c, Lotte M. de Boer^a, Sarah D. de Ferranti^{d,e}, Antonio Gallo^f, Susanne Greber-Platzer^g, Jacob Hartz^{d,e}, Lisa C. Hudgins^h, Daiana Ibarretxe^{i,j,k,l}, Meral Kayikcioglu^m, Reinhard Klingelⁿ, Genovefa D. Kolovou^o, Jun Oh^p, R. Nils Planken^{q,r}, Claudia Stefanutti^s, Christina Taylan^t, Albert Wiegman^{a,*}, Claus Peter Schmitt^{u,1}

^a Amsterdam UMC, University of Amsterdam, Department of Paediatrics, Amsterdam Cardiovascular Sciences, Amsterdam Gastroenterology Endocrinology Metabolism, Meibergdreef 9, Amsterdam, the Netherlands

^b Division of Paediatric Nephrology and Gastroenterology, Department of Paediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria

^c Blood Bank and Apheresis Unit Rambam Health Care Campus, Haifa, Israel

^d Department of Cardiology, Boston Children's Hospital, Boston, MA, USA

^e Department of Pediatrics, Harvard Medical School, Boston, MA, USA

^f Sorbonne Université, INSERM, UMR 1166, Lipidology and Cardiovascular Prevention Unit, Department of Nutrition, APHP, Hôpital Pitié-Salpêtrière, F-75013, Paris, France

^g Clinical Division of Paediatric Pulmonology, Allergology and Endocrinology, Department of Paediatrics and Adolescent Medicine, Medical University Vienna, Vienna, Austria

^h The Rogosin Institute, Weill Cornell Medical College, New York, NY, USA

ⁱ Vascular Medicine and Metabolism Unit (UVASMET), Hospital Universitari Sant Joan, Spain

^j Universitat Rovira i Virgili, Spain

^k Institut Investigació Sanitària Pere Virgili (IISPV)-CERCA, Spain

^l Centro de Investigación Biomédica en Red en Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Instituto de Salud Carlos III, Spain

^m Department of Cardiology, Medical Faculty, Ege University, 35100, Izmir, Turkey

ⁿ Apheresis Research Institute, Stadtwaldguertel 77, 50935, Cologne, Germany

^o Metropolitan Hospital, Department of Preventive Cardiology, 9, Ethn. Makariou & 1, El. Venizelou, N. Faliro, 185 47, Athens, Greece

^p University Medical Center Hamburg/Eppendorf, Martinistrasse 52, 20246, Hamburg, Germany

^q Department of Radiology and Nuclear Medicine, Amsterdam UMC, location AMC, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands

^r Amsterdam Cardiovascular Sciences, Atherosclerosis & Ischemic Syndromes, Amsterdam, the Netherlands

^s Department of Molecular Medicine, Lipid Clinic and Atherosclerosis Prevention Centre, 'Umberto I' Hospital 'Sapienza' University of Rome, I-00161, Rome, Italy

^t Paediatric Nephrology, Children's and Adolescents' Hospital, University Hospital of Cologne, Faculty of Medicine, University of Cologne, Kerpener Str. 62, 50937, Cologne, Germany

^u Pediatric Nephrology, Center for Pediatric and Adolescent Medicine, University of Heidelberg, Germany

ARTICLE INFO

Keywords:

Homozygous familial hypercholesterolaemia
Cholesterol
LDL
Lipoprotein apheresis
Paediatrics
Consensus statement

ABSTRACT

Homozygous familial hypercholesterolaemia is a life-threatening genetic condition, which causes extremely elevated LDL-C levels and atherosclerotic cardiovascular disease very early in life. It is vital to start effective lipid-lowering treatment from diagnosis onwards. Even with dietary and current multimodal pharmaceutical lipid-lowering therapies, LDL-C treatment goals cannot be achieved in many children. Lipoprotein apheresis is an extracorporeal lipid-lowering treatment, which is used for decades, lowering serum LDL-C levels by more than 70% directly after the treatment. Data on the use of lipoprotein apheresis in children with homozygous familial hypercholesterolaemia mainly consists of case-reports and case-series, precluding strong evidence-based guidelines. We present a consensus statement on lipoprotein apheresis in children based on the current available

* Corresponding author. Amsterdam UMC, location AMC, Department of Paediatrics, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands.

E-mail address: a.wiegman@amsterdamumc.nl (A. Wiegman).

¹ These authors contributed equally to this work.

[†] www.apheresis-research.org

evidence and opinions from experts in lipoprotein apheresis from over the world. It comprises practical statements regarding the indication, methods, treatment goals and follow-up of lipoprotein apheresis in children with homozygous familial hypercholesterolaemia and on the role of lipoprotein(a) and liver transplantation.

1. Introduction

Homozygous familial hypercholesterolaemia (HoFH) is a rare disease characterized by extremely elevated low-density lipoprotein cholesterol (LDL-C) [1]. These elevated LDL-C levels, present from birth, may cause life-threatening atherosclerotic cardiovascular disease (ASCVD) early in life, if not treated sufficiently. To prevent this, it is vital to diagnose HoFH as early as possible and start treatment from diagnosis onwards [1]. For many HoFH patients, it is mandatory to combine the optimal use of the currently available pharmacological lipid-lowering therapies (LLT) with lipoprotein apheresis (LA) [3].

LA comprises several methods of selective therapeutic apheresis which leads to an acute reduction of LDL-C by more than 70% per session [4,5]. LA has to be repeated weekly or biweekly, as LDL-C levels increase after each session [4,6]. Although the lipid-lowering effect of LA is strong, its impact on preventing ASCVD in HoFH is difficult to analyse. HoFH is rare, LA is not available for many patients around the globe and if available, it is not ethical to withhold children from LA to analyse the clinical efficacy. From historical reports on HoFH patients, we know that without LA treatment, severe life-threatening ASCVD may occur in early childhood [7].

There is an unfulfilled need for guidance on the treatment of LA in children with HoFH, especially in the current times with major advances in pharmacological LLTs [2]. Therefore, this consensus statement, initiated by the European Rare Kidney disease Network (ERKNet) and endorsed by the European Society of Paediatric Nephrology (ESPN) Dialysis Working Group, was developed to provide guidance to healthcare professionals on the treatment of LA in children with HoFH. These recommendations are based on the available evidence from observational studies in children and adults and the opinion of experts in the field of HoFH. Because the rareness of the disease and ethical considerations, there are no RCTs or prospective interventional studies on the LDL-C lowering effects of LA, and therefore the quality of evidence for many statements remains low [2]. Hence, it is important to use these statements as a guidance and adapt them to the individual patient's needs. In this consensus statement, we propose statements on the use of LA in the treatment of children with HoFH, including indication, methods, vascular access, treatment goals, monitoring clinical efficacy, side effects and the role of lipoprotein(a) (Lp(a)) and liver transplantation.

2. Methods

2.1. The consensus statement development groups

A core workgroup and a voting group were involved in the consensus statement. Participants were recruited via ERKNet and two international HoFH registries: HICC (HoFH, the International Clinical Collaborators; NCT04815005) and CHAIN (Children with Homozygous hypercholesterolemia on lipoprotein Apheresis: an International registry). Due to the focus of this consensus statement on indication, technique, treatment goals and follow-up, nurses and patient advocates have not been included. The core workgroup involved 21 HoFH experts from ten countries and working in different medical specialties (Supplementary Table 1). The voting group consisted of 19 experts in HoFH with different medical specialties from 13 countries (Supplementary Table 2). The core workgroup formulated key questions, performed a literature review, wrote the statements and rationales, rated the quality of evidence and wrote the manuscript. Subgroups worked on the statements and rationales on indication, methods of LA, vascular access, treatment

goals, monitoring clinical efficacy, monitoring side effects and the role of Lp(a) and liver transplantation. The voting group was asked to share their level of agreement and feedback for each statement.

2.2. Developing clinical questions

To give specific recommendations, clinical questions were developed for each topic as a basis for creating statements. These clinical questions were based on an overall question including patients, intervention, comparator and outcome (PICO) [8]. Patients were children under the age of 18 with a genetic or clinical diagnosis of HoFH following the criteria from Cuchel et al. [1] HoFH can be diagnosed genetically by confirmation of two pathogenic variants in the *LDLR*, *APOB*, *PCSK9*, or *LDLRAP1* gene, or can be diagnosed clinically when a patient has untreated LDL-C levels >10 mmol/L (>~400 mg/dL) together with either cutaneous or tendon xanthoma before the age of 10 years or untreated LDL-C levels consistent with HoFH in both parents [1]. The intervention was treatment with LA and the comparator was standard of care without LA. The outcome was safety, and efficacy in terms of LDL-C lowering, clinical and imaging findings of ASCVD. ASCVD was defined as ASCVD related to HoFH including angina pectoris, aortic stenosis, myocardial infarction, sudden cardiac death, percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG) and aortic valve replacement.

2.3. Literature review and studies included

PubMed and Embase databases were searched until 22nd of November 2021. All articles in English describing paediatric patients with HoFH were selected irrespective of the design of the study. For each topic, articles including relevant information for the specific topic were selected. To include the most recent literature up to April 2023, members of the workgroup added 11 additional references during the writing process, which were published after the database searches were performed. If this resulted in a need for adjustment of a statement, this was again reviewed by all participants. This occurred once, based on the most recent guidelines for LDL-cholesterol goals [1].

2.4. Grading system

We applied the grading system from the American Academy of Pediatrics (AAP) (Fig. 1) [9]. For each statement, the quality of evidence was graded and the strength of the recommendation was chosen based on the assessment of benefit or harm [9].

After the core workgroup agreed on the content and grading of the statements, these were sent to an external voting group, which was asked to share their level of agreement on a five-point Likert scale (strongly disagree, disagree, neither agree/disagree, agree and strongly agree) for each statement. Consensus was regarded as a minimum of 70% of the voters choosing 'agree' or 'strongly disagree' for each statement. If this was not reached, the statement was either revised or removed by the core working group based on the suggestions of the voting group, and proposed at the voting group again, until 70% agreement was reached. Finally, 70% agreement was obtained for 22 out of 24 statements. Two were removed as statement and brought as topics of discussion within the rationales on the specific topics.

3. Consensus statements

3.1. A. Indication for LA

3.1.1. Statements

1. We recommend starting LA in children diagnosed with HoFH if LDL-C levels are >7.8 mmol/L (>300 mg/dL) despite optimal lipid-lowering therapy. (X - strong)
2. We recommend starting LA in children diagnosed with HoFH and (subclinical) ASCVD if LDL-C levels are >3.4 mmol/L (>130 mg/dL) despite optimal lipid-lowering therapy. (X - strong)
3. We suggest considering starting LA in children diagnosed with HoFH without (subclinical) ASCVD if LDL-C levels are between 3.4 mmol/L (130 mg/dL) and 7.8 mmol/L (300 mg/dL) despite optimal lipid-lowering therapy. (X - moderate)
4. We recommend starting LA early as possible in life. (X - strong)

3.1.2. Rationale

Threshold of LDL-C level for LA indication. The fundamental rationale for anticipating LA treatment in HoFH children resides in the reduction of very-high LDL-C exposure that is associated with significant ASCVD risk.

There is sufficient evidence, that for prevention of ASCVD, the paradigm for LDL-C treatment goal level is, “the lower the better”. Current recommendations are that ideal LDL-C levels should be below 1.8 or 2.5 mmol/L (70 or 100 mg/dL) for the adult population without signs of ASCVD [1,10]. For HoFH patients, these treatment goals are difficult to reach under the current therapeutic options. The *threshold* of LDL-C for the indication of LA has originally been established on >13 mmol/L (>500 mg/dL) for HoFH and >7.8 mmol/L (>300 mg/dL) for heterozygous familial hypercholesterolaemia (HeFH) by the FDA [11]. We follow the recommendation of both the American Heart Association and the National Institute for Health and Care Excellence to start LA in both HoFH and HeFH patients with LDL-C levels >7.8 mmol/L (>300

mg/dL) despite optimal LLT. Optimal LLT is regarded as diet combined with multimodal pharmacological LLT. This can include ezetimibe, statins, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, evinacumab or lomitapide, depending on which LLTs are available, affordable and tolerable for the patient [2]. Gene editing using clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 may be a future treatment option for HoFH, but it may have limited applicability to children due to their growing liver [12]. There is consensus that the threshold for LA should be lower in FH patients with established ASCVD. In Germany, a threshold for all FH patients with ASCVD of 3.4 mmol/L (130 mg/dL) has been recommended, which is generally regarded as the threshold of high-normal LDL-C level [13]. Therefore, we recommend starting LA in children diagnosed with HoFH and (subclinical) ASCVD if LDL-C levels are >3.4 mmol/L (>130 mg/dL) despite optimal LLT. If LDL-C levels are between 3.4 mmol/L (130 mg/dL) and 7.8 mmol/L (300 mg/dL) despite optimal lipid-lowering therapy and no (subclinical) ASCVD is present, we suggest considering starting LA based on individual circumstances, such as age, vascular access options and additional cardiovascular risk factors.

The age at LA treatment commencement is associated with ASCVD event-free survival, together with treatment duration, and the current on-treatment LDL-C levels [14]. In theory, the same paradigm would be applicable as in the threshold discussion, “the sooner, the better”. LA is technically feasible in very young children and has been successfully chronically executed in children from the age of 2–3 years, provided there is a trained team that can face technical limitations such as low blood flows, consequence of the use of small calibre needles, and the risk of mild hypotension related to relatively high extra-corporal volumes [4, 15–18]. Observational studies support early onset of LA therapy in HoFH [17,19–23]. LA seems more effective in preventing development of ASCVD than stopping further deterioration of already acquired ASCVD, which would be an extra argument for early onset of therapy [20].

Evidence quality	Benefit or harm predominates	Balance of benefit and harm
Level A Well-designed randomized controlled trials, meta-analyses on applicable populations or independent gold standard studies of applicable populations	Strong recommendation	Weak recommendation
Level B Trials or diagnostic studies with minor limitations or consistent findings from multiple observational studies	Moderate recommendation	
Level C Single or few observational studies or multiple studies with inconsistent findings or major limitations	Weak recommendation	
Level D Expert opinion, case reports and reasoning from first principles		No recommendation may be made
Level X Exceptional situations where validating studies cannot be performed and benefit or harm clearly predominates	Strong recommendation Moderate recommendation	

Fig. 1. Grading system for the strength of the recommendations following the American Academy of Pediatrics system.

3.2. B. Methods of lipoprotein apheresis

3.2.1. Statements

- We suggest using selective methods for lipoprotein apheresis, for which equally efficient systems are available. (C – moderate)
- We suggest aiming for an acute reduction of LDL-C plasma levels of at least 70% with each apheresis session. (X – moderate)

3.2.2. Rationale

LDL-C can be removed by unselective plasma exchange and by selective LA methods, either as a plasma separation method or as a whole blood method [24]. Currently, there are six technically different options for selective extracorporeal LA available (see Table 1 for comparison) [25,26].

Although all existing systems are effective in removing LDL-C, a review of 76 studies on LA in FH, showed that in daily practice, selective methods (LA15, polyacrylate full blood adsorption and dextran sulphate full blood adsorption) were slightly more effective than plasma exchange (on average 71 vs. 63% LDL-C removal) [21]. Within the selective techniques, there are small differences in efficacy [27–29]. Apart from slightly less efficient LDL-C removal, plasma exchange and double filtration plasmapheresis (DFPP) bare the problem of removal of other components, such as HDL, fibrinogen and IgG [30,31]. On the other hand, some techniques claim selective removal of other unwanted substances. In addition to the removal of VLDL, IDL, LDL and Lp(a), dextran sulphate adsorption technique as well as HELP have been reported to remove PCSK9, soluble adhesion molecules (s-ICAM-1, s-E-Selectin, s-VCAM-1), coagulation factors (fibrinogen, platelet factor 4, etcetera)

and some pro-inflammatory cytokines; of these two, dextran sulphate adsorption technique seemed the most efficient in removal of inflammatory makers [27,32]. Due to the better efficacy in LDL-C removal and higher selectivity, we suggest to use selective methods for LA over plasma exchange. When combining LA with monoclonal antibodies such as alirocumab or evolocumab, which target PCSK9, it is advised to administer these treatments subsequent to LA treatment, since it can be absorbed by LA [33]. If costs are a limiting factor for performing LA, plasma exchange may be an alternative, especially in low-income countries.

Experience of the authors: Most data on efficacy are derived from studies in adults. Contrary to often lower reported values in adult patients, in children >70% acute LDL-C reduction per session can be achieved with selective techniques like HELP, LA15 and DFPP, as long as enough plasma is exchanged, since these systems do not saturate in children. Limitation of LA efficacy in daily practice with children is often caused by LA duration with limited blood and plasma flow due to poor vascular access quality. The recommended plasma exchange volume for the plasma separation techniques are between 40 and 60 cc/kg; for the whole blood systems between 1.3 and 1.5 times the total blood volume.

LA in small children: The extracorporeal volume can limit the use of some techniques in small children. This accounts especially for the whole blood systems. Most plasma separations techniques have been applied successfully in children aged >2 years old, with most experience in young children has been achieved with the LA15 Kaneka system that has a blood equivalent volume of 130 cc [16]. Patients >13 kg do not need blood priming with this system. Practical advice for the management of LA in young children includes a low blood flow at onset of therapy, starting with 15–30 ml/min, priming the extracorporeal system

Table 1
Comparison of lipoprotein apheresis methods.

Method	Extra corporeal volume	Selectivity	HDL-C removal	Fibrinogen removal	Lp(a) removal	Reported side effects	Advantages	Disadvantages
Polyacrylate full blood adsorption (DALI, Fresenius) haemoperfusion – whole blood technique	330–705 cc ^a	++	+/-	–	++	Bradykinine-related ^c	Very effective, selective, simple	Expensive, high extra-corporeal volume, contra-indication ACEi
Kaneka LA 15 Dextran sulphate adsorption - plasma separation	130–160 cc ^b (300 cc total)	++	+/-	–	++	Allergic, Bradykinine-related ^c , hypoCa	Very effective, selective, relatively low extra corporal volume	Complicated technique, contra-indication ACEi
Dextran sulphate full blood adsorption (Liposorber D, Kaneka) Haemoperfusion - whole blood technique	394 cc (DL-50), 484 cc (DL-75), 690 cc (DL-100)	++	+/-	–	++	Bradykinine-related ^c , hypoCa	Very effective, selective, simple	Expensive, high extra-corporeal volume, contra-indication ACEi
HELP (Braun) heparin-induced LDL precipitation	150 cc ^b (450 cc total)	+ [5]	+	++	++	Potentially bleeding risk, low blood pressure	Safe, proven impact on outcome, anti-inflammatory	Less selective, less effective, loss C3/C4, high loss of fibrinogen, complicated technique
Double/cascade filtration (DFPP) Plasma separation and filtration	222 cc	+	++	+	++	Occasionally hypotension, nausea, vomiting	No bradykinin release, simple technique	Less selective, less effective on the long run, loss of IgG, Alpha-2-Macroglobulin
Immuno-adsorption Anti Apolipoprotein B (Therasorb)	180 cc ^b	+	+(+)	+(+)	++	Occasionally hypotension, nausea, vomiting	Effective, selective	less effective and selective than other selective methods, expensive, relative long procedure
Plasma exchange Plasma filtration or plasmapheresis (centrifuge)	140–185 cc	–	++	++	++	Bleeding risk, fibrinogen loss, hypotension,	Most simple technique, widely used, cheap	Unselective, less effective, loss of plasma proteins, HDL-C removal, bleeding risk, anaemia

Data from Bambauer 2012, Klingel 2003 and information from the companies [25,26].

ACEi, ACE-inhibitor; HELP, Heparin Induced LDL precipitation; HDL-C, high-density lipoprotein cholesterol; hypoCa, hypocalcaemia; LA, lipoprotein apheresis; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a).

^a Depending on filter size 500, 750, 1000 & 1250 cc.

^b Expressed as estimated blood equivalent volume for the blood separation systems (LA15, HELP, immuno-adsorption; total = blood and plasma volume).

^c Abdominal pain, flushing, hypotension.

with normal saline or, in case of low blood pressure, human albumin and the involvement of skilled nurses experienced in conducting extra-corporeal blood purification techniques in children.

In conclusion, all available selective methods lead to a significant removal of LDL-C with preservation of other proteins. Acute reductions >70% are achievable, as long as optimal plasma volumes per kilogram body weight are applied [4]. Therefore, we suggest aiming for an acute LDL-C reduction of at least 70% per LA session.

3.3. C.Vascular access

3.3.1. Statements

- 7. Vascular access options should be discussed with the patient and families in detail and individual decisions should be taken considering age, vascular anatomy and individual needs. (ungraded)
- 8. In children not suited for peripheral vein puncture, we suggest starting with a functioning AVF. (C - moderate)
- 9. In children with AVF, the cardiac burden of the increased circulating volume should be monitored. (D - weak)
- 10. Vascular access should be placed and used by well-trained personnel. (ungraded)

3.3.2. Rationale

Various forms of vascular access are applicable for LA in youth: 1) peripheral vein needling; 2) arteriovenous fistula (AVF) or arteriovenous graft; and 3) a tunnelled central venous line (CVL), with or without a port. The provision of the optimal vascular access for LA should be patient focused, and based on a multidisciplinary approach in assessing and educating patients. Complications of vascular access depend on the access type (Table 2). Specific advantages and disadvantages of the different vascular access options should be explained, such as the need of regular needling and associated pain, the option of local anaesthetic crèmes to reduce puncture pain, LA session duration, and the associated risks of infection and access dysfunction due to dislocation and clotting, eventually requiring novel access placement at a different site..

Observational evidence suggests peripheral vein access for LA is feasible in children, with safe puncturing of the veins and pain tolerated [19]. Achievement of LDL-C treatment goals, number of missed sessions and the individual burden of regular vein punctures require close monitoring. In all other children, a permanent vascular access for long-term treatment needs to be established.

There is limited literature available on the use of AVF and CVL in children with HoFH. Even though concerning a different patient population, studies in children on chronic haemodialysis show that AVF are preferred over CVL, as CVLs are associated with a significantly higher risk of infection, access dysfunction, access replacement and vascular stenosis than AVF [15,17,34–37]. The duration of the LA sessions is

shorter with AVF, and a non-significant trend towards lower mean LDL-C levels has been observed [4]. It is unclear to what extent arteriovenous grafts are an alternative in children with veins too small for AVF.

In AVF, blood flows from the high resistance arterial system into the low resistance venous system, with a subsequent rise in venous return and cardiac output. It decreases arterial impedance and thus lessens the left ventricular afterload. The lowering of arterial impedance may also reduce the effective circulating volume of the systemic circulation, activating arterial baroreceptors, and leading to secondary increase in cardiac sympathetic tone, contractility, and output [38–40]. The impact of these effects of AVF on the cardiac function is controversial [41]. In patients on haemodialysis, the vast majority of patients tolerate AVF well [42]. At present, it is unknown in how far the AVF associated cardiac burden due to the increased circulating volume may represent an additional cardiac risk in children on LA. Respective AVF shunt volume should be monitored and AVF with large shunt volumes may require surgical flow reduction.

Vascular access sites are limited. Improved outcomes have been reported when skilled surgeons work with dedicated vascular access clinics [43]. Preoperative diagnostics and site selection, aseptic technique for access use, vascular access monitoring and prevention of thrombosis have recently been described in a consensus document for children requiring maintenance haemodialysis by the European Society for Paediatric Nephrology Dialysis Working Group; these recommendations apply for children on LA with an AVF as well [44]. Recent studies suggest that AVF, if provided by specialized surgeons, can be placed in children aged less than 2 years. Complications are thrombosis, stenosis or non-maturation occur in a minority, but maturation times of up to 6 months have been reported [37,45,46].

Experience of the authors: Five of the 10 centers of the core workgroup performing LA in children have positive long-term experience with peripheral vein puncture in children from the age of 3–6 years onwards with weekly to monthly LA and session durations of 2–6 h. Five centers primarily use AVF in children from 3 to 12 years onwards with weekly to monthly sessions as needed and session durations of 1.25–3 h. Successful 12 years usage of arteriovenous graft (AVG) was reported in a patient with veins too small for AVF creation. CVL were used in one center in children aged 3–7, but with high complication rates [15]. One center reported routine use of ports from the age of 6 years onwards, with weekly to twice-monthly sessions and 4–8 h of session duration; one center used a port for temporary vascular access in one patient. Due to the long treatment times and the need for surgical replacement of the port every few years, this vascular access may not be a preferable option. Most centers had a strong preference for one of the vascular access options, mainly related to the specialty of the treating physician. Nephrologists most often used AVFs whereas cardiologists used peripheral veins.

Table 2
Comparison of vascular access types.

Peripheral vein needling		Arteriovenous fistula		Central venous line	
Pro	Cons	Pro	Cons	Pro	Cons
Ready to use	Puncture pain	Less stigmatization than with CVL	Puncture pain	Pain free	Stigmatization
No stigmatization, normal body perception	Difficulties with frequent needling	Highest blood flow, short treatment time	Vascular surgery required	Safe vascular access for frequent use	High infection and obstruction (clotting) rates
No impact on physical activities	Low blood flow, longer session duration	Very low infection rate, lower rate of obstruction (clotting) than CVL	Difficult in small children, and need of long maturation time	Feasible in small children	Risk of dislocation
		Safe vascular access for frequent use	Potential cardiac burden with high shunt volume		Risk of thrombi/emboli and central vascular stenosis
		Less interference with physical activities than CVL			Interferes with physical activities

CVL, central venous line.

3.4. D. Treatment goals

3.4.1. Statements

11. In between weekly or biweekly apheresis sessions, we suggest using the adjusted Kroon formula to calculate the mean LDL-C plasma levels:

$$\text{LDL-Cmean} = \text{LDL-Cpost} + K (\text{LDL-Cpre} - \text{LDL-Cpost})$$

LDL-Cpost: LDL-C level directly after the LA session, LDL-Cpre: LDL-C level directly before the LA session.

K: rebound coefficient, 0.65 for HoFH patients.
(C – weak)

12. We recommend aiming for a mean LDL-C treatment goal of <3.0 mmol/L (<115 mg/dL). (X – strong)
13. For children with ASCVD, we suggest considering lower mean LDL-C treatment goals of <1.8 mmol/L (<70 mg/dL). (X – moderate)
14. We suggest considering reducing the frequency of lipoprotein apheresis if the mean LDL-C plasma levels stay within the treatment goal with the use of newly available effective lipid lowering drugs. (X – moderate)

3.4.2. Rationale

Although high-level evidence exists on the benefits of lowering serum LDL-C concentrations with respect to reducing cardiovascular risk [47,48], there is no evidence for the optimal LDL-C goal for HoFH children on LA. Previously, the proposed treatment goal for children with HoFH was set on <3.4 mmol/L (<130 mg/dL) [49]. However, observational studies have shown early development of ASCVD in children reaching these treatment goals [17,21]. Recently, it was suggested to further lower the treatment goal in children with HoFH to <3.0 mmol/L (<115 mg/dL) [1]. In line with this recommendation, we recommend aiming for a mean LDL-C treatment goal of <3.0 (<115 mg/dL) in children with HoFH on LA without ASCVD. For children with (subclinical) ASCVD, we suggest considering lower LDL-C goals of <1.8 mmol/L (<70 mg/dL), in line with the previous suggested treatment goal for adults with HoFH and ASCVD [49]. We believe that a lower goal may be too challenging and burdensome for children in daily practice and consequently not feasible in children with the current available therapeutic options.

Another reason to support these goals is the introduction of new, highly effective lipid lowering agents. The PCSK9 antibody evolocumab reduced LDL-C by 45% in an RCT including 157 paediatric HoFH patients and reduced LDL-C by 30% in two children with HoFH [50,51]. Evinacumab, a monoclonal antibody against ANGPTL3, reduced LDL-C by almost 50% on top of background LLT in 65 HoFH patients, including one adolescent [52]. In a recent observational report, two paediatric HoFH patients (12 and 16 years of age) were treated with a statin, ezetimibe and weekly LA. Addition of evinacumab decreased mean pre-apheresis LDL-C levels from 5.5 to 5.1 mmol/L to 2.5 and 2.2 mmol/L, respectively. Total plaque volumes were reduced by 76% and 85% after 6 months of evinacumab treatment [53], demonstrating that with drastic LDL-C lowering, atherosclerotic plaques can regress at young age, even in HoFH patients. With the accomplishments of the novel lipid-lowering therapies it might also be safe to reduce the frequency of LA, provided the mean LDL-C plasma levels stay within treatment goals. However, their efficacy in the prevention of ASCVD and mortality in paediatric patients has yet to be proven.

How to monitor LDL-C: While with lipid-lowering drugs, the LDL-C levels are relatively stable over time, with LA treatment, the LDL-C levels have a saw tooth-like pattern. Pre-LA LDL-C levels give an overestimation of the actual LDL-C level over time, while post-LA LDL-C levels give a considerable underestimation. Time-averaged

concentrations provide the best estimate of the mean LDL-C levels over time [54].

The Kroon formula was developed to estimate the mean LDL-C levels between two LA sessions on a biweekly scheme and based on a study on the rebound of lipoproteins after LA in 20 hypercholesterolaemic adult men (no HoFH) with a rebound coefficient of 0.73 [54]. Thompson et al. [55] calculated a rebound coefficient specifically for HoFH patients of $K = 0.65$ based on 11 adult HoFH patients who received biweekly LA. No large validation studies have been performed to evaluate this formula and no studies have been performed to validate this coefficient in paediatric patients nor in patients receiving LA at different frequencies other than biweekly. Therefore, the suggested Kroon formula with a coefficient of 0.65 only provides a rough estimate of the mean LDL-C levels in paediatric HoFH patients on LA once every two weeks and might even be less reliable if other frequencies are applied.

3.5. E. Monitoring clinical efficacy

3.5.1. Statements

15. We recommend performing echocardiography (with colour and Doppler) annually. (X - strong)
16. We recommend performing low dose CTCA before LA therapy is initiated. (X - strong)
17. We recommend, if potentially obstructive atherosclerotic plaque >50% is visible on CTCA, to detect and evaluate potential coronary ischemia by non-invasive functional test. (X - strong)
18. We recommend cardiac catheterization and coronary angiography for HoFH children when invasive intervention may be required, and for coronary imaging if CTCA is not feasible. (X - strong)

3.5.2. Rationale

Asymptomatic children with HoFH should be screened for subclinical ASCVD. Common consequences of HoFH include aortic stenosis (AS) and coronary non-calcified or calcified plaques [49]. AS is mainly evaluated by echocardiography, and seldom by invasive cardiac catheterization, contrast angiography or cardiac magnetic resonance imaging (MRI) [56,57]. Presence of (non-) calcified plaques, perivascular inflammation and hemodynamic obstructive lesions can be evaluated by prospective ECG-triggered CT coronary angiography (CTCA). Potential ischemia due to obstructive coronary artery stenoses should be primarily evaluated by non-invasive functional tests, such as exercise ECG, stress perfusion with PET-CT, cardiac MRI or Single Photon Emission CT Myocardial Perfusion (SPECT).

Ultrasonography: Subclinical and clinical aortic valvular disease (VD), ostia and proximal segments of the coronary arteries (not always easy to visualize), and any abnormality in cardiac function in HoFH children can be assessed by echocardiography with colour and Doppler [58]. Aortic valve regurgitation or stenosis, aortic root thickening, narrowing of the ostia and proximal segments of the coronary arteries, and abnormal left ventricular function, and narrowing of the internal diameter of the supraaortic aortic ridge and atheromatous plaques in the root and ascending aorta may be detected [59–62]. Of note, echo has lower sensitivity compared with CT scan in detecting calcification of the aortic valve and root. In line with Cuchel et al., we recommend echocardiography with colour and Doppler annually for evaluation of the heart and aorta in all HoFH patients on LA [1].

We do not recommend IMT for regular monitoring in clinical practice, as there are important limitations: it requires special expertise, the intra-observer variability is high, there are no reported standardized reference values for children, and accepted thresholds for defining the presence and progression of atherosclerosis in children by IMT are lacking.

CT coronary angiography (CTCA) (prospective ECG-triggered): ECG-triggered CTCA is recommended to detect potential hemodynamic

obstructive lesions with special focus on the coronary ostia and proximal segments, all risk factors for myocardial infarction. In addition, CTCA enables assessment of both non-calcified and calcified atherosclerotic plaques and thereby identification of subclinical ASCVD. Detection of subclinical ASCVD in HoFH children is an indication for lower LDL-C goals. CTCA is recommended before initiation of LA therapy, to guide treatment decision making and tailor treatment frequency and intensity. With newer therapies, repetitive CTCA may visualize regression of marked plaques in adolescents [53]. Radiation dose and hence repeated CTCA assessment is acceptable with the latest generation of CT-scanners [63]. In children, CTCA may result in a median effective dose of only 1 mSv when performed by 128-slice dual source CT [64]. CTCA on the latest generation of CT-scanners also enables image acquisition with a high temporal resolution that allows for application in newborns and children without sedation [64]. If CTCA is not available, one should consider referring patients to the nearest center with such scanner. Follow-up CTCA should be considered if a change in LA therapy intensity is considered. Cuchel et al. recommend ASCVD monitoring by CTCA at least once after the age of 3 years and follow-up CTCA as clinically indicated [1]. The optimal interval in general is unknown and should be individualized for each patient based on the achievement of LDL-C treatment goal, presence of ASCVD and results from previous CTCA.

Non-invasive functional tests: cardiac MRI is an accurate modality for assessment of myocardial ischemia and infarction. Cardiac MRI can safely serve as a “gatekeeper” for invasive angiography to avoid negative invasive diagnostic procedures and facilitate procedures for revascularization [65]. Both SPECT and stress perfusion with PET-CT are alternative imaging modalities used for ischemia detection in adults with chronic coronary syndrome, albeit with associated radiation dose [66,67]. Magnetic Resonance coronary angiography is under development, but still has its limitations for clinical use. We recommend to use non-invasive functional tests to detect and evaluate potential coronary ischemia if potentially obstructive atherosclerotic plaque >50% is visible on CTCA.

Cardiac catheterization and coronary angiography: in severely affected HoFH children with potentially obstructive CAD, cardiac catheterization and coronary angiography should be performed, for assessment of obstructive CAD and possible invasive interventions [percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG)] [68]. Invasive test should be guided by a combination of clinical findings and results from anatomical and/or functional testing.

3.6. F. Monitoring side effects

3.6.1. Statements

- 19. We recommend children on LA should be monitored for side effects during each LA session. (ungraded)
- 20. ACE-inhibitors must not be used during treatment with negatively charged membranes. (level X - strong)

3.6.2. Rationale

LA is overall well tolerated and safe in children and adults. Most described side effects of LA in children with HoFH are minor and do not affect the tolerability of the treatment (Table 3). There are five larger observations including a total of 105 HoFH patients and describing several thousand LA sessions in children [4,19,69–71]. 33–63% of the reported paediatric patients ever experienced an LA associated side effect [4,69], and side effects were described in 0.2–2% of the sessions only [19,70,71]. Most frequently reported were hypotension, nausea and technical issues, including problems with vascular access. The need of iron supplementation was reported in one paper in which 3/17 (18%) HoFH children on LA required iron supplementation [35]. None of the patients discontinued chronic LA treatment due to clinical symptoms or technical difficulties. Patients on LA should be monitored closely,

Table 3
Most commonly described potential adverse effects of lipoprotein apheresis.

CLINICAL SYMPTOMS	Hypotension Nausea/vomiting Stomach ache Fatigue Dizziness Angina Anaphylactic reactions (cutaneous flushing, nausea, headache and hypotension) Tingling/urticaria
BRADYKININ RELEASE RELATED	Nausea and vomiting, flushing, tongue swelling, severe abdominal pain, hypotension
IRON DEFICIENCY	Need for iron supplementation
VASCULAR ACCESS RELATED	Puncture difficulties Insufficient blood flow
LIPOPROTEIN APHERESIS RELATED	Obturation of the blood lines

especially during the first LA session, for clinical symptoms such as hypotension, nausea and vomiting. Biochemical follow-up should include next to lipid-metabolism, blood count and iron. In case of unselective plasma exchange, coagulation status and immunoglobulins may be monitored, especially with frequent LA, e.g. twice weekly.

Negatively charged membranes used in LA systems with dextran sulphate columns and modified polyacrylamide gels can induce acute bradykinin release, which in rare cases results in severe anaphylactoid reactions [22,72]. These membranes are used in polyacrylate full blood adsorption (DALI) [73] and in the dextran sulphate-based systems of Kaneka (LA15 and Liposorber D) [74,75]. Since plasma kallikrein is activated upon contact with the membranes, ACE-inhibitors are contraindicated in patients receiving LA, especially when systems with negative membranes are used [72,73]. Patients must be informed about this contra-indication. If there is no alternative therapy to ACE-inhibitors in single patients, the HELP system for LA may be considered, because this system does not activate the kallikrein-kinin system [73]. Angiotensin Receptor Blockers (ARB) may be an option to replace ACE-inhibitors [76,77]. Also without ACE-inhibitors, patients on these devices can experience reactions that are associated with bradykinin release: nausea and vomiting, flushing, tongue swelling, severe abdominal pain and hypotension [72].

Experience of the authors: To prevent side effects, including bradykinin-release-related side effects, multiple centers prime the membrane with albumin, which seems useful in preventing side effects. In one center, the bradykinin-release related symptoms during LA disappeared when the LA15 membrane was rinsed with saline instead of acetate.

Side effects related to different types of vascular access are described in the vascular access rationale. Side effects related to the anticoagulation used during the LA session are specific for the anticoagulation of choice, heparin or citrate; we therefore refer to the respective literature.

3.7. G. The role of Lipoprotein(a)

3.7.1. Statements

- 21. We suggest measuring Lp(a) levels in all children with HoFH at least at the time of diagnosis. (Level C – moderate)

3.7.2. Rationale

Besides elevated LDL-C levels, elevated levels of Lipoprotein(a) [Lp(a)] above 50 mg/dL or 125 nmol/L are considered ASCVD risk enhancing [78–84]. In patients with heterozygous FH, elevated Lp(a) levels are a predictor of ASCVD independent of LDL-C levels [85–95]. In children and adults with HoFH, Lp(a) levels are reported to be higher compared to patients with heterozygous FH and normolipidemic

controls [96–99]. Data on whether high Lp(a) is an independent risk factor for those patients is scarce [14,17,100,101]. Only one out of four available studies reported a significantly increased probability of ASCVD or death in HoFH patients with elevated Lp(a) compared to HoFH patients with non-elevated Lp(a) levels [14]; the other three were negative [17,100,101].

Paediatric guidelines recommend measuring Lp(a) in children with dyslipidaemias including familial hypercholesterolaemia [79,102–104]. Although the exact impact of Lp(a) as a risk factor for ASCVD in HoFH is unclear, we suggest measuring the Lp(a) levels of children with HoFH at least at the time of diagnosis. Knowing a child's Lp(a) level can help to define their ASCVD risk beyond LDL-C and improve compliance with a lifetime adoption of a heart-healthy lifestyle [105]. Secondly, measuring Lp(a) levels provides insight in the true LDL-C levels, because measured LDL-C may be higher than true LDL-C in patients with markedly elevated Lp(a) levels [106,107]. Finally, a high Lp(a) may be taken into consideration as an additional indication for initiating LA, in case of LDL-C levels between 3.4 and 7.8 mmol/L (130 and 300 mg/dL). LA is effective in lowering Lp(a) levels (60–70% per session) and its pro-inflammatory oxidized phospholipids in HoFH patients, but its impact on clinical risk reduction of ASCVD is uncertain [16,22,108–117]. In patients with isolated Lp(a), LA-mediated reductions of Lp(a) do seem to reduce the number of events, but these results are mainly derived from observational data and firm conclusions cannot be drawn [118–125].

Lp(a) levels are predominantly genetically determined: they are relatively low at birth and tend to increase during childhood [126–128]. We therefore suggest to repeat the measurement of Lp(a) in children with Lp(a) levels close to the ASCVD risk enhancing cut-off at the moment of deciding to start LA [127]. Since LDL-C levels are determinative for LA management, regular monitoring of Lp(a) will have no impact on the management and, therefore, is not recommended.

3.8. H. The role of liver transplantation

3.8.1. Statement

22. Liver transplantation may be considered in HoFH children with persistently elevated LDL-C levels and progressive ASCVD despite optimal available and tolerated pharmacological treatment and lipoprotein apheresis. (Level C - weak)

3.8.2. Rationale

If patients have access to LA and new, highly effective drugs such as PCSK9 inhibitors, lomitapide and evinacumab, LDL-C can be reduced to the LDL-C goal. However, these treatments may not be widely available. If a patient has persistently elevated LDL-C levels and progressive ASCVD despite optimal LLT treatment including before mentioned new LLT drugs and LA, liver transplantation may be considered as a treatment option.

It is estimated that 75% of the LDL receptors are located in the liver. By replacing the liver with poor LDL receptor function with a normal liver, LDL-C levels decrease to normal levels within a few weeks [129–131]. The risks of liver transplantation and post-transplant immunosuppressive therapy should be carefully balanced against the risks of persistently elevated LDL-C levels, and the benefits of the new potent LLTs. A complete review of the impact of liver transplantation is beyond the scope of this paper. In short, the risks include surgical complications, in particular cardiovascular hemodynamic instability, hemorrhage, thrombosis of the hepatic artery, hepatic vein, or portal vein and biliary complications; acute and chronic rejection, infection and side effects of immunosuppression [132,133].

Data on the effects of liver transplantation on cardiovascular burden are scarce, short-term and usually vaguely described. Regression of coronary artery disease has been described [130,134–137] and survival up to 28 years has been reported [138]. Besides LDL-C lowering, a

yet-to-be proven benefit of liver transplantation is a reduction in Lp(a) [130,139]. Although liver transplantation reduces the LDL-C levels, some case reports describe progression of aortic stenosis [130,131,140,141]. In addition to ASCVD benefits, there may be an improvement in the quality of life with liver transplantation compared to weekly or biweekly LA [142,143].

3.9. Conclusion and research topics to be developed

This consensus statement provides guidance on several topics on performing LA for the treatment of HoFH in children based on the available literature and expert opinion of a large group of experts involved in the treatment patients with HoFH. Conclusions of the most important practical statements are summarized in Fig. 2.

While developing this paper, we identified gaps in research. Therefore, we suggest several topics for further research. Furthermore, there is a need for guidance regarding establishing and operating LA services specifically tailored for children with HoFH. Offering generalized advice is challenging due to the diverse conditions unique to each center and country. Factors such as variation in costs, the method of LA, and the setting in which LA is conducted, including whether it occurs within a (paediatric) dialysis unit, contribute to significant variability. The provision of guidance for establishing and operating LA services requires further exploration.

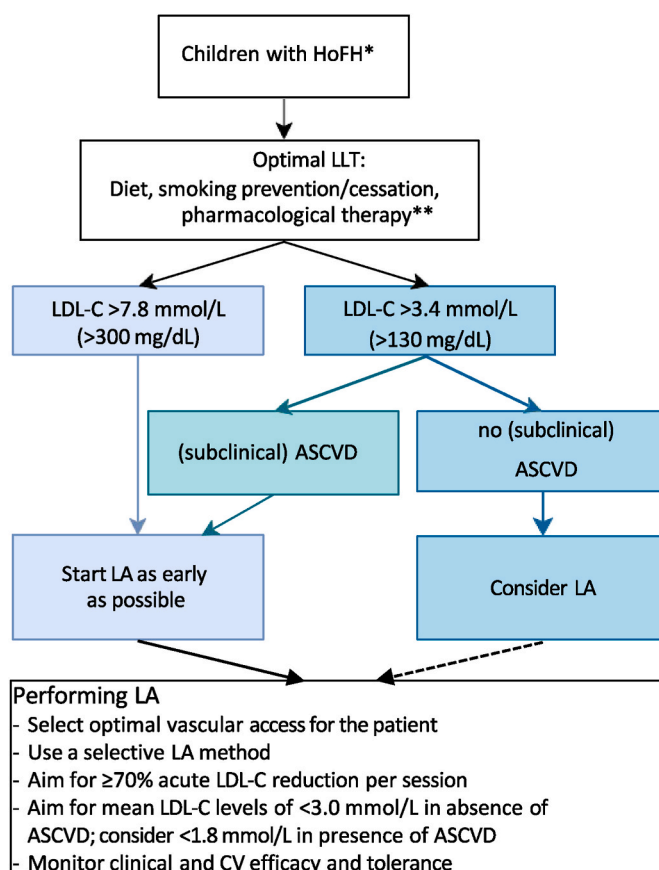


Fig. 2. Graphical abstract.

*Criteria for diagnosis of HoFH [1]. **Optimal pharmacological lipid-lowering therapy is regarded as combination therapy with ezetimibe, statins, proprotein convertase subtilisin/kexin type 9 inhibitors, evinacumab and/or lomitapide, depending on which therapies are available, affordable and tolerable for the patient [2].

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; HoFH, homozygous familial hypercholesterolaemia; LA, lipoprotein apheresis; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy.

Identified topics for future research:

- i. Specific effect of LA on ASCVD in children with HoFH, especially relative to the novel, potent lipid lowering therapies
- ii. Prospective monitoring of different vascular access for LA for efficiency and safety
- iii. Cardiac impact of the additional shunt volume of AVF (and AVG)
- iv. Impact of LA on quality of life and psychosocial health of children
- v. Risk of elevated Lp(a) levels on ASCVD in paediatric HoFH patients
- vi. Cost effectiveness of treatment with LA in children with HoFH

Financial support

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

M. Doortje Reijman: coordinated the project and, Writing – original draft. **D. Meeike Kusters:** coordinated the project and, Writing – original draft. **Jaap W. Groothoff:** coordinated the project and, Writing – original draft. **Klaus Arbeiter:** Writing – review & editing. **Eldad J. Dann:** Writing – review & editing. **Lotte M. de Boer:** Writing – review & editing. **Sarah D. de Ferranti:** Writing – review & editing. **Antonio Gallo:** Writing – review & editing. **Susanne Greber-Platzer:** Writing – review & editing. **Jacob Hartz:** Writing – review & editing. **Lisa C. Hudgins:** Writing – review & editing. **Daiana Ibarretxe:** Writing – review & editing. **Meral Kayikcioglu:** Writing – review & editing. **Reinhard Klingel:** Writing – review & editing. **Genovefa D. Kolovou:** Writing – review & editing. **Jun Oh:** Writing – review & editing. **R. Nils Planken:** Writing – review & editing. **Claudia Stefanutti:** Writing – review & editing. **Christina Taylan:** Writing – review & editing. **Albert Wiegman:** coordinated the project and, Writing – original draft. **Claus Peter Schmitt:** coordinated the project and, Writing – original draft. All authors researched data for the article, contributed substantially to discussion of the content, wrote or reviewed rationales and reviewed the manuscript before submission.

Declaration of competing interest

SDdF received grants from the National Institutes of Health/National Heart, Lung, and Blood Institute of the National Institutes of Health, the Family Heart Foundation and holds a patent for UpToDate, with royalties paid. AG received grants and personal fees from Amgen, Sanofi and Regeneron, Mylan Viatris, MSD, Akcea Therapeutics, Amryt, Servier, Novartis and Ultragenyx. SGP received study funding from Amgen. JH received a research grant from the National Heart, Lung, and Blood Institute of the National Institutes of Health under Award Number K23HL145109. DI received advisory honoraria from Amryt, and honoraria for lectures from Sanofi, Sobi and Novartis. CPS received advisory honoraria from Baxter, Iperboreal and Stadapharma, lecturing honoraria from Fresenius and research funding from Baxter. MK received honoraria from Abbott, Abdi Ibrahim, Amryt, LIB Therapeutics, Novo-Nordisk, and TR-pharma; research funding from Amryt Pharma, and participated in clinical trials with Amgen, Ionis, LIB Therapeutics, Novo Nordisk, Sanofi. RK, as head of the Apheresis Research GmbH, Cologne, Germany received financial grants for scientific research projects, honoraria for consulting and presentation of lectures including travel expenses from the companies Diamed, Cologne, Germany, and Asahi Kasei Medical, Tokyo, Japan. GK has given talks, attended conferences, received consultancy fees and participated in trials sponsored by Amgen, Novartis, Sanofi, Servier, Amryt. AW received research grants from Amgen, Regeneron, Novartis, Silence Therapeutics, Esperion, and Ultragenyx and advisory honoraria from Amryt, and Novartis. KA, EJD, LMDb, JWJ, LCH, GDK, JO, RNP, MDR, CS and CT have nothing to

declare.

Acknowledgments

The authors acknowledge the valuable contributions of the members of the voting group who participated in the Delphi technique: Martin P. Bogsrud (Unit for Cardiac and Cardiovascular Genetics, Oslo University Hospital, Oslo, Norway), Eric Bruckert (Pitié-Salpêtrière Hospital and Sorbonne University, Cardio metabolic Institute, Paris, France), Anna Colpo (Therapeutic Apheresis Unit, Department of Transfusion Medicine, Padova University Hospital, Padova, Italy), Marina Cuchel (Division of Translational Medicine and Human Genetics, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, USA), Tomas Freiburger (Centre of Cardiovascular Surgery and Transplantation, Brno, Czech Republic), Jacques Genest (McGill University Health Center, Montreal, Canada), Samuel S. Gidding (Geisinger Health, Danville, USA), Dieter Haffner (Department of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Pediatric Research Center, Hannover, Germany), Ulrich Laufs (Clinic and Policlinic for Cardiology, University Hospital Leipzig, Leipzig, Germany), Christian Loewe (Department Of Bioimaging and Image-Guided Therapy, Medical University of Vienna, Vienna, Austria), Luis Masana (University Rovira & Virgili, Reus-Tarragona, Spain), Brian McCrindle (The Hospital for Sick Children, University of Toronto, Toronto, Canada), Francesco Sbrana (U.O. Lipoaferesi - Fondazione Toscana “Gabriele Monasterio”, Pisa, Italy), Rukshana Shroff (Great Ormond Street Hospital and Institute of Child Health, University College London, London, United Kingdom), Gilbert Thompson (Imperial College London, London, United Kingdom), Julia Thumfart (Department of Pediatric Gastroenterology, Nephrology and Metabolic Diseases, Charité Universitätsmedizin Berlin, Berlin, Germany), S. Lale Tokgözoğlu (Hacettepe University, Ankara, Turkey), Alpo Vuorio (Department of Medicine, University of Helsinki, Finland), Gerald F. Watts (Medical School, University of Western Australia, and Department of Cardiology, Lipid Disorders Clinic, Royal Perth Hospital, Perth, Australia).

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.atherosclerosis.2024.117525>.

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