Cardiovascular Outcome of Pediatric Patients With Bi-Allelic (Homozygous) Familial Hypercholesterolemia Before and After Initiation of Multimodal Lipid Lowering Therapy Including Lipoprotein Apheresis

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Twenty-four patients with bi-allelic familial hypercholesterolemia commencing chronic lipoprotein apheresis (LA) at a mean age of 8.5 ± 3.1 years were analysed retrospectively and in part prospectively with a mean follow-up of 17.2 ± 5.6 years. Mean age at diagnosis was 6.3 ± 3.4 years. Untreated mean LDL-C concentrations were 752 mg/dl ± 193 mg/dl (19.5 mmol/l ± 5.0 mmol/l). Multimodal lipid lowering therapy including LA resulted in a mean LDL-C concentration of 184 mg/dl (4.8 mmol/l), which represents a 75.5% mean reduction. Proprotein convertase subtilisin/kexin type 9-antibodies contributed in 3 patients to LDL-C lowering with 5 patients remaining to be tested. After commencing chronic LA, 16 patients (67%) remained clinically stable with only subclinical findings of atherosclerotic cardiovascular disease (ASCVD), and neither cardiovascular events, nor need for vascular interventions or surgery. In 19 patients (79%), pathologic findings were detected at the aortic valve (AV), which in the majority were mild. AV replacement was required in 2 patients. Mean Lipoprotein(a) concentration was 42.4 mg/dl, 38% had >50 mg/dl. There was no overt correlation of AV pathologies with other ASCVD complications, or Lipoprotein(a) concentration. Physicochemical elimination of LDL particles by LA appears indispensable for patients with bi-allelic familial hypercholesterolemia and severe hypercholesterolemia to maximize the reduction of LDL-C. In conclusion, in this rare patient group regular assessment of both the AV, as well as all arteries accessible by ultrasound should be performed to adjust the intensity of multimodal lipid lowering therapy with the goal to prevent ASCVD events and aortic surgery. **(Am J Cardiol 2020;136:38−48)**

Elevated low-density lipoprotein cholesterol (LDL-C) concentrations, often exceeding 1,000 mg/dl (26 mmol/l), resulting in infantile or juvenile atherosclerotic cardiovascular disease (ASCVD) represent a typical clinical picture of patients suffering from bi-allelic familial hypercholesterolemia (FH), that is, homozygous FH (hoFH) or compound heterozygous FH (c-hetFH).[1,2,3] The genetic basis of this rare autosomal dominant disorder comprises bi-allelic mutations in the genes encoding LDL receptor (LDLR), apolipoprotein B, proprotein convertase subtilisin/kexin type 9 (PCSK9), or LDLR adaptor protein 1, all resulting in defective or even absent LDLR function. The hoFH or c-hetFH genotype is predictive for a high risk of excessive morbidity and mortality even in early childhood.[2,4,5] Due to

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the high number of possible mutations causing FH and due to the possible involvement of additional genetic, epigenetic, and environmental factors, the phenotype of FH is highly variable, and subjects carrying the same mutation may exhibit substantially different lipid and clinical profiles. The fundamental pathophysiological rationale for multimodal and escalating lipid lowering therapy (LLT) in FH is the reduction of the lifetime ASCVD risk associated with accumulating cholesterol burden. Here we describe the results from a retrospective and partially prospective long-term follow-up of 24 ho/c-hetFH patients who commenced chronic lipoprotein apheresis (LA) as pediatric patients to evaluate cardiovascular outcome and efficacy of long-term multimodal LLT.

Methods

Inclusion criteria for this open, observational retrospective and partially prospective multicenter study were the genetically proven diagnosis of hoFH or c-hetFH, the initiation of chronic LA as pediatric patients, that is, before the age of 18 years, and written informed consent of parents or legal guardians of the participating children and adolescents. There were no exclusion criteria, if these criteria were met. Fourteen specialized nephrological treatment centers including 8 departments for pediatric nephrology at university hospitals across Germany had been identified and agreed to participate. All patients had been approved for LA reimbursement according to German guidelines. Ethical approval for the study had been obtained for every study site.

Diagnoses, clinical characteristics, medication, laboratory data including genetic testing, and cardiovascular events were documented from routine patient files and findings annually. The grading of subclinical ASCVD included small focal plaque at carotids, abdominal aorta, iliofemorals, or renal arteries, or minor AV pathologies (dysplastic functional bicuspid AV, AV regurgitation [AVR] I°, AV stenosis [AVS] I°). Descriptive valve anatomy, semiquantitative grading of AVR, and severity of AVS in combination with clinical symptoms could be analysed during long-term follow-up. 3 grades were used for semi-quantitative evaluation of AVR and AVS, that is, I°, mild, II°, moderate, and III°, severe. Echocardiograms were qualitatively rated as positive or negative regarding a supravalvular component of AVS putatively representing aortic root atheroma. The start of chronic LA was defined as day zero. The most recent information available from the study sites was designated as time of current assessment. Details of lipid measurement are summarized in the online supplement.

Different methods of selective LA were used at initiation of LA, namely temperature optimized double filtration plasmapheresis (DFPP) in 17 patients, HELP apheresis in 2, polyacrylate whole blood adsorption in 2, dextran sulfate plasma adsorption in 2, and dextran sulfate whole blood adsorption in 1. During the further course DFPP became the preferred method. At the time of the current assessment, 23 patients were on regular treatment with DFPP (22 with temperature optimized DFPP, 1 patient with simple DFPP), and 1 patient above the age of 18 years was treated with polyacrylate whole blood adsorption. Additional information on LA techniques can be found in the online supplement.

Results

Twenty-four patients (10 female) with genetically proved hoFH or c-hetFH commencing chronic LA before the age of 15 were enrolled, representing all patients meeting the inclusion criteria in the participating centers. Since birth mean follow-up was 17.2 ± 5.6 years with a range of 9.1 years to 32.2 years. Mean age at time of diagnosis of FH was 6.3 ± 3.4 years (Figure 1). In these, 21 were diagnosed due to clinical findings of lipid deposition in xanthomas or xanthelasmas. Three patients (#4, #9, and #19) were diagnosed 1 to 2 years after birth due to the known hoFH of older siblings. All patients exhibited highly elevated LDL-C concentrations at the time of diagnosis with a mean LDL-C level of 752 ± 193 mg/dl (19.5 ± 5.0 mmol/l) (Figure 2). All patients had a positive family history for ASCVD. 13 patients within this cohort were siblings from 6 parents (Figure 2). In 2 families, (related to patients #15, #18, and #19), siblings with hoFH died at the age of 2, and 7 years respectively before or shortly after LLT was initiated. Biallelic mutations with complete or partial impairment of LDLR function as the underlying genetic cause of FH (suppl. Table 1) were found in all patients. Patients #1-9 shared the same homozygous mutation. Notably the 4 female patients had a substantially lower mean untreated LDL-C concentration (569 mg/dl [14.8 mmol/l]) compared with the 5 male patients (982 mg/dl [25.5 mmol/l]) (suppl. Table 2). Mean Lipoprotein(a) (Lp(a)) level, representing pre-LA concentrations, was 42.4 ± 31.5 mg/dl with a median of 35.8 mg/dl, ranging from 3.0 mg/dl to 119.0 mg/dl. At the time of current analysis, 7 patients had arterial hypertension requiring blood pressure lowering medication, and renal function was without impairment in all patients.

The clinical course of the analysed patients with regard to the cardiovascular status and ASCVD complications is summarized in Figure 1. Additional clinical details are provided in supplementary Table 1. After commencing chronic LA, 16 patients (67%; 7 female), had remained clinically stable and free of cardiovascular events, without the need for vascular interventions or surgery or any detection of ASCVD progression. However, in 14 of these patients, findings of subclinical ASCVD were documented, for example, small focal plaque at carotids, abdominal aorta, iliofemorals, or renal arteries, or minor AV pathologies (i.e., dysplastic functional bicuspid AV, AVR I°, or AVS I°). So far, in 2 patients no subclinical ASCVD was documented by routine imaging techniques. Clinically relevant ASCVD progression occurred in 8 patients (female: 3, 38%) with cardiovascular events (Figure 1, Table 2, suppl. Table 2). Patient #20 (female) exhibited the most severe course with rapidly progressive ASCVD already at the time of diagnosis before commencing LA. Death occurred after 2.5 years with weekly LA due to progressive ASCVD in coronary, peripheral and cerebrovascular territories. ASCVD included myocardial infarction in 3 patients (#12, #20, and #21) and subsegmental pulmonary embolism in 1 patient (#6,

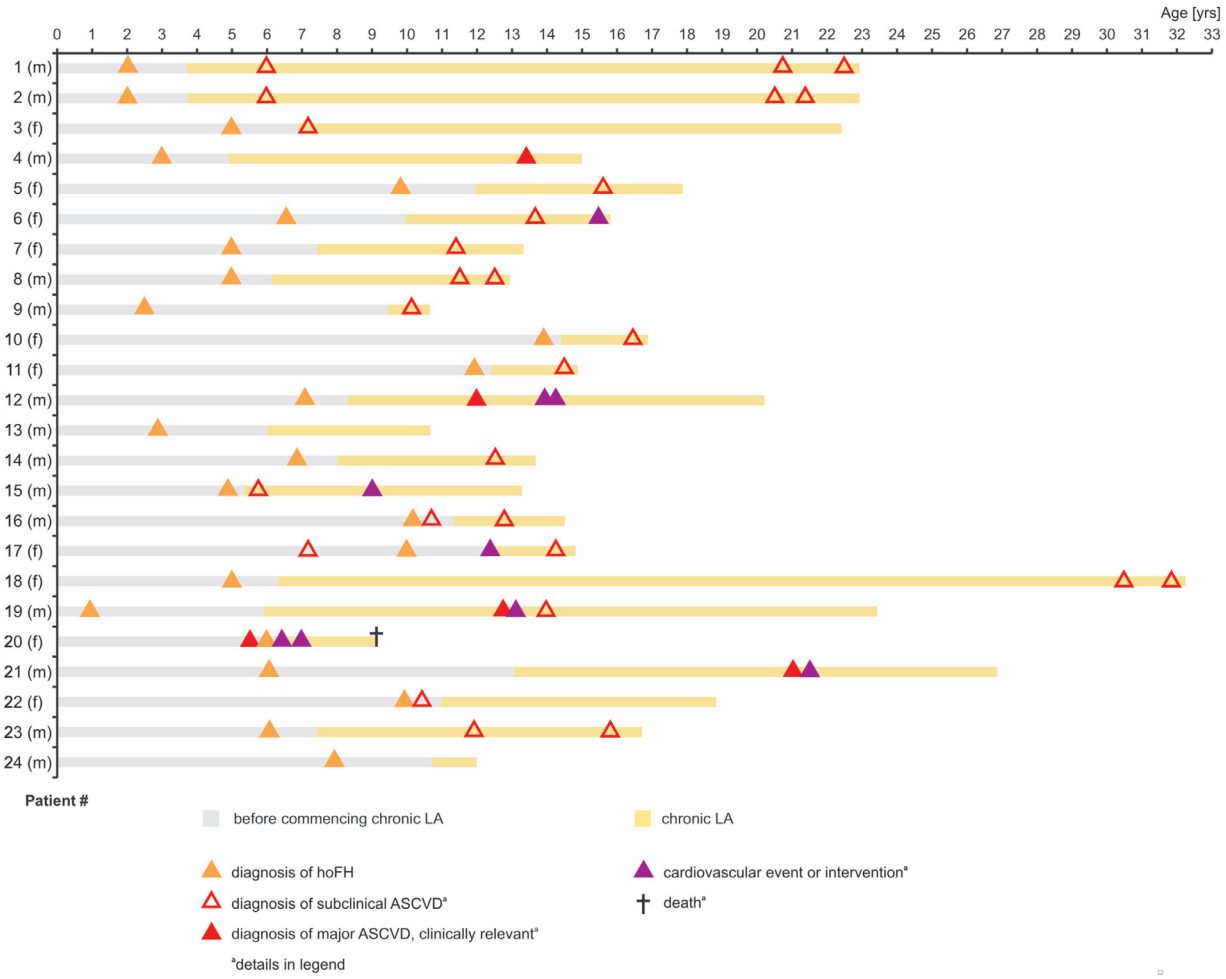

Figure 1. Patients' clinical courses before and after commencing chronic lipoprotein apheresis. Triangles represent diagnoses of ho/c-hetFH, subclinical or clinically relevant findings of ASCVD both including AV pathologies, or cardiovascular events or interventions. Total length of horizontal bars indicates patients' age at time of current analysis. [a]Details of the clinical course of individual patients is available in the supplementary Table 2. Gender is indicated with f, female, m, male.

Figure 1). The number of patients was too small to assess a gender effect.

Pathologic findings at the AV were detected in 19 patients (79%). Results are summarized in Figure 3 and Table 2. AV was bicuspid in 1 patient, or had become dysplastic and functional bicuspid in 5 patients (22%). AVR was found in 18 patients (75%). It was asymptomatic and mild (I°) in most patients (n = 14, 58%). AVS was detected in 10 patients (42%). AVS was mild in 6 patients (#3, #10, #11, #17, #20, #23), partially with signs of leaflet calcification. Supravalvular components of atheromatous lesions at the aortic root contributing to AVS were described in 7 patients. In 4 patients it was associated with dysplastic, functional bicuspid morphology of the AV. In patient #4, 8 years after initiation of LA, AVS was diagnosed without any other ASCVD manifestation at the age of 13. Patient #12 who presented with moderate AVS at the age of 14, additionally suffered myocardial infarction with coronary stenting. An implantable cardioverter-defibrillator was necessary 4 months later. Patient #15 exhibited a dysplastic, functional bicuspid AV with regurgitation which required AV replacement due to severe AVS at the age of 9, approximately 4 years after initiation of chronic LA. His brother also affected by hoFH with a quite similar manifestation suffered, before being disgnosed, sudden cardiovascular death at the age of 2 due to a huge aortic root atheroma and AVS. In patient #19, also with a dysplastic, functional bicuspid aortic valve with regurgitation, severe valvular, and supravalvular AVS was diagnosed at 12 years, 6 years after initiation of LA. AV was replaced 4 months after diagnosis of AVS at the age of 13. In this family clinical courses of 3 siblings were remarkably different. His older sister (#18) was treated with chronic LA for almost 26 years with only subclinical findings of ASCVD in recent years. A second sister died due to myocardial infarction at the age of 7, a few months after initiation of LA. Figure 3 shows the distribution of Lp(a) concentrations for all patients and for the subgroups in Figure 3. 13 patients (54%) exhibited a Lp(a) level above 30 mg/dl and 9 patients (38%) exceeded 50 mg/dl. The 4 patients with AVS II° or III° all had Lp(a) levels below 30 mg/dl. Exact Lp(a) concentrations for all individual patients are shown in supplementary Table 2.

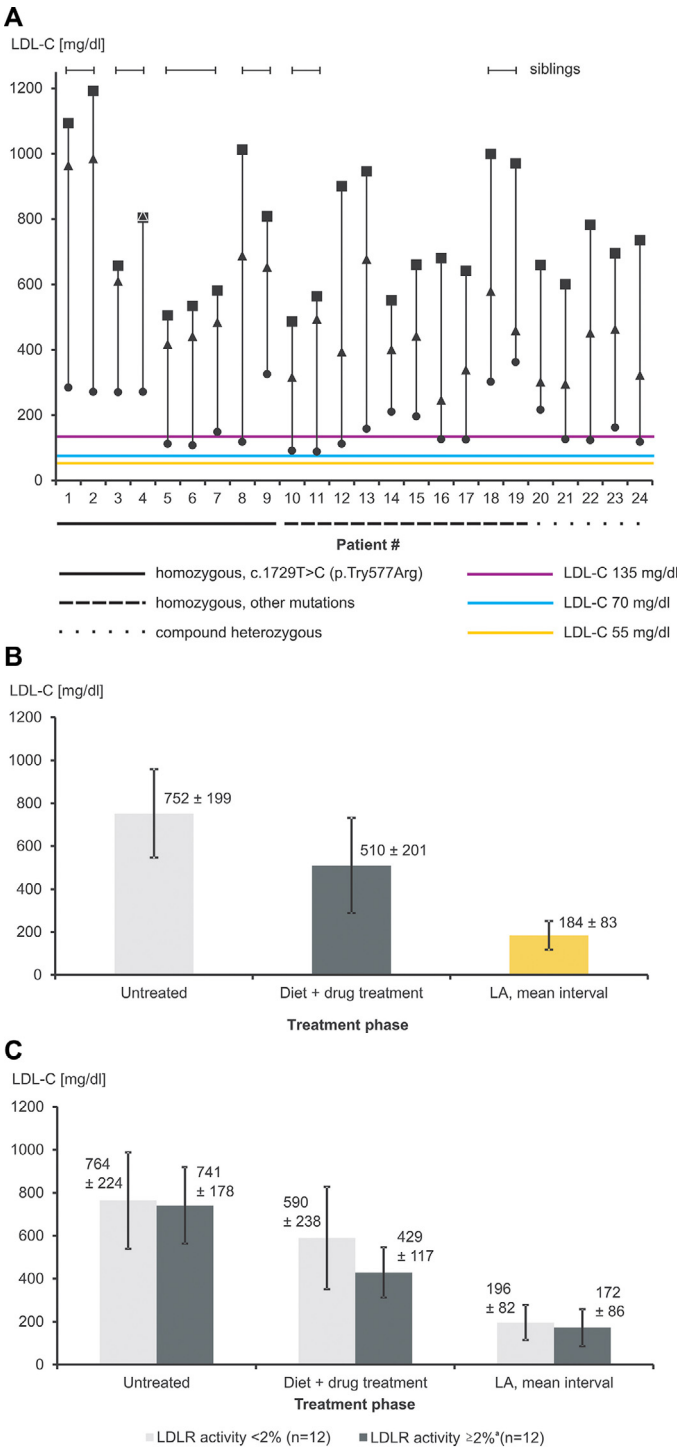

Figure 2. **(A)** Results of lipid lowering therapy in 24 patients who commenced chronic lipoprotein apheresis (LA) treatment before the age of 15. Squares: baseline LDL-C concentrations before any treatment; triangles: LDL-C concentrations after lifestyle counselling including diet, and drug treatment with statins and/or ezetemibe, prior to commencing LA; circles: average LDL-C concentrations with LA. Patients who exhibited mutation c.1729T>C. (p.Try-p577Arg), other homozygous mutations, or compound heterozygous mutations are indicated with continuous, dashed lines, or dotted lines respectively. Mean LDL-C concentrations at different phases of lipid lowering therapy with lipoprotein apheresis (LA) as final escalating step. Mean LDL-C represents interval mean calculated according to the Kroon formula,[6] [see online supplement] after commencing regular LA. Mean LDL-C concentration pre-LA was 245.5 mg/dl ± 98.4 mg/dl, and post-LA was 71.6 mg/dl ± 35.8 mg/dl. Error bars indicate SD. **(B)** All patients. (C) Patients stratified by mutation and putative LDLR activity (see supplementary Table 1). Left bars: putative LDLR activity <2% (#1-9, #15-17), right bars: putative LDLR ≥ 2%. [a]includes mutations with not exactly characterized LDLR activity.

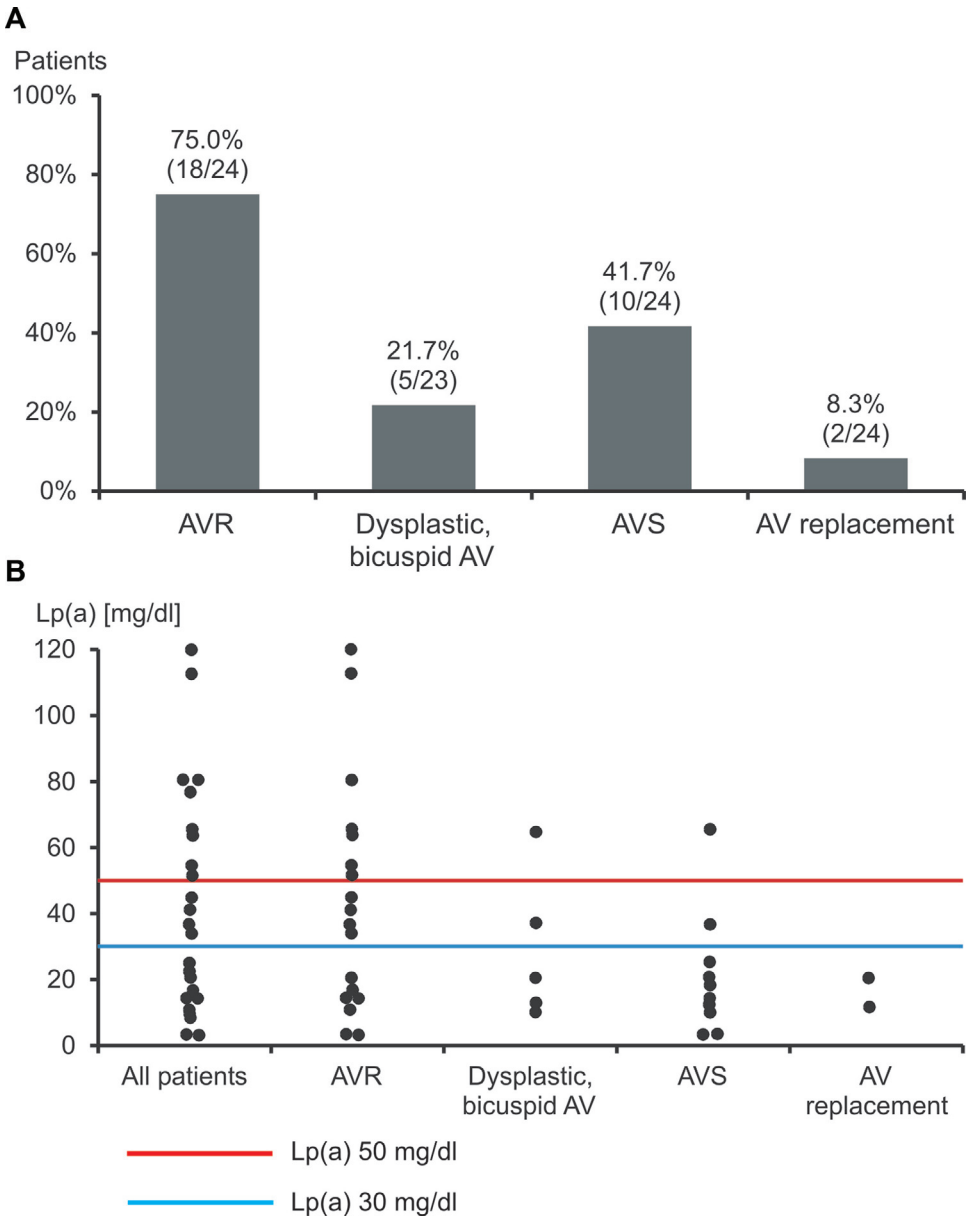

Figure 3. (A) Proportions of patients exhibiting aortic valve regurgitation (AVR), dysplastic and functional bicuspid AV, AV stenosis (AVS) including supravalvular components, and patients with AV replacement. Numbers in brackets show absolute numbers of patients. **(B)** Lp(a) values before lipoprotein apheresis for all patients and within the subgroups shown in Figure 3. The lines depict Lp(a) concentrations of 30 mg/dl (threshold of increasing Lp(a) associated risk, LDL-C mediated risk prevails) and 50 mg/dl (threshold of almost linear further increase of Lp(a) associated risk).

After diagnosis of hoFH or c-hetFH, treatment with statins, ezetimibe, or a combination of both was initiated in all patients (Table 1), achieving a mean lowering of LDL-C by 32.2% ± 18.0%. Despite the medication mean LDL-C concentration remained highly elevated with 510 ± 201 mg/dl (13.2 ± 5.2 mmol/l) (Figure 2) leading to initiation of LA. In 21 patients lipid lowering medication was continued with chronic LA (Table 1). Statins were discontinued in patients #1-4 in accord with absent LDLR function. Patients #12 and #21, who both suffered myocardial infarctions despite long-term weekly LA, received the PCSK9 inhibiting antibody evolocumab for further escalation of multimodal LLT (Figure 1). Patient #13 received evolocumab since the age of 10. Based on the underlying mutation, a remaining LDLR activity of 5-15% can be assumed in all 3 patients (supplementary Table 1). Additional reduction of mean LDL-C levels by 35% (#12), 19% (#13), and 42% (#21), respectively was achieved. Weekly intervals of LA remained without change. In accord with the mutational status (supplementary Table 1) evolocumab was not effective in patients #3, #5, #15 to #19, and #22, or was not tried in #1, #2, and #4, and #6 to #9. Based on the genetic findings it might be an additional treatment option to intensify LLT in patients #10, #11, #14, #23, and #24 but had to be postponed due to parents' concerns. The LDLR activity as determined by patient mutations had a marginally

Table 1
Lipid lowering therapy at time of commencing LA and at presentation for current analysis

Patient	Medical Treatment Until Commencing LA	At Time of Commencing LA					Years With LA Until Current Analysis	Current Medical Treatment	At Presentation for Current Analysis				
		Age (yrs)	Size (cm)	Weight (kg)	Treatment Frequency	Treated Plasma Volume (l)			Age (yrs)	Size (cm)	Weight (kg)	Treatment frequency	Treated plasma volume (l)
1	A	3.7	92	13.3	w	0.6	19.2	EZ	22.9	165	57.0	w	4.5
2	A	3.7	92	11.7	w	0.6	19.2	EZ	22.9	165	53.0	w	4.5
3*	EZ	6.9	117	21.4	w2	1.2	15.5	0	22.4	175	59.8	w	3.0
4†	S + EZ	4.9	107	18.1	2w	1.2	10.1	0	15.0	168	55.6	w	3.0
5	P	11.9	149	39.0	w2	1.8	5.9	A + EZ	17.9	156	51.9	w2	3.4
6	A + EZ	10.0	138	37.2	w2	2.7	5.9	A + EZ	15.8	152	63.0	w2	4.0
7	A + EZ	7.4	122	28.1	w2	1.5	5.9	A + EZ	13.3	150	58.4	w2	3.1
8	P	6.1	113	18.0	w	1.2	6.8	A + EZ	12.9	150	43.6	w2	2.0
9	P	9.4	95	13.8	w	1.0	1.2	P	10.7	142	39.1	w	2.0
10	A + EZ	14.4	142	54.3	w	2.3	2.5	EZ	16.9	152	72.7	w2	4.2
11	A	12.4	142	46.1	w	2.0	2.5	EZ	14.9	158	68.8	w2	4.0
12	P	8.3	125	26.5	w	2.2	11.9	A + EV	20.2	174	73.0	w	4.5
13	A + EZ	6.0	98	14.3	w	2.6	4.6	A + EZ + EV	10.7	137	34.8	w	3.2
14	A	8.0	120	23.0	w	2.0	5.7	A	13.7	158	49.1	w	2.5
15	P + EZ	5.3	117	24.0	w	2.0	7.9	S + EZ	13.3	163	86.9	w2	3.0
16	A + EZ	11.3	144	40.3	w	3.0	3.2	A + EZ	14.5	162	54.0	w2	3.5
17	A	12.5	146	32.0	w2	1.0	2.3	A + EZ	14.8	152	39.1	w2	1.8
18	S	6.3	n.d.	n.d.	w	n.d.	25.9	A + EZ	32.2	153	54.0	w	3.5
19	S + EZ	5.9	n.d.	n.d.	w	n.d.	17.5	A + EZ	23.4	175	61.0	w	3.5
20‡	A + EZ	6.6	124	27.0	w	1.5	2.5‡	A + EZ	9.1‡	132‡	22.7‡	w‡	1.5‡
21	P	13.1	166	64.0	w	3.0	13.8	A + EZ + EV	26.9	176	144.0	w	4.0
22	S + EZ	11.0	144	32.4	w	2.2	7.9	R + EZ	18.8	163	58.0	w	3.4
23§	P	7.4	120	21.0	w2	2.0	9.3	0	16.7	174	54.8	w2	3.0
24	R + EZ	10.7	131	32.0	w	1.4	1.3	R + EZ	12.0	135	35.0	w	1.4

Abbreviations: A = atorvastatin; EV = evolocumab; EZ = ezetimibe; P = pravastatin; R = rosuvastatin; S = simvastatin; yrs = years.

Mean treated plasma volume at commencing LA was 1,782 ml (±716 ml) corresponding to 1.6 (±0.8) estimated plasma volumes per treatment, mean estimated plasma volume was 1,251 ml (±557 ml). Initial treatment volumes had a range from 600 ml plasma per treatment in the patient with the smallest body weight (#2, 11.7 kg, estimated plasma volume 490 ml) to 3,000 ml (#21, 64.0 kg, estimated plasma volume 2,690 ml). Mean treated plasma volume at current analysis was 3,188 ml (±932 ml) corresponding to 1.4 (±0.3) estimated plasma volumes per treatment. Treatment volume at current analysis ranged from 1,500 ml to 4,500 ml per treatment. Treatment frequencies of LA are indicated as w, weekly, 2w, bi-weekly, and w2, twice per week. Plasma volumes were evaluated per treatment session.

* statins, EZ, EV were not effective, due to logistic reasons LA frequency remained at a weekly regimen.

† statins, EZ were not effective.

‡ data at last LA, patient died at the age of 9 years.

§ patient's parents refused to continue taking any medication.

significant impact on the efficacy of drug treatment (Figure 2). In the group of patients with LDLR activity <2%, LDL-C reduction was 22.8% versus 42.1% in the remaining patients ($p = 0.048$ vs untreated LDL-C). Standardization of escalating LLT, for example, initial or subsequent choice of a high-intensity statin, early combination with ezetimibe, or finally a trial with a PCSK9 antibody had a clinically relevant effect of additional LDL-C reduction (Table 1).

Mean age at commencing LA was 8.5 ± 3.1 years (Figure 1, Table 1). The mean time of patients receiving chronic LA until the current analysis was 8.7 ± 6.7 years, with a range from 1.2 years to 25.9 years. At time of commencing LA, most patients received LA treatment weekly or twice per week (6 patients, Table 1). The mean frequency was 1.2 ± 0.5 per week. Treated plasma volumes were regularly adjusted to the patients' physical parameters, and achieved LDL-C reduction (Table 1, Figure 2). At the time of the current analysis, treatment frequencies were weekly in 14 patients and twice per week in 10 patients (Table 1). The mean frequency increased to 1.4 ± 0.5 per week. Multimodal LLT including chronic LA resulted in a 75.5% (± 8.9%) mean reduction of LDL-C levels compared with untreated patients (Figure 2). Mean LDL-C reduction achieved by a single LA session was 62.1% (± 15.5%), with mean pre-LA LDL-C levels of 246 ± 98 mg/dl (6.4 ± 2.5 mmol/l), and mean post-LA LDL-C levels of 72 ± 36 mg/dl (1.9 ± 0.9 mmol/l) (Figure 2). During the long-term course of regular LA, pre-LA LDL-C levels reached a rather constant steady-state level. The current mean interval LDL-C level showed a decrease to 184 ± 83 mg/dl (4.8 ± 2.1 mmol/l), that is, a further reduction of 63.9% (± 15.5%) compared with the level before commencing LA. In 11 patients (46%; #5, #6, #8, #10 − #12, #16, #17, #21, #22, and #24) multimodal therapy including lipid lowering medication and LA resulted in mean LDL-C concentrations below the pediatric target of 135 mg/dl (3.5 mmol/l) (Figure 2, suppl. Table 1). thirteen of 24 patients still had a substantial distance to target LDL-C concentrations, and thus maintained a substantial LDL-C-related residual cardiovascular risk. Figures get even worse regarding the adult target recommendations for high risk patients of 70 mg/dl (1.8 mmol/l) in the US or 55 mg/dl (1.4 mmol/l) in Europe. The LDLR activity as determined by patient mutations had no effect on the efficacy of LA treatment (Figure 2).

Chronic LA treatment was well tolerated by all patients after analysis of in total 217.1 patient years covering more than 13,500 LA treatment sessions. The most frequent adverse events were related to vascular access. Due to the small calibre of cubital veins in young children, in 20 patients creation of an arteriovenous fistula (AVF) was performed. In total 24 complications occurred in 11 patients, which necessitated thrombectomy, percutaneous intervention, or surgical revision. In 13 patients long-term patency of AVFs was free of complications. A mean figure of 0.11 AVF complications per documented patient year resulted. Figures appear favourable compared with pediatric hemodialysis patients, for whom AVFs have been recommended as first choice, if anatomically feasible.[7] A permanent central venous catheter was necessary for vascular access in 3 patients. Due to frailty of blood vessels creation of an AVF was not possible in patients #15, and #20. In patient #23 a catheter was used for 2 years without complications due to the child's temporary refusal of AVF puncture. In total 3 septic catheter complications occurred in 2 of these patients. In patient #15 3 thrombotic catheter complications occurred, finally involving the superior vena cava. Long-term oral anticoagulation was required, additional to the indication related to his mechanic AV replacement. In total use of a permanent catheter for regular LA was associated with 0.4 thrombotic or septic complications per documented patient year. Two patients experienced symptoms of a severe allergic reaction when LA had been performed with a whole blood adsorption system. Minor adverse events typically associated with out-patient LA treatment[8] comprised transient hypotension, dizziness, hematoma at vascular access, or nausea and were not assessed in detail. Monitoring of hemoglobin, ferritin, and transferrin saturation was regularly performed as recommended.[9] At the time of the current analysis 10 patients received iron supplementation. Mean height at LA initiation was 125 ± 20 cm with a mean body weight of 28.9 ± 13.7 kg and a body mass index (BMI) of 17.5 ± 3.3 kg/m^2. BMI increased to 23.6 ± 7.2 kg/m^2 at the most recent documentation. Height of all patients was within the range of international growth references for children and adolescents, which shows that long-term LA had no overt negative impact on normal growth.[10] In few patients, adipose values of weight and BMI developed in the long-term due to issues of compliance with lifestyle recommendations and dietary restrictions. Any impact on the future clinical course remains hypothetical.

Discussion

Severe hypercholesterolemia and likelihood of premature death from ASCVD complications still make bi-allelic FH, that is, hoFH or c-hetFH a therapeutic challenge. Twenty-four patients were included in this retrospective and partly prospective investigation, who commenced regular LA treatment before the mean age of 9 years. Long-term clinical profiles were analysed with a mean follow-up of 17.2 years since birth. The diagnosis of FH in general is classified as high-risk morbid condition by the 2019 European dyslipidemia guidelines.[11] The 2018 American Heart Association (AHA) dyslipidemia guidelines also classify FH as a high-risk condition, and define persistently elevated LDL-C ≥ 160 mg/dl (≥4.1 mmol/l) and family history of premature ASCVD as risk enhancers.[12] In children with hoFH or c-hetFH above 10 years of age a LDL-C target <135 mg/dl (<3.5 mmol/l) has been suggested.[5,11] This appears as an unsatisfactory compromise with respect to the current LDL-C target of <55 mg/dl (<1.4 mmol/l) for adult FH patients with established ASCVD according to the 2019 European guidelines.[11] The 2018 AHA guidelines had set the <70 mg/dl (<1.8 mmol/l) threshold for adult patients which was in place in Europe since 2016.[12]

Pre-treatment LDL-C concentrations in the investigated 24 patients were averaging 752 mg/dl (19.5 mmol/l). In patients #1 to 9 sharing the same homozygous mutation with <2% LDLR function, mean untreated LDL-C concentrations were 42% lower in females. In a large cohort of

Table 2
Morphology of the aortic valve (AV), diagnoses and findings regarding the AV and the aortic arch

Patient#	AV Morphology	AVR With Graduation		AVS With Graduation And Findings Regarding the Aortic Root, Before Commencing Chronic LA		AVS With Graduation And Findings Regarding The Aortic Root, During Chronic Regular LA,		AV Replacement	
			Age (yrs)*		Age (yrs)		Age (yrs)		Age (yrs)
1	Tricuspid	I°	20	0		0		0	
2	Bicuspid	I°	21	0		0		0	
3	Tricuspid	I°	7	0		I°	7	0	
4	Tricuspid	I°–II°	13	0		I°–II° (supravalvular component)	13	0	
5	Tricuspid	I°	15	0		0		0	
6	Tricuspid	I°	13	0		0		0	
7	Tricuspid	I°	11	0		0		0	
8	Tricuspid	I°	11	0		0		0	
9	Tricuspid	I°	10	0		0		0	
10	Bicuspid†	I°	16	0		I° (supravalvular component)	16	0	
11	Bicuspid†	I°	14	0		I°	14	0	
12	Bicuspid†	I°	12	0		II° (supravalvular component)	12	0	
13	Tricuspid	0		0		0		0	
14	Tricuspid	I°	13	0		0		0	
15	Bicuspid†	II°	6	0		III° (supravalvular component)	9	AV replacement, mechanical valve	9
16	Tricuspid	0		0		0		0	
17	Tricuspid	I°	7	I°		I°, no change		0	
18	Tricuspid	I°	32	0		0		0	
19	Bicuspid†	II°–III°	12	0		III° (supravalvular component)	12	AV replacement, mechanical valve	13
20	Tricuspid	I°	6	I° (supravalvular component)		I°, (supravalvular component), no change		0	
21	Tricuspid	0		0		0		0	
22	Tricuspid	0		0		0		0	
23	Tricuspid	0		0		I° (supravalvular component)	16	0	
24	Tricuspid	0		0		0		0	

Abbreviations: AV = aortic valve; AVR = AV regurgitation; AVS = AV stenosis.

The respective diagnosis, intervention or event is given with the age at the appropriate time. For semi-quantitative evaluation of AV regurgitation (AVR) and AV stenosis (AVS) 3 grades were used, i.e. I°, mild, II°, moderate, and III°, severe (following recommendations of the German Society for Pediatric Cardiology). Supravalvular component of AVS refers to findings of stenosing atheromatous lesions at the aortic root close to the AV.

* age at time of diagnosis;

† dysplastic, functional bicuspid.

167 patients from South Africa and the Netherlands, not including the mutation of patients #1 to 9, such LDLR independent gender effects were not documented.[13] In this cohort 2 mutations were represented by 35, or 8 patients of mixed gender. LDL-C concentrations of males and females were equal, or 27% higher in females, respectively. This observation merits further research.

Multimodal LLT including chronic LA with a final mean frequency of 1.4 treatments per week resulted in a mean LDL-C concentration of 184 mg/dl (4.8 mmol/l), which represents a 75.5% mean reduction compared with the untreated baseline. The consequence should be a huge reduction of patient ASCVD risk, as a 39 mg/dl (1 mmol/l) change in LDL-C concentration has been demonstrated to produce a clinically meaningful 20% to 25% reduction in the relative risk of cardiovascular events.[14] LDL-C reduction was 32.2% with diet and medication alone. After commencing regular LA an additional reduction of 63.9% LDL-C were achieved. During LA, even mean pre-LA LDL-C with 246 mg/dl (6.4 mmol/l) showed 52% reduction compared with the concentration before commencing LA. Higher frequency of regular LA and continuous optimization of concomitant components of LLT are putative factors of the effectively lowered LDL-C concentrations.[15] A long-term follow-up of 133 patients with hoFH from South Africa and the UK confirmed that the risks of death from any cause and from cardiovascular causes, representing 80% of deaths, were determined by the on-treatment level of LDL-C.[16] Therefore, a significant unmet clinical need regarding LDL-C target attainment remains. The threshold of 70 mg/dl (1.8 mmol/l) LDL-C concentration was attributed with major clinical relevance for the process of atherosclerosis, because LDL-C concentrations going below were associated with reduction of atheroma volume as revealed by intravascular ultrasound studies.[17]

PCSK9-inhibition with monoclonal antibodies has become a standard of LLT. Effective treatment depends upon LDLR function. Evolocumab contributed to the LDL-C lowering in 3 patients, was or is putatively ineffective in 15 patients, and remains to be tested in 5 patients. The microsomal triglyceride transfer protein (MTP) inhibitor lomitapide could be another LDLR independent option for combined drug treatment, or adjunctive to LA in hoFH or c-hetFH patients.[18,19] Lomitapide is currently not available in Germany. Another drug to treat FH in the future irrespective of LDLR function might be Evinacumab, an angiopoietin-like 3 (ANGPTL3) blocking antibody.[20]

AVS is the most common type of valvular heart disease.[21] The prevalence of AVS is increasing with age up to 2.8% in adults over 75 years of age. Prevalence of AVS was 41.7% with a mean age of first diagnosis at 11 years in these 24 highly select patients with bi-allelic FH. AVS had a supravalvular component in one third putatively reflecting progression of aortic root atheromas, which were described in 50% to 70% in hoFH patients.[22] Bicuspid AV is a congenital heart anomaly, with a prevalence of 0.5% to 2% in the population.[23] Atherosclerotic mechanisms of inflammation and calcification following cholesterol deposition can cause cuspal fusion, resulting in dysplastic functional bicuspid AV morphology and AVR, which must be assumed in 5 patients (21%) of this study. More than 25% of patients with bicuspid AV undergo aortic surgery, often concurrent with aortic valve replacement.[24] 2 of the 5 patients already needed AV replacement. Notably, patients #1 and #2, a pair of monozygotic twins had different morphologies of the AV, which was described in few cases before.[23]

Lp(a) is an independent causal cardiovascular risk factor, enhancing the risk of premature or progressive ASCVD.[25,26] Lp(a) has all the atherogenic properties of the LDL particle, which is reinforced by bound oxidized phospholipids, accumulation in the vascular wall, and potential prothrombotic effects.[25,26] In addition to ASCVD, there is also an association of Lp(a) with progressive AV calcification and stenosis.[27] If patients with FH additionally exhibit increased mean concentrations of Lp(a) this might be associated with an elevated risk of ASCVD.[28] Above 30 mg/dl an increasing Lp(a)-associated risk is observed in genetically homogeneous Caucasian populations. Above 50 mg/dl the curve of Lp(a) and ASCVD risk association follows an almost linear fashion. Although mean Lp(a) was increased with 42.4 mg/dl in these 24 patients a separate role of Lp(a) in AV pathologies cannot be disentangled. In patient #14 exhibiting an extremely progressive and fatal course of ASCVD, Lp(a) concentration was only 15 mg/dl. In contrast, patients #1 and #2 exhibiting in general a very favorable course with only subclinical findings of ASCVD until their current age of 23 years, had Lp(a) concentrations >100 mg/dl. For those patients in particular, LA may be the best available treatment option because Lp(a) is eliminated with the same efficacy as LDL-C. Regular pulsed physicochemical elimination of lipoproteins in particular oxidized LDL particles by LA can improve endothelial barrier function and reduce inflammatory changes. Positive hemorheological effects improving endothelial function represent another important mechanism of LA action.[29]

In conclusion, LA still appears indispensable for patients with bi-allelic FH and severe hypercholesterolemia to maximize the reduction of LDL-C. LA was safe in this cohort of 24 patients commencing regular LA at the mean age of 8.5 years during a mean observation period of 8.7 years. No overt correlation was observed of the development or progression of AV pathologies with other ASCVD complications, or Lp(a) concentration. Regular standardized assessment of both the AV, and all arteries which are accessible by ultrasound should be performed to adjust the intensity of multimodal LLT with the goal to prevent ASCVD progression, potentially leading to serious clinical sequelae. Prevention of aortic surgery is a major goal. Attainment of current LDL-C targets would be desirable from a pathophysiological point of view, but still represent an unmet clinical need for the vast majority of this rare patient group. Continuous attention to all components of multimodal LLT is mandatory for the long-term treatment of patients with bi-allelic FH. Major issues for patient therapy optimization are standardized use of all available drugs, and regular LA treatment considering biweekly schedules. Delicate fine-tuning of the patient intensity of multimodal LLT is required to balance LDL-C target attainment across from the related psychosocial burden for children or adolescents and their families. New drugs, in particular those targeting LDLR independent metabolic pathways should be prospectively investigated in well characterized patient cohorts.

Data statement: Consent to use clinical, laboratory and genetic information of the, since childhood, investigated patients suffering from a rare hereditary disease included the assurance that raw data would remain confidential and would not be shared with third parties.

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Conflict of Interest Statement

Andreas Heibges and Reinhard Klingel are employees of Apheresis Research Institute, which received research grants from Diamed, Cologne Germany, and Asahi Kasei Medical, Tokyo Japan. For all other authors none conflict of interest is declared.

Supplementary materials

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