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ORIGINAL ARTICLE
Epidemiology and prevention

Management of children with heterozygous familial hypercholesterolaemia worldwide: a meta-analysis

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Aims

Heterozygous familial hypercholesterolaemia (HeFH) is one of the most frequent monogenic disorders in the world, leading to premature atherosclerotic cardiovascular diseases. The aim of this meta-analysis was to evaluate the efficacy and safety of lipid-lowering therapy (LLT) and achievement of low density lipoprotein cholesterol (LDL-C) goal in children with HeFH.

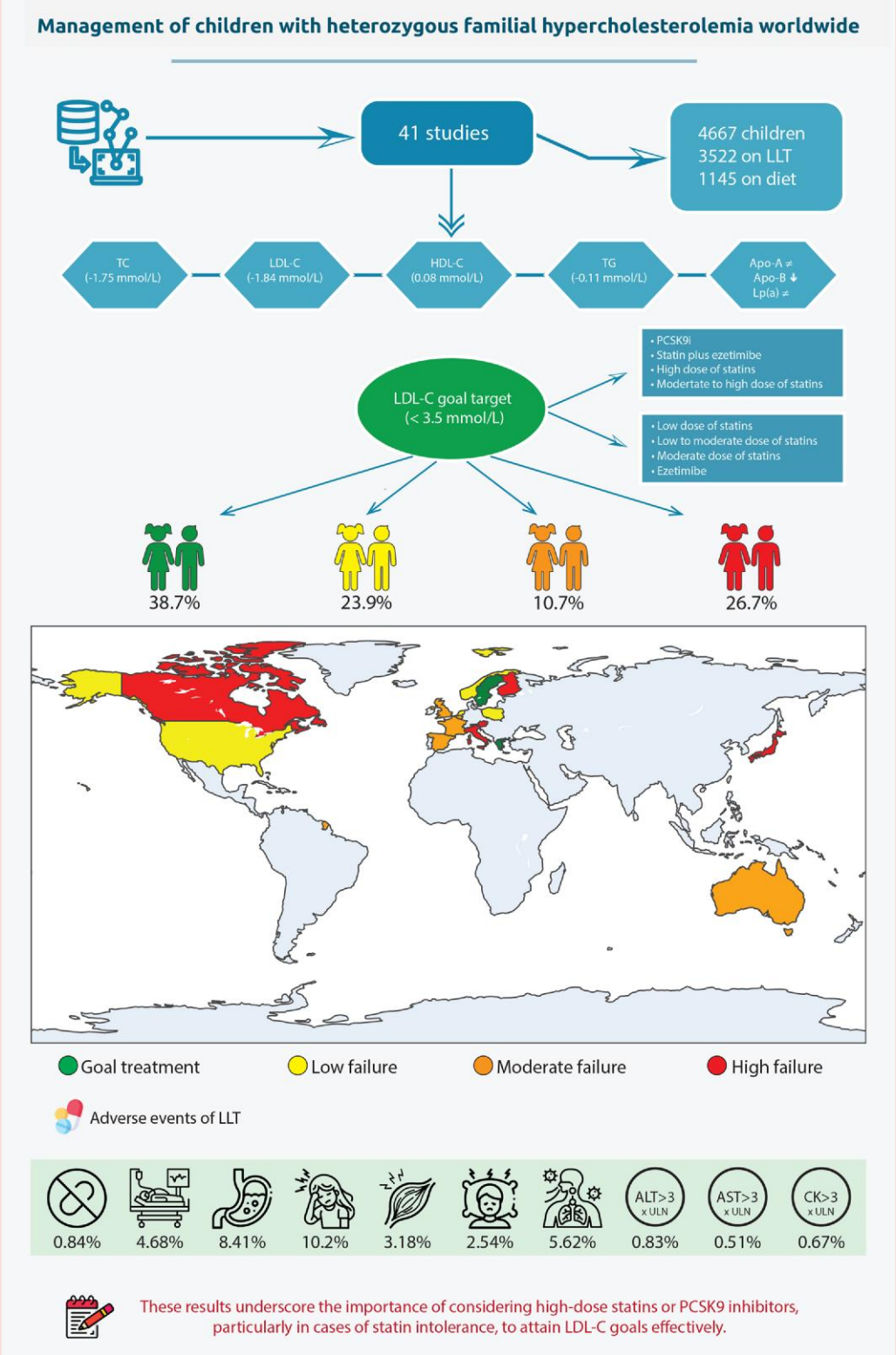
Methods and results

The main endpoint was efficacy of goal achievement for LDL-C and other lipid parameters: total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), apolipoprotein B, and lipoprotein(a), and the LLT safety [adverse events (AEs), including endocrine function, and growth indices]. The secondary endpoint was an effect of LLT on attainment of LDL-C goal treatment (<3.5 mmol/L/130 mg/dL). A total of 41 studies with 4667 paediatric patients at mean age 12.08 ± 2.4 years were included. Seventeen reported the efficacy and safety of LLT therapy compared to control, while the remaining assessed LLT through pre- and post-treatment. At median follow-up of 18.8 months, the group on LLT had significantly higher mean reductions of TC, LDL-C, TG, and increased HDL-C compared to control [−1.75 mmol/L (−67.7 mg/dL), −1.84 mmol/L (−71.2 mg/dL), −0.11 mmol/L (−9.74 mg/dL), 0.08 mmol/L (3.1 mg/dL), respectively, $P < 0.001$ for all]. In the subgroup analysis according to different types of LLT, we observed a significantly higher mean reduction of LDL-C by statin combined with ezetimibe treatment, followed by statins in monotherapy, PCSK9 inhibitors, and monotherapy with ezetimibe [−2.48 mmol/L (−95.9 mg/dL), −2.16 mmol/L (−83.5 mg/dL), −2.03 mmol/L (−78.5 mg/dL), and −1.50 mmol/L (−58 mg/dL), respectively, test for overall effect: $P < 0.001$]. The pooled LDL-C was reduced by 33.44% [−2.14 mmol/L (−82.8 mg/dL), $P < 0.001$] and failed to reach the goal treatment (<3.5 mmol/L) by 12.6% (95% CI, 12.4–12.9%). A total of 38.7% of children achieved the LDL-C goal, 23.9% fell short by up to 10%, 10.7% experienced moderate failure (were over the LDL-C target between >10% and 20%), and 26.7% failed by more than 20% to reach the LDL-C target. When comparing different regions, only Sweden and Greece achieved the LDL-C goal < 3.5 mmol/L in the follow-up. Netherlands, Norway, Poland, USA, UK, France, Spain, Belgium, and Austria required 2.2%, 3.4%, 3.5%, 8.9%, 10.2%, 11.2%, 11.2%, 15%, and 19.4% additional reduction in LDL-C respectively to achieve the LDL-C goal of < 3.5 mmol/L. All other countries required over 20% additional reduction in LDL-C to achieve the LDL-C goal. For other investigated countries, over 20% mean LDL-C reduction was required. All parameters related to endocrine function and demographic indices were unaffected by LLT therapy ($P > 0.05$). The AEs were not reported significantly higher when compared to the control, and the prevalence of therapy discontinuation was only 0.8%.

Conclusion

Despite the efficacy of LLT in children with HeFH and the low occurrence of discontinuation-related adverse events, achieving LDL-C treatment goals was relatively rare, with large differences between the investigated countries. These results underscore the importance of considering early combination therapy of statins and ezetimibe, and PCSK9 inhibitors (if available) to attain LDL-C goals effectively.

Graphical abstract



Keywords Heterozygous familial hypercholesterolaemia • Children • Efficacity • Safety • LDL-C target

Introduction

Heterozygous familial hypercholesterolaemia (HeFH) is the most common genetic metabolic disorder globally, with even 30 million patients affected with raised elevated low density lipoprotein cholesterol (LDL-C) levels.[1,2] If left untreated, it can lead to premature atherosclerotic cardiovascular disease, even early coronary heart disease (CHD) deaths.[1,2] Heterozygous familial hypercholesterolaemia has a high prevalence, affecting ~1 in 250 individuals worldwide, and even higher (1:70–1:100) in some population isolates due to the founder effect.[2,3] The mortality rate related to circulatory system diseases in these patients is even 100 times higher compared to the general population.[3,4] While the prevalence likely underestimates the actual numbers, given that cardiovascular disease (CVD) is the primary global cause of death,[5] the true extent of underdiagnosis and undertreatment among individuals in the general population with HeFH remains largely undetermined. Nevertheless, individuals with these conditions frequently go undetected in most countries.[6,7]

Although most individuals with HeFH may not exhibit symptoms of CHD until adulthood, prolonged exposure to elevated LDL-C levels leads to cumulative damage of the CV system.[8,9] In addition, despite compelling evidence of clinical benefits, HeFH poses a significant burden, with the majority of cases remaining undetected due to the asymptomatic nature of the disease until clinical manifestations become overt. Certainly, there remains a very low awareness, detection, and treatment of severe hypercholesterolaemia even among adults.[10,11] This delayed detection often results in underestimating the documented benefits of statin treatment, especially the impact of early treatment on early mortality.[12] Furthermore, the detection and management of HeFH in children have been shown to be cost-effective from both healthcare and societal perspectives across various countries.[6,9] Consequently, it is crucial to initiate treatment for high LDL-C levels from childhood to prevent premature morbidity and mortality in people with HeFH.[13,14]

Regarding the treatment of FH in children, conflicting opinions remain among healthcare professionals about strategic management (including intensity) with lipid-lowering therapy (LLT), their safety and efficacity (what makes it ineffective in high proportion of children HeFH patients).[15,16] Thus, in this meta-analysis, we aimed to evaluate the efficacy and safety of LLT as well as the achievement of lipid treatment goals in children with HeFH in different regions and with different types of LLT.

Methods

Search strategy and selection criteria

We followed to the methodology recommended by the Cochrane Collaboration, and the reporting standards outlined in the 2020 Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guideline.[17] A PECOS (population, exposure, comparison, outcomes, study design) model, as outlined in Supplementary material online, *Table S1*, was used to shape the clinical question, and devised the search strategy.

Our comprehensive search covered databases from their inception through 31 December 2023, including PubMed-Medline, EMBASE, Scopus, Google Scholar, the Cochrane Central Registry of Controlled Trials, and ClinicalTrial.gov. Key search terms included: 'heterozygous familial hypercholesterolemia', 'HeFH', 'pediatric familial hypercholesterolemia', 'children', 'adolescents', 'pediatrics', 'treatment', 'lipid-lowering therapy', 'statins', 'PCSK9 inhibitors', 'ezetimibe', 'dietary regimens', 'dietary interventions', and 'outcomes' (see Supplementary material online, *Table S2*). Furthermore, we conducted a thorough review by examining the references cited in the selected articles and relevant review articles. Additionally, abstracts from selected congresses, including scientific sessions of the European Society of Cardiology (ESC), the American Heart Association (AHA), European Atherosclerosis Society (EAS), American College of Cardiology (ACC), and National Lipid Association (NLA), were screened to identify any additional relevant articles. To enhance the search strategy's sensitivity, the wild-card term '*' was used.

Articles were eligible if they reported the treatment with LLT in paediatric patients with HeFH and met the following inclusion criteria: (i) trials or cohorts reporting treatment with LLT compared to control or comparison before-after treatment in the same group, (ii) available mean change of lipidic profile and/or adverse events (AEs), and (iii) genetically confirmed diagnosis of HeFH. Exclusion criteria were: (i) studies with unclear methodologies to obtain the estimates of the LLT efficacy and safety, (ii) ongoing trials (unless they reported relevant interim results), (iii) studies only investigating diet regiments without LLT treatment, and (iv) articles not published in English.

The search, screening, and data extraction were carried out independently by two reviewers (J.L. and S.S.). Any disagreements were resolved through discussions with senior investigators (I.B. and M.B.), while the analysis and interpretation of the data were performed by two different researchers (S.B. and I.B.). Irrelevant articles were excluded based on screening of titles and abstracts. Each trial underwent an independent assessment of the risk of bias by the same investigators using the revised Cochrane RoB2 tool, which includes five domains (randomization process, deviation from intended interventions, missing outcome data, outcome measurement, and selection of reported results). The risk of bias in each study was categorized as 'low', 'high', or 'unclear'.[18] To assess the risk of bias in cohort studies, the Newcastle-Ottawa Scale (NOS) was employed. The three domains were evaluated based on the following criteria: (i) selection, (ii) comparability, and (iii) exposure. The risk of bias in each study was categorized as 'good', 'fair', or 'poor'.[19]

Outcome measures

The primary endpoint was the efficacy and safety of LLT in children with HeFH. The secondary endpoint was the effect of LLT on the achievement of lipid treatment goals. The efficacy parameters of LLT therapy (statins, ezetimibe, statin combined with ezetimibe, and PCSK9 inhibitors) on lipid profiles included total cholesterol (TC), triglycerides (TG), LDL-C, high density lipoprotein cholesterol (HDL-C), apolipoprotein B (apoB), apolipoprotein A (apoA), and lipoprotein(a) [Lp(a)]. Safety parameters included endocrine function [cortisol, dehydroepiandrosterone sulfate (DHEA-S), follicular stimulating hormone (FSH), luteinizing hormone (LH), oestradiol in girls, and testosterone in boys], demographic indices [weight, height, body mass index (BMI), and body surface area], and AEs compared to the control group and its prevalence.

The effect of LLT on the achievement of LDL-C [absolute LDL-C threshold of <3.5 mmol/L (<130 mg/dL)] and to identify the LDL-C treatment goal variations in different regions were the main outcome. We determined the number of patients who achieved LDL-C < 3.5 mmol/L (<130 mg/dL), and in addition, we classified the per cent of failed to reached the target of LDL-C using the value of LDL-C < 3.5 mmol/L (<130 mg/dL) as reference line: low failure (1–10% not reached the target/additional reduction of LDL-C by 1–10% was required), moderate failure (>10–20% not reached the target/additional reduction of LDL-C by >10–20% was required), and high failure (>20% not reached the target/additional reduction of LDL-C by >20% was required). Furthermore, based on the dose of LLT that was used, we have classified patients into several groups: low intensity, moderate intensity, high intensity, and combined LLT. In cases where the LLT doses used were different and were not able to be included to the above groups, the groups of low to moderate and moderate to high have been also employed.[20]

Data synthesis and statistical analyses

The meta-analysis was conducted using R Statistical Software (v3.5.1, Boston, MA, USA), using the packages 'meta' and 'metafor' for meta-analysis and the RevMan [Review Manager (RevMan) Version 5.1, The Cochrane Collaboration, Copenhagen, Denmark], with two-tailed $P < 0.05$ considered significant.

Weighted mean difference (WMD) with 95% confidence interval (CI) is presented as summary statistics, and for categorical variable, relative risk ratio with the 95% CI was used. Mean and standard deviation values were estimated using the method described by Hozo *et al.*[18] A random-effects

Table 1 **Main characteristics of studies included in the meta-analysis**

Study (year)	Study design	Location (country)	Sample (*n*)	LLT (dose)	Age (year)	Female (%)	LDL-C reduction in the follow-up (mmol/L/%)	How far from the LDL-C goal in the follow-up	Adverse events	Follow-up (months)
Ducobu 1992[23]	RCTs	Belgium	32 LLT	Low	<17 years	31.2	2.45 (37.21)	0.65 (15.66)	R	36
Sinzinger 1992[24]	RCTs	Italy	16 LLT	Low	6–13	43.7	1.89 (28.08)	1.35 (27.89)	R	52
Knipscheer 1996[25]	RCTs	Netherlands	53 LLT	Low	12 ± 2.3	62.2	1.83 (26.72)	1.53 (30.48)	R	3
			18 Diet		12.1 ± 3.4	77.7				
Lambert 1996[26]	RCTs	Canada	65 LLT	Low to moderate	12.9 ± 2.4	0%	1.73 (27.50)	1.07 (23.46)	R	2
Couture 1998[27]	RCTs	Canada	63 LLT	Moderate	12.5 ± 2.3	41.2	2.09 (36.99)	0.07 (1.97)	NR	1.5
Stein 1999[28]	RCTs	USA and	67 LLT	Low to	13.3 ± 0.3	0%	1.62 (25.10)	1.37 (28.19)	R	12
		Finland	65 Diet	Moderate	13.1 ± 0.3	0%				
Stefanutti 1999[29]	RCTs	Italy	8 LLT	Low	8.9 ± 2.2	56.2	1.97 (29.76)	1.16 (24.95)	R	12
			8 Diet		8.4 ± 3.1					
McCrindle 2002[30]	RCTs	Canada	20 LLT	Low	13.7 ± 2.6	42.8	1.07 (16.80)	1.81 (34.15)	R	9
			16 Diet		13.9 ± 4.2	31.2				
McCrindle 2003[31]	RCTs	USA, EU	140 LLT	Moderate	14.1 ± 2.0	32	2.27 (40.11)	−0.10 (−2.95)	R	6.5
		Canada	47 Diet		14.1 ± 2.2	27.6				
de Jongh, 2002[32]	RCTs	Netherlands	106 LLT	Moderate	14.4 ± 2.1	44	2.15 (40.72)	−0.36 (−11.5)	R	6
			69 Diet		14.6 ± 2.5	47.8				
de Jongh 2002[33]	RCTs	Netherlands	28 LLT	Moderate	14.5 ± 2.0	46	2.14 (40.30)	−0.32 (−10.09)	R	7
			22 Diet		14.6 ± 2.5	50				
Vohl 2002[34]	RCTs	Canada	47 LLT	Moderate	7–17	40.4	0.30 (5.37)	1.80 (34.03)	NR	1.5
Dirisamer 2003[35]	Prospective observational	Austria	20 LLT	Low to moderate	13.4 ± 2.0	60	1.96 (30.43)	0.99 (22.1)	R	12
Hedman 2003[36]	Prospective observational	Finland	20 LLT	Low	10.3 ± 2.9	65	1.30 (21.31)	1.31 (27.29)	R	2
Wiegman 2004[37]	RCTs	Netherlands	106 LLT	Moderate	13.0 ± 3.0	54	3.52 (56.96)	−0.83 (−31.2)	R	24
			108 Diet		13.0 ± 2.9	53				
Koeijvoets 2005[38]	RCTs	Netherlands	193 LLT	Moderate	12.8 ± 5.9	51.8	1.43 (22.84)	1.34 (27.74)	NR	24
Clauss 2005[39]	RCTs	USA	35 LLT	Moderate	15 ± 2	100	1.6 (28.47)	0.53 (13.18)	R	6
			19 Diet		15 ± 2	100				
Hedman 2005[40]	Prospective observational	Finland	30 LLT	Low to moderate	9.2 ± 3.1	63.3	1.78 (28.25)	1.03 (22.79)	R	24

Continued

Table 1 *Continued*

Study (year)	Study design	Location (country)	Sample (*n*)	LLT (dose)	Age (year)	Female (%)	LDL-C reduction in the follow-up (mmol/L/%)	How far from the LDL-C goal in the follow-up	Adverse events	Follow-up (months)
Rodenburg 2006[41]	RCTs	USA	90 LLT	Low to	12.9 ± 3.0	53	1.50 (24.31)	1.18 (25.27)	NR	24
			88 Diet	Moderate	12.9 ± 2.8	51				
Van der Graaf 2006[42]	CT	Netherlands	84 LLT	Moderate	12.6 ± 2.1	56	1.93 (33.86)	0.28 (7.43)	R	22.5
Van der Graaf 2008[43]	RCTs	Netherlands	122 LLT	Moderate to high	14.3 ± 1.8	43	1.95 (34.39)	0.23 (6.18)	R	8.2
			126 LLT + E	High	14.0 ± 1.9	42	2.87 (49.31)	−0.54 (−18.31)		
Yeste 2009[44]	Prospective observational	Spain	11 LLT	High	9.6 ± 3.2	45.4	1.84 (29.53)	0.90 (20.5)	NR	8
Clauss 2009[45]	Prospective observational	USA	26 LLT	High	12.3 ± 1.9	65.3	2.0 (34.48)	0.31 (8.16)	NR	13.6
Avis 2010[46]	RCTs	USA, Spain	131 LLT	Moderate	13.7 ± 1.8	55	2.73 (44.98)	−0.15 (−4.49)	R	13
		Netherlands	46 Diet	to high	14.2 ± 2.1	48				
Gandelman 2011[47]	CT	Canada Norway	39 LLT	Low to moderate	11.1 ± 1.8	49	2.38 (40.68)	−0.02 (−0.58)	R	2
Kusters 2013[48]	Prospective observational	Netherlands	193 LLT	Low to moderate	12.9 ± 2.1	53.6	1.66 (27.08)	0.98 (21.92)	NR	120
Kusters 2015[49]	RCTs	France	93 LLT	High	8.3 ± 1.6	57	1.55 (26.18)	0.88 (20.14)	R	3
		Norway	45 Diet							
Braamskamp 2015[50]	Prospective (non-randomized) observational (open label)	Netherlands	197 LLT	Moderate to high	11.6 ± 3.3	56	2.62 (42.95)	−0.01 (−0.29)	R	24
Harada-Shiba 2016[51]	RCTs	Japan	14 LLT	Low	11.1 ± 1.8	0	1.96 (29.43)	1.21 (25.74)	R	12
Langslet 2016[52]	Prospective observational	14 Countries	271 LLT	Moderate to high	10.2 ± 1.8	46.4	2.67 (43.63)	−0.04 (−1.16)	R	48
Henning 2017[53]	Prospective	Poland	27 LLT	Low to	9.57 ± 3.2	NR	1.69 (32.01)	0.10 (2.79)	NR	12
	Observational		40 Diet	moderate	9.57 ± 3.2					
Saltijeral 2017[54]	Prospective cohort	Spain	217 LLT	High	15 ± 8.9	46.5	0.65 (15.44)	0.07 (1.97)	NR	52
Ramaswami 2017[55]	Prospective	UK	111 LLT	Moderate	9.8 ± 2.5	47.2	2.21 (36.71)	0.32 (8.40)	NR	24
	Observational		165 Diet	to high	10.1 ± 2.4	51.4				
Humphries 2018[56]	Prospective	UK	135 LLT	Moderate	9.5 ± 3.5	49.6	1.90 (32.31)	0.49 (12.31)	NR	12
	Observational		165 Diet		10.7 ± 3.2	48.5				
Bogsrud 2018[57]	Retrospective	Norway	177 LLT + E	Moderate	9.1 ± 3.0	48	2.20 (37.93)	0.11 (3.06)	NR	51
	Observational		125 Diet	to high	7.7 ± 3.0	50.2				
Pang 2018[58]	Prospective observational	Australia	40 LLT	Moderate	12.1 ± 3.2	NR	2.63 (37.79)	0.84 (19.40)	NR	NR
Benekos 2020[59]	Prospective observational	Greece	72 LLT	Moderate to high	9 ± 3	63	2.78 (46.33)	−0.27 (−8.39)	R	3
Daniels 2020[60]	RCTs	USA	42 PCSK9i	Moderate	12.4 ± 2.6	45.5	1.35 (30.10)	−0.34 (−10.79)	R	2
Santos 2020[61]	RCTs	Sweden	104 PCSK9i	High	13.7 ± 2.3	44	2.13 (44.56)	−0.84 (−31.70)	R	6

Continued

Table 1 *Continued*

Study (year)	Study design	Location (country)	Sample (*n*)	LLT (dose)	Age (year)	Female (%)	LDL-C reduction in the follow-up (mmol/L/%)	How far from the LDL-C goal in the follow-up	Adverse events	Follow-up (months)
Lewek 2021[62]	Retrospective observational	Poland	16 LLT	Moderate to high	9 ± 3	NR	2.81 (44.04)	0.08 (2.24)	NR	24
Peretti 2023[63]	Retrospective and prospective observational	France	135 LLT 99 Diet	Low to moderate	14 ± 3 13 ± 3	53 55	2.99 (43.31)	0.44 (11.2)	NR	26

LDL-C goal treatment (<3.5 mmol/L/130 mg/dL).
LLT, lipid-lowering therapy; R, reported; NR, non-reported.

model (Der Simonian and Laird method) was applied to estimate the pooled prevalence of AEs across the studies. The 95% CIs for the prevalence reported in the individual studies were estimated from the proportion of cases of AEs and sample size using the binomial exact method (Clopper-Pearson method). An inverse variance method was used for weighting each study in the meta-analysis. Analysis is presented in forest plots, the standard way for illustrating the results of individual studies and meta-analysis.

Likewise, we calculated the effect of different type of LLT on lipid profile and safety parameters using sub-analysis. The meta-analyses were performed with the random-effects model. Heterogeneity between studies was assessed using Cochrane Q test and I^2 index. As a guide, $I^2 < 25\%$ indicated low, 25–50% moderate, and >50% high heterogeneity.[21] To assess the additive (between-study) component of variance, the reduced maximum likelihood method (tau^2) incorporated the occurrence of residual heterogeneity into the analysis.[22] Publication bias was assessed using visual inspections of funnel plots and Egger's test.

Results

Study selection and patient population

A total of 6782 articles were retrieved from the search after removing duplicates from the various databases. These articles underwent initial screening based on title and abstract, resulting in 98 articles that underwent a full-text review. Following a rigorous selection process, 41 studies with 4667 patients and a median follow-up of 18.8 months were included in the analysis.[23–63] Out of the 41 articles, 22 were randomized controlled trials (RCTs), and 19 were cohort studies. Seventeen articles reported the efficacy and safety of LLT therapy compared to control (25, 28–33, 37, 39, 41, 46, 49, 53, 55–57, 63), while the remaining 24 assessed LLT pre- and post-treatment (23, 24, 26, 27, 34–36, 38, 40, 42–45, 47, 48, 50–52, 54, 58–62). The PRISMA flow diagram is depicted in Supplementary material online, *Figure S1*, and the key characteristics of the included studies are presented in *Table 1*. The mean age of patients was 12.08 ± 2.4, and 46% were females. Out of 41 studies, 7 (16.7%) used low intensity LLT, 9 (21.4%) low to moderate, 10 (23.8%) moderate, 7 (16.7%) moderate to high, and 7 (16.7%) high intensity or combination therapy (*Table 1*).

Efficacy of lipid-lowering therapy on lipidic profile and lipoproteins

The pooled analysis showed that the group commenced on LLT had higher baseline TC with a WMD of 0.25 mmol/L (9.7 mg/dL) (95% CI: 0.02–0.49, $P = 0.04$) and LDL-C of 0.23 mmol/L (8.9 mg/dL) (95% CI: 0.05–0.41, $P = 0.01$) compared to control (see Supplementary material online, *Figure S2*). TG and HDL did not differ between the groups ($P > 0.05$ for all, Supplementary material online, *Figure S3*), as did Lp (a), apoB, and apoA ($P > 0.05$ for all, Supplementary material online, *Figure S4*). At median follow-up of 18.8 months, the group on LLT had significantly higher mean TC reduction −1.75 mmol/L (67.7 mg/dL) (95% CI: −1.95 to −1.55; $P < 0.001$), LDL-C reduction −1.84 mmol/L (71.2 mg/dL) (−2.13 to −1.54; $P < 0.001$), increased mean HDL-C by 0.08 mmol/L (3.1 mg/dL) (0.01–0.15; $P = 0.03$), and reduced TG −0.11 mmol/L (9.74 mg/dL) (−0.16 to −0.07; $P < 0.001$), compared to control (see Supplementary material online, *Figures S5* and *S6*). In addition, the LLT significantly reduced apoB (−0.32 g/L; $P < 0.001$), while apoA and Lp(a) were not affected significantly compared to control ($P > 0.05$, for both). The same results were achieved with the inverse analysis we applied (see Supplementary material online, *Figures S7* and *S8*). A summary of efficacy of LLT is shown on *Figure 1*.

In the subgroup analysis according to different types of LLT, using an inverse analysis model, we observed a significantly higher mean reduction of TC with statins combined with ezetimibe [WMD −2.73 (−105.6 mg/dL), 95% CI, −3.12 to −2.34 mmol/L] followed by

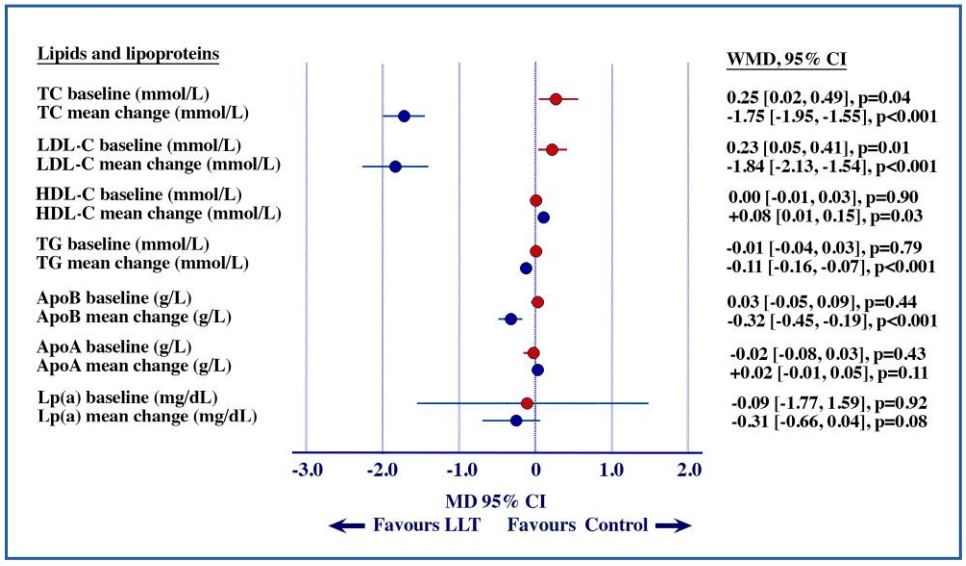


Figure 1 Summary of baseline/follow-up of lipids in LLT group compared to control.

PCSK9is [in monotherapy as an add-on to statins with/without ezetimibe; −2.27 (−87.8 mg/dL), −2.39 to −2.15 mmol/L], statins in monotherapy [−2.21 (−85.5 mg/dL), −2.45 to −1.98 mmol/L], and only ezetimibe [−1.50 (−58 mg/dL), −1.68 to −1.32 mmol/L; test for overall effect: $P < 0.001$; Supplementary material online, *Figure S9*]. According to the above order of treatment, a mean reduction of LDL-C was similar: statins plus ezetimibe [WMD −2.48 (−95.9 mg/dL), 95% CI, −3.13 to −1.83 mmol/L], statin monotherapy [−2.16 (−83.5 mg/dL), −2.33 to −1.99 mmol/L], PCSK9is [in monotherapy as an add-on to statins with/without ezetimibe; −2.03 (−78.5 mg/dL), −2.39 to −2.15 mmol/L], and ezetimibe monotherapy [−1.50 (−58 mg/dL), −1.71 to −1.29 mmol/L; test for overall effect: $P < 0.001$, *Figure 2*]. Lipid-lowering therapy also significantly affected TG, from −0.07 mmol/L (−6.2 mg/dL) for ezetimibe, through −0.15 mmol/L (−13.3 mg/dL) for statin in monotherapy, to −0.35 mmol/L (−31 mg/dL) for statins and ezetimibe in combination; no significant effect was observed for PCSK9 inhibitors (see Supplementary material online, *Figure S10*). The overall test for subgroup differences was not statistically significant for HDL-C [$P = 0.76$, respectively; with only statins that showed significant increase of HDL-C by 0.05 mmol/L (2 mg/dL), Supplementary material online, *Figure S11*].

LDL-C goal achievement using different types of lipid-lowering therapy

At median follow-up of 18.8 months, the pooled LDL-C was reduced for 33.44% [−2.14 (−2.30, −1.98), $P < 0.001$] and failed to reach the goal (LDL-C < 3.5 mmol/L) for all investigated HeFH children by 12.6% (95% CI, 12.4–12.9%) (*Table 1*). Among the 3522 children treated with LLT (1145 were on the dietary interventions), 1362 (38.7%) achieved the LDL-C goal, while 843 (23.9%) fell short by up to 10%, 377 (10.7%) experienced moderate failure (additional 10–20% overall LDL-C reduction was required), and 940 (26.7%) failed by more than 20% to reach the LDL-C target (see Supplementary material online, *Figure S12A*).

When comparing different regions, only Sweden and Greece achieved the LDL-C goal, followed by the Netherlands, Norway, Poland, USA, UK, France, Spain, Belgium, and Austria (with the following additional required LDL-C reduction to be on the goal: 2.2%, 3.4%, 3.5%, 8.9%, 10.2%, 11.2%, 11.2%, 15%, and 19.4%, respectively). Australia, Canada, Italy, Finland, and Japan experienced more than a 20% mean LDL-C reduction failure (*Figure 3*). Similarly, when comparing different types of LLT, the HeFH children that were administered moderate to high dose of statins, high dose of statins, high-dose statins combined with ezetimibe, and PCSK9 inhibitors most often achieved the LDL-C goal while groups using only statins (low, moderate, low to moderate, and moderate) and ezetimibe as monotherapy did not reach the treatment goal (Graphical abstract, Supplementary material online, *Figure S12B*).

Safety and tolerability of lipid-lowering therapy in children

All parameters related to endocrine function, including cortisol, DHEA-S, FSH, LH, oestradiol in girls, and testosterone in boys, were unaffected by LLT therapy ($P > 0.05$ for all; Supplementary material online, *Figure S13*). Similarly, demographic indicators such as height, weight, BMI, and surface area of the children increased comparably in both the LLT and control groups ($P > 0.05$ for all; Supplementary material online, *Figure S14*). At the end of the follow-up period, no significant differences were observed in changes from baseline for ALT, AST, and CK ($P > 0.05$ for all; Supplementary material online, *Figure S15*). A summary of LLT safety profile for demographic, endocrine, and liver/muscle enzyme parameters is provided in *Figure 4*.

The prevalence of treatment-emergent adverse events (TEAEs) was 4.68%, with a discontinuation rate of only 0.84%. Apart from headaches (10.2%), the prevalence of other AEs was below 8.0%, including gastrointestinal effects, myalgia, sleep disorders, influenza-like disease, skin reactions, temporary increases in ALT, AST, CK, as well as ALT > 3 × ULN, AST > 3 × ULN, and CK > 3 × ULN (8.41%, 3.18%, 2.54%, 5.62%, 3.71%, 1.89%, 1.50%, 0.52%, 0.83%, 0.51%, and 0.67%, respectively; *Figure 5A*). Finally, the AEs were not reported significantly higher when compared to the control group (*Figure 5B*, Supplementary material online, *Figures S16–S19*).

Risk of bias assessment

The assessment of risk of bias in the included studies using RoB2 for RCTs and NOS for cohort studies showed that most studies had

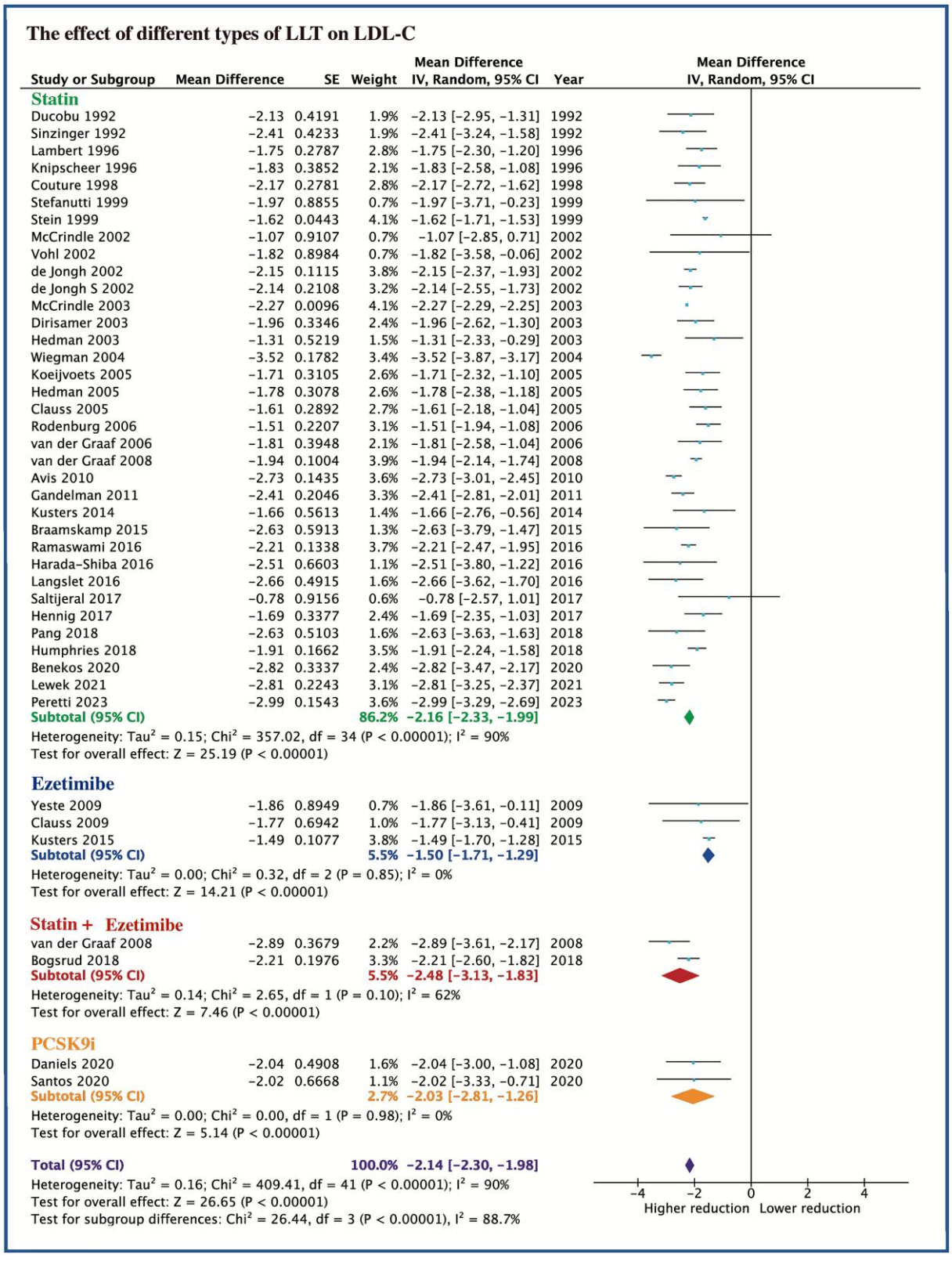


Figure 2 The effect of different types of LLT on LDL-C.

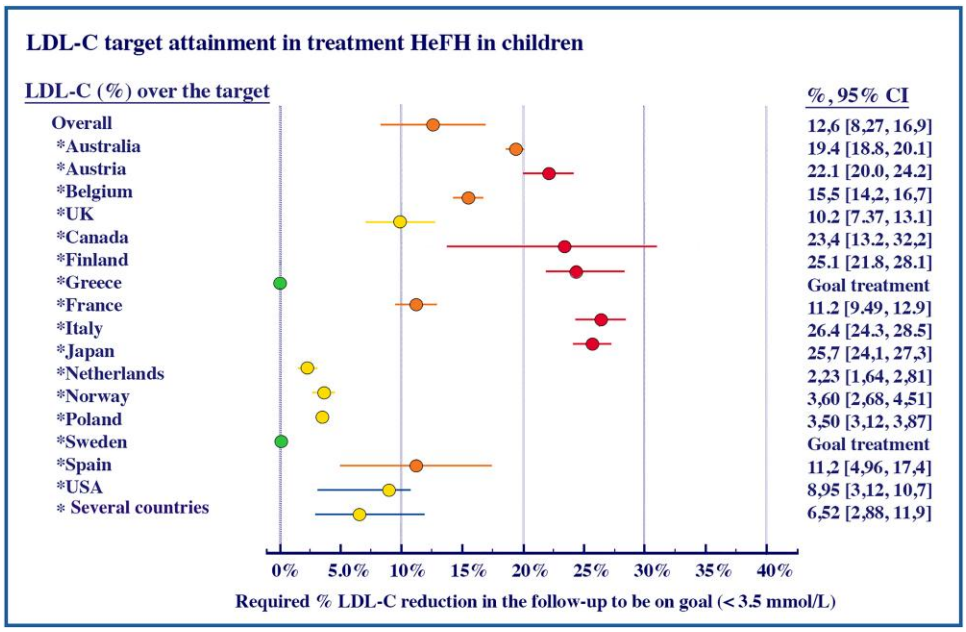


Figure 3 LDL-C target attainment in children with HeFH.

moderate to high quality level in defining objectives and the main outcomes (see Supplementary material online, *Tables S4* and *S5*).

Discussion

To the best of our knowledge, the present meta-analysis is the first to evaluate the efficacy and safety of various types of LLT in children with HeFH, as well as the achievement of LDL-C treatment goals in children with HeFH globally and across different regions. This large analysis not only assesses the efficacy of lipid parameters reduction with the therapy, goal achievement for different therapy intensification and combination, but also presents strong safety of the LLT in children, one of the most important reasons of therapy non-adherence in HeFH children. This also perfectly completes the results of the recent cross-sectional study from the Familial Hypercholesterolemia Studies Collaboration (FHSC) registry.[64,65]

The results from our meta-analysis, encompassing 41 studies and involving 4667 children with HeFH and at mean age of 12 years, showed a significant efficacy of LLT on lipid profile. Subgroup analysis indicated a substantial mean reduction in LDL-C with statin combined with ezetimibe treatment, followed by PCSK9 inhibitors, statins, and sole ezetimibe treatment, strongly emphasizing the need to use combination LLT and/or PCSK9 inhibitors as the most effective method to achieve a therapeutic target for LDL-C. Overall, LDL-C was reduced by 33.44%, with insufficient reduction by 12.6% to reach the treatment goal for the whole pooled HeFH cohort. Approximately 38.7% of children achieved the LDL-C goal, for 23.9% additional LDL-C reduction by up to 10% was required, 10.7% experienced moderate failure, and 26.7% failed by more than 20% to reach the LDL-C target. Regional comparisons showed that only Sweden and Greece achieved the LDL-C goal and many countries fell up to 10 or more than 20% mean LDL-C reduction failure.

Prior systematic reviews and meta-analyses addressing dietary interventions for individuals with HeFH have indicated insufficient efficacy, particularly in managing HeFH among children.[66,67] The efficacy and safety of LLT especially statins have been continuously debated with some studies suggesting that that statins are safe only in the short-term.[68,69] In contrast, other research recommends statins as the preferred pharmacological agents for treating HeFH, in conjunction with dietary and physical activity management, across all age groups.[44,68,69] For children unable to attain the LDL cholesterol goal with the initially prescribed statin dosage, higher statin doses or the addition of another lipid-lowering agent may be necessary[70,71] In our meta-analysis, the effectiveness of high doses of statins, statins combined with ezetimibe, and/or PCSK9 inhibitors demonstrated significantly greater efficacy in lipid control compared to low-dose statins, low-to-moderate statins, moderate statins, and ezetimibe in monotherapy.[72–74]

In the recently published analysis from the FHSC registry with 11 848 HeFH children or adolescents included (50.2% were female; median age 9.6 years; 89.9% genetic diagnosis), the authors showed that at registry entry, 28.5% of children and adolescents were taking LLT, which increased with age in both sexes. A total of 29.1% of children and adolescents were prescribed statins (from 10% for those younger than 5 years to 41.0% for those at age 15–18 years), and only 5.7% were prescribed ezetimibe (to <8% for those aged 15–18 years).[64] The most common prescribed statins were atorvastatin (43.2%), simvastatin (24.4%), and rosuvastatin (18.4%). Only 0.4% individuals were taking PCSK9 inhibitors. Median LDL-C concentration among HeFH children and adolescents on LLT was 4.35 mmol/L (168 mg/dL), compared with 5.00 mmol/L (193 mg/dL) for those not taking any medication. We have shown here that more than every third child with HeFH achieved their goal of 3.5 mmol/L (130 mg/dL), with worse results in the real-word cohort from the FHSC registry, where among those taking statins or ezetimibe, every fourth boy and every fifth girl had LDL-C < 3.4 mmol/L. Similarly to our results, compared with monotherapy with statins or ezetimibe, the combination therapy of statin and ezetimibe was associated with an increased likelihood of having LDL-C < 3.4 mmol/L (age-adjusted and sex-adjusted OR 1.83, 95% CI 1.19–2.82) compared with no therapy.[64]

However, despite the results of LLT efficacy, the LDL-C target was not achieved in the majority of children (61.3% vs. 38.7%; $P < 0.001$) globally, with a lack of success in the majority of countries. To anticipate

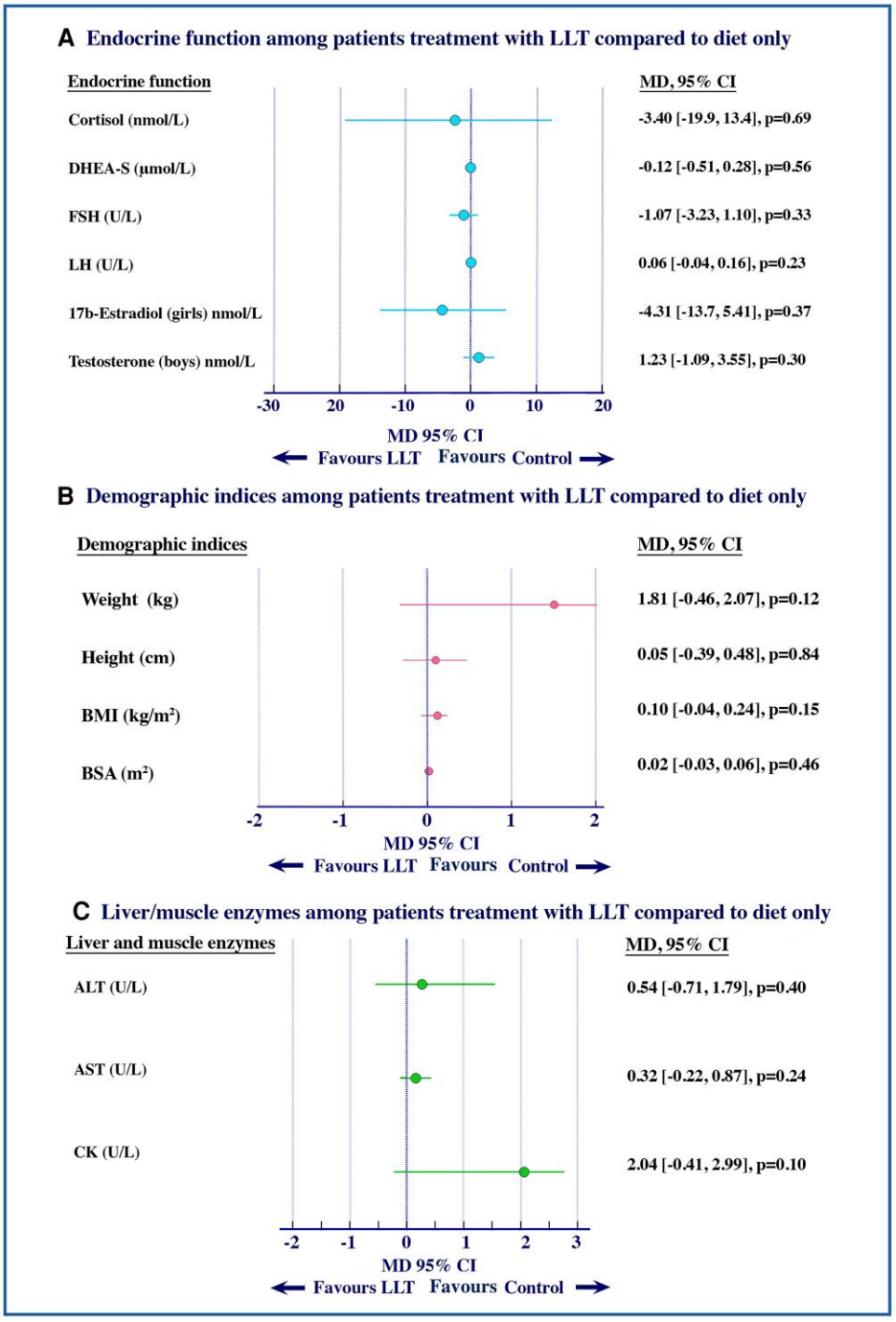


Figure 4 Summary of the endocrine function (*A*), demographic indices (*B*), and liver/muscle enzymes (*C*) among patients treatment with LLT compared to diet only.

the risk of non-adherence, it is critically important to consider initiating treatment as early as possible, even with a low dose (with detailed dietary and lifestyle recommendations). During each visit, closely monitoring LDL-C levels until the target is reached and gradually increasing the dose of LLT while assessing for therapy tolerability. Our results also confirmed large efficacy and safety of the lipid-lowering combination therapy of statins and ezetimibe, which is severely underused in HeFH children worldwide. Furthermore, our findings underscore the significance of PCSK9 inhibitors, which are already available in many countries for children with FH. Novel therapeutic options, such as monoclonal antibodies, may be considered a substantial advancement in paediatric FH treatment (also in case of statin intolerance). However, our data are limited to two clinical trials, and further trials are still necessary to establish their safety profile and long-term

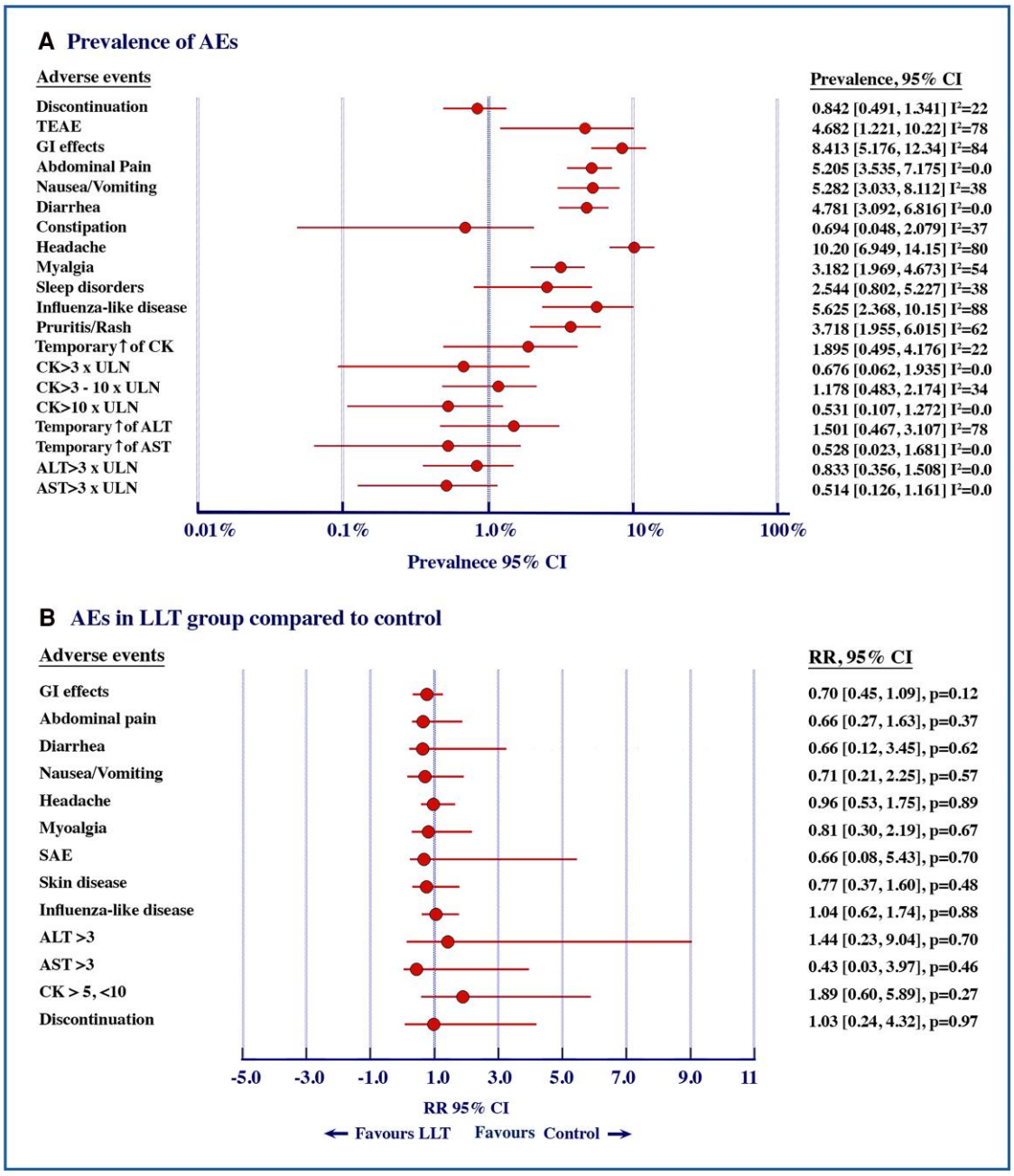


Figure 5 Adverse events of LLT; (*A*) prevalence of adverse events; (*B*) adverse events in LLT group compared to control.

effects.[59,60,75] In line with this, the evaluation of achievement of lipid treatment goals in HeFH children in various regions seems to be impacted by the year of the publication, which is not surprising considering not only the recent availability of more potent LLTs but also the changes in LDL-C clinical targets, which were essentially reduced since the late 90s.[2,3] Finally, despite being the most prevalent metabolic genetic disorder, HeFH remains underrecognized and undertreated. There should be a strong emphasis on early diagnosis and therapy. Implementing a multidisciplinary, family-centric approach as early as possible is crucial, as studies indicate that early-stage treatment with high dose of LLT significantly reduces future CVD risks in paediatric patients. As discussed above, based on these results, we cannot finally conclude on the factors that may have contributed to better or worse outcomes in FH children management in the investigated countries. However, the best case systemic examples that are already efficient in some countries are recommended to be followed to improve the effectiveness of the diagnosis (the earlier the better with regional or universal screening introduction) and therapy optimization, with lipid-lowering combination therapy and larger access to new innovative drugs, such as PCSK9 inhibitors.[76,77]

In last decades, there is unjustified fear of parents to treat their HeFH children with statins and other LLT, what is the main reason of therapy non-adherence, and in the consequence cardiovascular and vascular complications observed in children, adolescents, and young adults

with HeFH.[14,78] Thus, despite LLT being the gold standard for dyslipidaemia treatment and managing high CV risk, ensuring safety and tolerability in children is of paramount importance. Our findings indicate that LLT did not adversely affect parameters related to endocrine function, demographic indicators, and liver/muscle enzymes. Adverse events were not significantly higher in the HeFH compared to the control group, and the prevalence of discontinuation was only 0.8%. The prevalence of TEAEs was also low. Apart from headaches, the prevalence of other AEs was very low, encompassing gastrointestinal effects, myalgia, sleep disorders, influenza-like disease, skin reactions, and temporary increases in liver/muscle enzymes. Importantly, AEs were not reported significantly higher when compared to the control group.

Strength and limitations

Our meta-analysis has some limitations. Moderate heterogeneity between studies was observed in several analyses (e.g. regional differences in healthcare systems and variations in genetic diagnosis), although the random-effects method was employed to mitigate the impact of this heterogeneity. The examination of potential publication bias using Egger and funnel plots was not conducted for studies with fewer than 100 patients, which were excluded from this type of analysis. The available data do not allow us to draw robust conclusions regarding the effectiveness and safety of new drugs, particularly PCSK9 inhibitors, and the varied doses used, mainly due to the limited number of trials. Subsequent studies may be necessary to determine the optimal dosage and timing of PCSK9 inhibitor therapy in children. Additionally, we cannot draw definitive conclusions regarding the benefits of initiating LLT in children at 8 years compared to 10 years, as different protocols are utilized in various regions. Despite our best attempts, within the meta-analysis design, we cannot decisively exclude some overlapping of the patients in the HeFH cohorts in the analyses from the same research groups. Finally, many countries, especially those with lower income, did not report the management of HeFH in children, potentially indicative of underrecognition and undertreatment.

In conclusion, in children with HeFH, LLT therapy significantly reduced lipid levels without impacting growth, hormones, or liver/muscle enzymes. Despite the low occurrence of discontinuation-related adverse events, achieving LDL-C treatment goals proved challenging in most of the investigated countries. These findings emphasize the significance of considering high-dose statins, lipid-lowering combination therapy, or PCSK9 inhibitors, to attain LDL-C goals effectively.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Authors' contribution

All authors contributed to the writing of this manuscript and approved the submitted version. No outside editorial/medical writing support was provided.

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The results of the meta-analysis were presented at the ESC Congress 2024 in London during the moderated session entitled 'Cardiovascular Disease in Special Populations: Paediatric Cardiology', 30 August 2024.

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Conflict of interest: M.B.: speakers bureau: Amgen, Daiichi Sankyo, KRKA, Polpharma, Mylan/Viatris, Novartis, Novo-Nordisk, Pfizer, Sanofi-Aventis, Teva, Zentiva; consultant to Adamed, Amgen, Daiichi Sankyo, Esperion, NewAmsterdam, Novartis, Novo-Nordisk, Sanofi-Aventis. grants from Amgen, Daiichi Sankyo, Mylan/Viatris, Sanofi, and Valeant. S.S.: honoraria from: Sandoz/Novartis; KRKA, Pro. Med, Bausch Health. I.G.-B.: speakers bureau: Amgen, Akcea Therapeutics, Daiichi-Sankyo, Novartis, Sanofi, Ultragenyx; consultant to Amgen, Regeneron, Aegereon, Akcea Therapeutics, Daiichi-Sankyo, Novartis, Sanofi, Amarin, and Ultragenyx. C.E. has received honoraria from Almirall, Esteve, Amgen, Bayer, Boehringer, Sanofi, MSD, Mylan, Servier, Ferrer, Daiichi-Sankyo, Novartis, Pfizer, Viatris, as speaker or advisor. D.G.: research grants, speaker honoraria, or travel reimbursement from: Amgen, AstraZeneca, Bayer, Berlin Chemie, Boehringer Ingelheim, Egis, Galenica, Gedeon Richter, GSK, MSD, Novartis, Novo Nordisk, Pfizer, Sanofi, Servier, Terapia, Viatris, Vifor, Zentiva. F.P.: has received personal fees for lectures from Novo Nordisk. R.D.S. has received honoraria related to consulting, speaker activities or research from: Amgen, Chiesi, Daiichi-Sankyo, Eli-Lilly, Ionis, Esperion, Libbs, Novartis, Novo-Nordisk, Sanofi/Regeneron, MSD, PTC Therapeutics, Ultragenyx, and Torrent. A.F.G.C.: Consultant to Dompé SpA, Sharper SpA, Viatris SpA, Zentiva SA. C.J.L: speaker and Consultant for Amgen and Consultant for Novartis on their injectable lipid agents, Consultant for New Amsterdam Pharma on new lipid agents and Speaker and Consultant for GOED and DMS Nutritional Products on Omega-3; all other authors do not declare any conflict of interest in relation to the results of this paper.

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