Statin safety in children at increased risk for cardiovascular disease

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Abstract

Statins have been proven efficacious in reducing the incidence of atherosclerotic cardiovascular disease (CVD) in adults. However, the process of atherosclerosis commences early in childhood, especially when predisposing conditions are present, such as hypercholesterolaemia or the metabolic syndrome. Early initiation of treatment to reduce the risk for CVD is therefore warranted and several studies have evaluated the efficacy and safety of statin therapy in childhood. In this review, we sought to provide an overview of paediatric studies on statin therapy, with an important focus on safety. Studies for various indications, such as familial hypercholesterolaemia and cardiac transplantation, were identified. The data made us conclude that the efficacy of statins in children is largely similar to what is observed in adult populations. The only three studies on the pharmacokinetics and pharmacodynamics of these compounds also show a drug profile very similar to that found in adults. With respect to safety, a plethora of studies has so far evaluated adverse events and growth and maturation as well as liver and muscle toxicity. Although future studies should more firmly establish lifelong safety, our review supports the notion that statin therapy in childhood is safe.

Key words: HMG-CoA reductase inhibitors, prevention, paediatric, atherosclerosis, lipoprotein.

Atherosclerosis in childhood

Atherosclerotic cardiovascular disease (CVD) is the most common cause of death worldwide in humans. In the past decades, a plethora of studies has tried to elucidate its pathogenesis and clinical characteristics and has searched for the optimal therapy. This has led to the development of treatment guidelines with statin therapy at their core. These guidelines have their focus on patients who have already suffered a cardiovascular event (secondary prevention) or adults with multiple risk factors, and an increased future risk for CVD (primary prevention). However, already in the 1970s autopsy studies showed that atherosclerosis is not only a disease of the elderly, but that atherosclerotic lesions are present in the aorta and coronaries of children and very young adults [1, 2]. Unsurprisingly, these studies led to a more intense focus on the pathogenesis of atherosclerosis at young age as well as on strategies to modify this process from childhood onwards.

Most studies on early atherosclerosis and early prevention of CVD were performed in patients with heterozygous familial hypercholesterolaemia (FH). The reason can be found in the fact that FH constitutes a frequent disorder (prevalence 1:500) with a rather extreme atherosclerotic phenotype. The molecular basis of the disease is an inherited low-density lipoprotein cholesterol (LDL-C) receptor deficiency or dysfunction leading to elevated LDL-C levels from birth onwards. Clinically, the disease is characterised by premature cardiovascular events [3]. Even though these events are rare in childhood, children with FH already have functional and morphological changes of the vessel wall which indicates that the atherosclerotic process has already been initiated. This is reflected by a significantly increased intima-media thickness (IMT) of the carotid artery in children with FH compared to unaffected siblings, as measured by ultrasound sonography (Figure 1A) [4]. Numerous studies have shown that the carotid IMT constitutes a validated predictor for cardiovascular events in adults. Therefore, carotid IMT is widely accepted as a surrogate marker for atherosclerotic CVD in adults [5]. Furthermore, children with FH have impaired flow-mediated dilatation (FMD), another indicator of endothelial dysfunction [6]. FMD is assessed by sonographically measuring the percentage of dilatation of the brachial artery to achieve hyperaemia, in response to suspension of temporarily induced hypoxia in the lower arm (Figure 1B) [7]. In addition, as in adults with CVD, inflammatory markers are increased in children with FH [8]. These observations do not only illustrate the established relationship between atherogenic lipoproteins and atherosclerosis [3, 9], but also point to the increased susceptibility to atherosclerosis in FH children.

Recently, the American Heart Association published a 'Scientific Statement' on cardiovascular risk reduction in high-risk paediatric patients. In this paper, three categories of CVD risk during childhood were defined: Tier I for clinical evidence of manifest coronary artery disease <30 years of age ('high risk'), Tier II for pathophysiological evidence of accelerated atherosclerosis ('moderate risk'), and Tier III for epidemiological evidence of a high-risk setting for accelerated atherosclerosis (at risk) (Table I). As an example, children homozygous for FH and children with Kawasaki disease with coronary aneurysms are assigned to Tier I whilst children with heterozygous

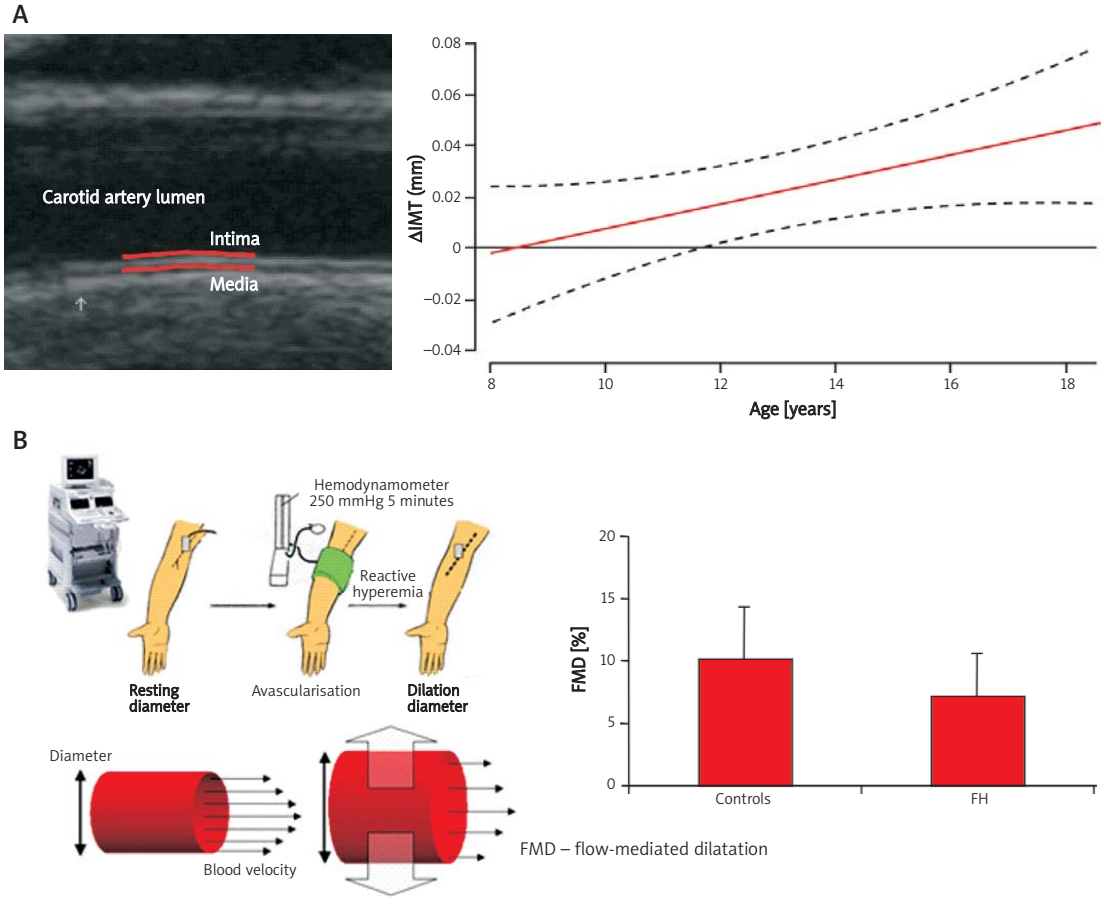

Figure 1. Morphological (A) and functional (B) changes of the vasculature in children with familial hypercholesterolaemia

Table I. Tiers of cardiovascular disease risk during childhood according to the 'American Heart Association's Scientific Statement' [10]

Tier	Category	Definition	Example of condition
I	High risk	Manifest CAD <30 years of age: clinical evidence	Homozygous familial hypercholesterolaemia
II	Moderate risk	Accelerated atherosclerosis: pathophysiological evidence	Heterozygous familial hypercholesterolaemia
III	At risk	High-risk setting for accelerated atherosclerosis: epidemiological evidence	Post-cancer-treatment survivors

CAD – coronary artery disease

FH and children with Kawasaki disease without coronary involvement are allocated to Tiers II and III, respectively. For every category, Tier-specific cut points and treatment goals concerning body mass index (BMI), blood pressure, fasting glucose, HgbA1c and LDL-C are advised. Treatment of dyslipidaemia, in particular elevated LDL-C, is the spearhead for all three categories of patients [10].

In adults, statins – or HMG-CoA reductase inhibitors – are the cornerstone of treatment for hypercholesterolaemia, and the experience with this drug class in children is rapidly increasing. Statins act by restraining the activity of the enzyme HMG-CoA reductase in hepatocytes, where it plays a key role in the pathway for cholesterol synthesis. As a result, intracellular cholesterol levels decrease, which subsequently leads to a compensatory upregulation of the LDL-C receptors on the surface of the hepatocytes. This leads to increased clearance of LDL-C from the circulation and to lower plasma LDL-C levels. In hepatocytes, cholesterol is then stored or excreted into the bile [11]. Statins have been proven to be effective, well tolerated and safe agents that indeed reduce CVD mortality in adults [12]. Also in children with FH, statins are generally preferred over other lipid-lowering medication such as bile acid binding resins for reasons of efficacy and compliance [13, 14]. Several clinical studies so far have shown that statins are effective and well tolerated in children [15-41]. Nevertheless, the safety of statin therapy during childhood remains a concern in clinical practice, especially where it applies to long-term or even lifelong safety. Therefore, this review will mainly focus on various safety aspects of statin therapy in children, after a brief paragraph on efficacy.

Efficacy of statin therapy in children

Several clinical trials have evaluated the lipid-altering efficacy of various statins and doses in paediatric populations. These were mostly trials in children with FH, although a number of studies have been performed in paediatric renal and heart transplant patients and children with nephrotic syndrome. Furthermore, a trial in children with systemic lupus erythematosus is currently ongoing [42]. Recently, two meta-analyses were published that assessed the efficacy of statins in children with FH [43, 44]. These meta-analyses showed that the lipid-lowering effect of different types and doses of statins was comparable to adult populations. In our meta-analysis the LDL-C lowering efficacy in the included trials ranged from 21 to 39% [43]. So far, there are no long-term follow-up data available to evaluate the effect of statin therapy started during childhood on cardiovascular endpoints later in life. However, two years of treatment with pravastatin in FH children led to decreased IMT progression when compared to placebo [18]. After this study, children who were on placebo changed to statin treatment and the children in the pravastatin group remained on statin therapy. The IMT was assessed once again after an average treatment period of 4.5 years. Those data revealed that the age of statin initiation was an independent predictor of IMT after follow-up, indicating that earlier initiation of statin treatment delays the progression of carotid IMT to a greater extent in adolescents and young adults [45]. In another study, treatment with simvastatin restored endothelial function, as measured by FMD, in children with FH [6], which suggests that early treatment still can normalize endothelial function. There are no data available on (surrogate) endpoints for indications other than FH.

According to the above-mentioned scientific statement of the American Heart Association, LDL-C should be ≤100 mg/dL (2.6 mmol/L) and ≤130 mg/dL (3.3 mmol/L) for patients at high and moderate risk respectively [10]. To reach these targets, some patients will require LDL-C reductions of more than 39%, which is the highest reduction obtained in a paediatric study to date. Therefore, more effective regimens than the ones studied so far should be developed. Currently, studies in FH children are ongoing with the most powerful statin available, rosuvastatin [46], as well as with the combination of simvastatin and ezetimibe, a cholesterol absorption inhibitor [47].

Pharmacology

To our knowledge, the only statin investigated in children with respect to pharmacokinetics and

pharmacodynamics is pravastatin. Studies in adults showed that the oral absorption of pravastatin averages 34% with an 18% bioavailability. Furthermore, the maximum plasma concentration (Cmax) is reached approximately 1 hour after ingestion, and the half life is 1-3 hours. Clearance of pravastatin is for 47% renal and for 53% by non-renal routes. The cytochrome P450 system is not involved in the metabolism of pravastatin [48]. Two studies investigated the pharmacokinetics in children with FH, using pravastatin 10-20 mg without any concomitant medication [20, 41] and one study focussed on cardiac transplant patients [33]. In the two studies in children with FH using pravastatin 10-20 mg alone, the pharmacological profile was largely similar to that of adults. The Cmax, as in adults treated with pravastatin, was highly variable, ranging from 1.6 to 55 ng/mL in the study of Wiersma et al. [41]. The study of Hedman et al. showed a significant inverse correlation between Cmax and age, weight and BMI [20]. Although the difference was not significant, the prepubertal patients in the study of Wiersma also tended to have a higher Cmax than the pubertal children ($p=0.09$), and Cmax was also inversely correlated with age. However, both studies found no correlation between Cmax and the percentage decrease of LDL-C, suggesting that plasma levels are not representative for the response to pravastatin. These studies do not indicate that pravastatin should be prescribed in a dosage according to body weight or age, or that different dosage regimens from those in adults should be applied for children. However, for prepubertal children, half the starting dose for adults may be sufficient [41]. This is in line with the registration of pravastatin by the 'European Medicines Agency'; for children with FH a dosage of 20 mg is advised when <14 years of age and 40 mg when aged ≥14.

Another study of Hedman et al. evaluated pharmacokinetics and pharmacodynamics of pravastatin 10 mg in paediatric and adolescent cardiac transplant recipients who were on a regimen of triple immunosuppression [33]. Those patients received pravastatin therapy because it has been shown to decrease the incidence of rejection and to improve patient survival in adult patients after cardiac transplantation [49]. In this paediatric population the Cmax and area under the curve (AUC), which is a measure of total exposure to a drug dose, were nearly 10-fold higher than in children with FH who did not receive immunosuppressive therapy. Elimination half life was similar to that observed in children with FH. Despite the much higher plasma concentrations, LDL-C decreased by a moderate 27% and no clinically significant side effects were reported. The underlying mechanism causing the higher plasma concentration is most likely an interaction with the concomitant immunosuppressive medication [33].

Conclusively, we can appreciate from these studies that the pharmacological profile of pravastatin in children and adolescents is roughly similar to that of adults, but that higher blood plasma levels in young children may warrant a lower starting dose in this group. Furthermore, higher blood plasma levels do not necessarily lead to more profound LDL-C reductions or adverse safety outcomes. To our knowledge, it is unknown to what extent the pharmacological profile of pravastatin in children can be extrapolated to other statins.

Clinical studies

Statins have been extensively studied in adult patients for several indications and, in general, they have an excellent safety profile. A small percentage of patients experiences muscle- and liver-related adverse events, which are the main concerns of statin therapy in adults. However, these and other safety outcomes in adults cannot be simply extrapolated to paediatric patients. Naturally, in the latter population, outcomes on growth and (sexual) development are of crucial importance as well. Furthermore, specific concerns have been expressed regarding the hormonal status in children treated with statins. Since cholesterol is an important precursor for the synthesis of steroid and sex hormones [50] that are crucial for growth and development, the hypothesis that the levels of these hormones might be influenced by statin therapy is obvious. Therefore, in our opinion, the following safety outcomes should be considered when statin safety is examined in children: clinical adverse events, growth and sexual development, levels of steroid and sex hormones, creatinine kinase (CK) levels as an indicator for muscle damage, and alanine aminotransferase (ALAT) as well as aspartate aminotransferase (ASAT) to detect possible liver cell dysfunction.

Since 1996, several clinical studies have evaluated statin safety in children by assessing (some of) those safety parameters (Table II). Altogether, these studies constitute a total of 38,000 person follow-up years in 1084 patients. The studies concerning children with FH have recently been discussed in three reviews: our group performed a meta-analyses on six high quality randomized controlled clinical trials (RCT) [43], Arambepola et al. [44] performed a meta-analysis on efficacy and reviewed safety data of 18 clinical studies including RCTs as well as open-label crossover trials and prospective case series, and Iughetti et al. [51] wrote an extensive narrative review about the treatment of children with FH. These reviews all supported the notion that statin therapy is safe and efficacious in children with FH.

With respect to the occurrence of clinical adverse events of any kind, the meta-analysis earlier published by our group revealed no significant

Table II. Overview of clinical studies on statin therapy in children

Characteristics of studies					Safety outcomes						
Study, year [ref.]	**Design**	**Indication**	**Treatment of subjects**	**Duration**	**Any adverse event**	**Growth**	**Sexual development**	**Hormones**	**CK**	**ASAT**	**ALAT**
Hedman, 2005 [16]	Prospective cohort study	FH	n=30: pravastatin 5-60 mg	12-24 mo	'Most symptoms mild'	Remained normal	Remained normal	No clinically significant change in test., oestr. ACTH	No clinically significant elevations	No clinically significant elevations	No clinically significant elevations
Clauss, 2005 [17]	RCT	FH	n=35: lovastatin 20-40 mg n=19: placebo	6 mo	Statin: 23 Placebo: 13	No significant difference	Not reported	No change in FSH, cortisol, DHEAS, LH	No elevations ≥10×ULN	No elevations ≥3×ULN	No elevations ≥3×ULN
Wiegman, 2004 [18]	RCT	FH	n=110: pravastatin 20-40 mg n=104: placebo	26 mo	Number of subjects with an AE not reported	No significant difference	No difference in Tanner Stage progression	No significant difference in corticotr., cort., DHEAS, FSH, LH, thyrotr., oestr., test.	Statin: 1 Placebo: 1 (elevation ≥10×ULN)	Statin: 0 Placebo: 2 (elevation ≥3×ULN)	No elevations ≥3×ULN
McCrindle, 2003 [19]	RCT	FH	n=140: atorvastatin 10-20 mg n= 47: placebo	6,5 mo	Statin: 88 Placebo: 29	Not reported	No significant difference in Tanner Stage progression	Not reported	No elevations ≥10×ULN	Statin: 2 Placebo: 0 (elevation ≥3×ULN)	Statin: 1 Placebo: 0 (elevation ≥3×ULN)
Wiersma, 2004 [41]	Prospective cohort study	FH	n=24: pravastatin 20 mg	1,5 mo	'No serious AEs, well tolerated'	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Hedman, 2003 [20]	Prospective cohort study	FH	n=20: pravastatin 10 mg	2 mo	'Few transient AEs'	Not reported	Not reported	Not reported	No elevations	No elevations	No elevations
Dirisamer, 2003 [21]	Prospective cohort study	FH	n=20: simvastatin ≤20 mg	12 mo	5 subjects with an AE	Not reported	Not reported	Not reported	n=2 'slightly higher'	No elevations	n=1 'slightly higher'
De Jongh, 2002 [22]	RCT	FH	n=106: simvastatin 40 mg n=69: placebo	12 mo	Statin: 93 Placebo: 57	No significant difference	No significant difference in Tanner Stage progression	No difference cort., test., oestr., FSH, significant difference DHEAS	Statin: 1 Placebo: 0 (elevation ≥10×ULN)	Statin: 2 Placebo: 0 (elevation ≥3×ULN)	Statin: 2 Placebo: 0 (elevation ≥3×ULN)
Vohl, 2002 [23]	RCT	FH	n=47: simvastatin 20 mg n=17: placebo	1,5 mo	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

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Athyros, 2002 [24]	Prospective cohort study	FH	n=16: atorvastatin 10-40 mg and cholestyramine	36 mo	'No statin related side-effects'	'No effect on growth'	Not reported	Not reported	Not reported	Not reported	Not reported
McCrindle, 2002 [25]	Rand. cross-over trial	FH/ FCH	n=38: colestipol 10 g (arm I) and pravastatin 10 mg, colestipol 5 g (arm II)	2×4,5 mo	Not reported	Not reported	Not reported	Not reported	No significant change	No significant change	No significant change
Stein, 1999 [26]	RCT	FH	n=67: lovastatin 40 mg n=65: placebo	12 mo	No AEs	No significant difference	No significant difference in Tanner Stage progression	No change test., LH. Significant difference DHEAS (↑)	No elevations ≥10×ULN	No elevations ≥3×ULN	No elevations ≥3×ULN
Stefanutti, 1999 [15]	Non-rand. parallel matched trial	FH	n=8: simvastatin 10 mg and diet n=8: diet only	12 mo	'No side-effects observed'	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Couture, 1998 [27]	RCT	FH	n=47: simvastatin 20 mg n=16: placebo	1,5 mo	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Knipscheer, 1996 [28]	RCT	FH	n=18: pravastatin 5 mg n=18: pravastatin 10 mg n=18: pravastatin 20 mg n=18: placebo	3 mo	5 mg group: 3 10 mg group: 6 20 mg group: 1 Placebo: 9	Not reported	Not reported	No significant change in ACTH, cort., TSH	5 mg group: 6 10 mg group: 11 20 mg group: 8 Placebo: 8 (elevation ≥10xULN)	No elevations ≥3×ULN	No elevations ≥3×ULN
Lambert, 1996 [29]	RCT	FH	n=17 (men): lovastatin 10 mg n=18 (men): lovastatin 20 mg n=19 (men): lovastatin 30 mg n=15 (men): lovastatin 40 mg	2 mo	10 subjects with ≥1 AEs reported	Not reported	Not reported	No difference FSH, LH, test., androstenedione, progest. Significant difference DHEAS between groups (↑↓)	n=3 elevations ≥3×ULN	Small but significant increase	No significant increase

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Ducobu, 1992 [30]	Prospective cohort study	Hyp. chol.	n=32: 5-20 mg	24-26 mo	Not reported	'Remained in same percentile'	Not reported	Not reported	No significant change	No significant change	No significant change
Sinzinger, 1992 [31]	Prospective cohort study	Severe hyp. chol.	n=13: lovastatin 20 mg or lovastatin 20 mg and 8 g cholestyramine	52 mo	'No sign. change in any of the safety parameters'	'Remained in same percentile'	Not reported	Not reported	Not reported	Not reported	Not reported
Mahle, 2005 [32]	Retrospect. cohort study	Card. trans.	n=90: pravastatin 0.1-0.3 mg/kg (+immuno-suppression)	Mean follow-up 6.1±3.7 years	2 patients discontinued: n=1 leg pain n=1 headache	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Hedman, 2004 [33]	Prospective cohort study	Card. trans.	n=19: pravastatin 0.1-0.3 mg/kg (+immuno-suppression)	2 mo	Not reported	Not reported	Not reported	Not reported	No significant increase	No significant increase	No significant increase
Seipelt, 2004 [34]	Retrospect. chart review	Card. trans.	n=20: pravastatin 5-20 mg (+immuno-suppression)	6-62 mo	'No unusual conditions reported'	Not reported	Not reported	Not reported	n=1 'asympt. CK increase'	No elevations	No elevations
Chin, 2002 [35]	Retrospect. cohort study	Card. trans.	n=38: atorvastatin 0.2±0.1 mg/kg (+immuno-suppression)	13.3±0.3 mo	n=2 muscle pain	Not reported	Not reported	Not reported	n=2 asympt. elevations ≥10×ULN, n=2 'mild elevations'	Not reported	No significant difference
Penson, 2001 [36]	Retrospect. cohort study	Card. trans.	n=20: pravastatin 10-20 mg (+immuno-suppression)	Not reported	'No clinical evidence of myositis'	Not reported	Not reported	Not reported	No significant changes	No significant changes	Not reported
Butani, 2003 [37]	Retrospect. case-control study	Renal trans.	n=7: pravastatin 10-20 mg n=9: renal trans. recipients who did not receive pravastatin (+immuno-suppression)	12 mo	'No adverse reactions'	'No noticeable change in growth velocity'	Not reported	Not reported	No elevations	Not reported	Not reported

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Study, year [ref.]	Design	Indication	Treatment of subjects	Duration	Any adverse event	Growth	Sexual development	Hormones	CK	ASAT	ALAT
Argent, 2003 [38]	Prospective cohort study	Renal trans.	n=9: hypercholesterolaemic subjects treated with atorvastatin 5-30 mg (+immunosuppression)	7-11 mo	'No myalgia, n=1 mild nausea with spontaneous recovery'	Not reported	Not reported	Not reported	No significant change	No significant change	No significant change
Sanjad, 1997 [39]	Prospective cohort study	Ster. res. nephr. syndr.	n=12: lovastatin ≤40 mg or simvastatin ≤20 mg	12-60 mo	'Well tolerated'	Not reported	Not reported	Not reported	Remained normal	Remained normal	Remained normal
Coleman, 1996 [40]	Prospective cohort study	Ster. res. nephr. syndr.	n=7: simvastatin 5-40 mg	10 mo	Not reported	'Growth parameters were maintained'	Not reported	Not reported	Not reported	Not reported	Not reported

CK – creatinine kinase, ASAT – aspartate aminotransferase, ALAT – alanine aminotransferase, RCT – randomized controlled trial, FH – familial hypercholesterolaemia, mo – months, FSH – follicle stimulating hormone, DHEAS – dehydroepiandrosterone sulphate, LH – luteinizing hormone, ULN – upper limit of normal, AE – adverse event, corticotr. – corticotrophin, cort. – cortisol, thyrotr. – thyrotropin, oestr. – oestradiol, test. – testosterone, rand. – randomized, FCH – familial combined hyperlipidaemia, progest. – 17-hydroxyprogesterone, hyp. chol. – hypercholesterolaemia, card. trans. – cardiac transplant recipients, retrospect. – retrospective, renal trans. – renal transplant recipients, ster. res. nephr. syndr. – steroid-resistant nephrotic syndrome

difference between statin- and placebo-treated children, quantified by a relative risk (RR) of 0.99 (95% confidence interval (CI): 0.79-1.25) [43]. Furthermore, in none of the non-randomized or non-placebo-controlled studies in children with FH, or in studies in paediatric cardiac transplant and nephrotic syndrome patients, were differences in the occurrence of adverse events found.

Notably, our meta-analysis did suggest a statistically significant effect of statin therapy on growth which at least deserves discussion. The pooled height change over four RCTs with a duration ranging from 6 to 26 months was 0.33 cm (95% CI 0.03-0.63) higher in subjects treated with a statin compared with those on placebo. When data on height change of the separate studies are considered, only the subgroup of male participants in a study with simvastatin 40 mg revealed a significant difference of 0.8 cm (95% CI 0.20-1.40) [22, 43]. Because this was a relatively large subgroup of 60 patients treated with simvastatin versus 35 on placebo, this value substantially influenced the outcome of data pooling. Although statistically significant, the difference found in this study is likely attributable to chance. From a more practical point of view, one could also doubt the clinical significance of the small absolute difference of 0.33 cm. Other clinical studies on statin safety in children that were not included in this meta-analysis did not indicate an effect on growth [16, 24, 30, 31, 37, 40]. Overall, we think it is unlikely that statin treatment affects natural growth.

Four studies in children with FH [18, 19, 22, 26] investigated sexual maturation by assessing the advancement in Tanner stage classification during the study. In this classification, sexual maturation is ordered in five stages according to characteristics of pubic hair, testicle size (males) and breast development (females). These four RCTs did not find differences between statin- and placebo-treated subjects.

Furthermore, several studies evaluated steroid and sex hormones [16-18, 22, 26, 28, 29]. An important restriction in the assessment of these hormones is the natural variability over time, influenced by various known and probably also unknown factors, which hampers the possibility of correction for such factors. This makes a valid comparison between groups difficult, especially when the number of subjects

per group is limited. In addition, the naturally skewed distribution confines statistical approaches to hormonal changes. The studies that evaluated the effect of statins on hormone levels report contradictory results. Small but significant differences, both positive and negative, were reported for DHEAS, ACTH and LH [16, 22, 26, 29]. These differences did not affect clinical outcomes such as sexual development. Therefore, based on the currently existing data, we consider it highly probable that these differences are attributable to methodological limitations.

Although muscle toxicity of statins is described in adult patients [52], no significant differences in clinical muscle related events or CK levels were found in paediatric studies [15-22, 24-26, 28-39]. We are aware of one published case of rhabdomyolysis due to statin therapy in a child [53]. Temporary and mild elevations of CK are quite frequently observed in statin-treated children but are often preceded by intensive physical activity and resolve spontaneously within a short time. Nevertheless, monitoring of CK levels in children treated with statins is advised at basline, 4 weeks after initiation of therapy and subsequently every 3 to 6 months [54].

A similar argumentation applies to liver toxicity. Although extensively evaluated, actually none of the studies on statin safety in children have reported impaired liver function or liver cell damage due to statin therapy [16-22, 25, 26, 28-30, 33-36, 38, 39]. However, as for CK, monitoring of ALAT and ASAT is advised at baseline, 4 weeks after initiation of therapy and subsequently every 3 to 6 months [54].

Finally, the psychological impact of statin therapy was investigated in one study in children with FH [55]. Because statin therapy is a lifelong issue, this is an important matter to consider. In the study, a questionnaire was sent to 69 children treated with simvastatin. Of these children, 62% felt safer by taking the medication and 81% expressed that they had no difficulties with the knowledge that they would have to take the medication for the rest of their life.

In conclusion, the currently available studies all support the safety of statin therapy in children with FH, paediatric cardiac and renal transplant recipients and children with steroid-resistant nephrotic syndrome. Future studies on statin safety should, in our opinion, focus on three aspects. Because atherosclerosis is slowly progressive over life and the indications for statin therapy so far identified constitute chronic conditions, statin therapy should almost always be continued for life. It was in 1987 that the first statin was approved by the American Food and Drug Administration; hence there are no follow-up data of more than 20 years, for children in particular this lifespan is even shorter. Although methodologically complex, this warrants further studies with a long – ideally lifelong – follow-up. Secondly, studies in larger populations might further clarify the clinical importance of rare side-effects or possibly subtle physiological changes such as change in height or minor influence on hormone levels induced by statin therapy. Finally, because drug safety can only be considered in the light of weighing the risk of medication use versus clinical benefit for the individual patient, efficacy of statin therapy (started) in childhood on hard clinical endpoints should be investigated. This does not only apply to the indications mentioned in this review, but might also be considered for other conditions increasing risk for CVD such as diabetes mellitus and metabolic syndrome. We do realize however that methodological and ethical issues will, in practice, make it impossible to carry out such research.

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