(FMD) and arterial stiffness (AS) changes are more sensitive than intima-media thickness (IMT) in detecting early-onset atherosclerosis in children as they capture the earliest functional changes within the arterial wall [2, 3]. However, FMD and AS measurements are technically challenging and relatively complex, partly accounting for the variations in normative values across paediatric studies. Nonetheless, most studies show marked impairment in FMD within the superficial femoral or brachial arteries in untreated children with FH [4-8]. Furthermore, FMD impairment was worse in children who had a positive family history of premature cardiovascular disease or who presented with elevated glucose levels [9, 10]. Moreover, increased AS at the carotid arteries is consistently documented in children with FH [3, 10, 11]. Conversely, reports of carotid intima media thickness (IMT) in children with FH are variable, with most, but not all, studies reporting an increase [6, 12-14]. Noteworthy variables such as sex (males more than females), age, circulating levels of apoprotein B, fibrinogen, triglycerides, and a positive family history of premature coronary heart disease (CHD) have been identified as influencing factors for the vascular outcomes [6, 12]. Currently, the recommended approach for managing FH involves the use of statins, inhibitors of hydroxymethylglutaryl-CoA (HMG-CoA) reductase, when dietary modifications and adequate physical activity fail to lower LDL-C levels below 4.5 mmol/L (180 mg/dL) after 3 to 6 months [16]. Elevated levels of LDL-C, particularly oxidized LDL-C, are recognized as a principal contributor to premature atherosclerosis in FH [17]. In addition to lowering serum LDL-C, statins can mitigate atherosclerosis progression by upregulating endothelial cell NO synthase [4, 5]. According to the UK NICE FH guidelines and the European consensus guidelines, the recommended age for statin treatment is 10 years, although individuals at high risk with LDL-C levels above 5 mmol/L can start treatment as early as the age of 8 [1]. Within Europe, several statins, including simvastatin, pravastatin, lovastatin, fluvastatin, rosuvastatin, and atorvastatin, each with varying potencies, have received approval for use in children and adolescents with FH based on demonstrated efficacy in reducing the serum LDL-C levels [18-25]. However, no specific guidelines currently stipulate the choice of statin type for pediatric use, and there is limited information regarding the impact of statins on vascular function in children with FH. Here, we review the literature on the changes in vascular function at superficial arteries as assessed by ultrasound in adolescents with FH under statin treatment. Our aim is to strengthen the current practical guidelines regarding the initiation of statin therapy and ultimately establish specific LDL-C targets for children and adolescents with FH.

Methods

Literature search

We conducted a comprehensive literature search on studies investigating the effect of statin treatment on FMD, AS, and IMT in children or adolescents with FH. The search was performed using the PubMed database in November 2023. Our inclusion criteria encompassed studies employing ultrasound methods. Conversely, studies were excluded if they met the following criteria: 1) studies featuring a mixed cohort of children, including those with FH and other dyslipidemias or high-risk disorders, or 2) studies involving combined pharmacological therapies of statins and other lipid-lowering drugs. For articles related to FMD, the following search terms were used: familial hypercholesterolemia AND flow-mediated dilation AND (statins OR hydroxymethylglutaryl-CoA reductase inhibitors) AND (children OR adolescents). In total 11 articles were retrieved of which only two reported on children with FH under statin treatment. For articles related to AS, we used: Familial hypercholesterolemia AND arterial stiffness AND (statins OR hydroxymethylglutaryl-CoA reductase inhibitor) AND (children OR adolescents) as well as Familial hypercholesterolemia AND arterial compliance AND (statins OR hydroxymethylglutaryl-CoA reductase inhibitor) AND (children OR adolescents) were used in PubMed search to find articles on arterial stiffness. A total of 12 articles were found, of which only 3 reported sonographic stiffness indices (stiffness index, augmentation index, elastic modulus) at the carotid artery. Our analysis exclusively considered carotid artery studies, as in FH the process of elasticity reduction is more pronounced in the carotid arteries than in the aorta due to their musculo-elastic characteristics [26]. For articles on IMT, we used the following terms: familial hypercholesterolemia AND intima-media thickness AND (statins OR hydroxymethylglutaryl-CoA reductase inhibitor) AND (children OR adolescents). This search yielded 44 articles, of which 13 studies reported changes in IMT in children and adolescents receiving statin treatment. Among these, two articles were reviews of studies on IMT, while four articles described the same study population at various time points (2, 5, 10 and 20 years of therapy, respectively). We only included studies using automated carotid artery IMT measurements.

All studies are summarized in Table 1, 2 and 3.

Results

Vascular changes during statin treatment

Flow-mediated dilation: We retrieved only 2 studies investigating the impact of statins on vascular function as assessed by measuring FMD [4, 27]. Both studies reported an increase in FMD following simvastatin treatment, after either 1 month or 7 months, respectively (Table 4). de Jongh et al. observed a significantly greater improvement in FMD among adolescents treated with simvastatin compared to placebo. Interestingly, FMD levels in statin-treated FH children reached levels similar to those of non-FH controls (15.5 ± 5.4 % vs. 15.6 ± 6.8 %). These authors also found an inverse correlation between the absolute FMD change and changes in

Table 1: Summary of flow-mediated dilation studies in children and adolescents with familial hypercholesterolemia, treated with statins.

Author, publication year, (Ref.)	Participants		Statin			Mean LDL-C reduction (%)	Main results
	At baseline	At follow-up	Type	Dose (mg)	Duration		
de Jongh, 2002 (4)	FH with statins (n = 28, 14.6 ± 2.0 yrs), FH with placebo (n = 22, 14.6 ± 2.0 yrs), ctr (n = 19, 14.2 ± 3.1)	FH with statins (n = 28), FH with placebo (n = 22), ctr (n = 19)	simvastatin	40	28 wks	39.8	Impaired FMD in FH compared to control group at baseline. Increased FMD after short-term simvastatin therapy.
Ferreira, 2007 (27)	FH (n = 18, 10.28 ± 3.97 yrs), ctr (n = 18, 10.33 ± 3.33 yrs)	FH (n = 18), ctr (n = 18)	simvastatin	10	4 wks	37	Impaired FMD in FH at baseline. FMD restoration after 1-month simvastatin therapy.

Data are presented as mean ± standard deviation. ctr, control; FH, familial hypercholesterolemia; FMD, flow-mediated dilation; wks, weeks; yrs, years

Table 2: Summary of arterial stiffness studies in children and adolescents with familial hypercholesterolemia, treated with statins.

Author, publication year, (Ref.)	Participants		Statin			Mean LDL-C reduction (%)	Method	Main results
	At baseline	At follow-up	Type	Dose (mg)	Duration			
van der Graaf, 2006 (23)	FH (n = 84, 12.6 ± 2.1 yrs)	FH (n = 79)	fluvastatin	20-80	2yrs	33.9	M-mode arterial wall stiffness	Carotid arterial wall stiffness was not affected during fluvastatin therapy.
Hennig, 2020 (28)	FH (n = 57, 9.57 ± 3.26 yrs)	FH with diet only, (n = 11), FH with statin (n = 15)	rosuvastatin	5-40	1yr	34.4	Beta stiffness index	Significant decrease in the carotid beta index stiffness after 1 year of statin treatment.

Data are presented as mean ± standard deviation. FH, familial hypercholesterolemia; yrs, years

LDL-C and triglycerides (TG) levels (-2.13 ± 0.99 mmol/L; -0.19 ± 0.37 mmol/L). Ferreira et al. also reported significant reductions in total cholesterol (TC) (-29%), LDL-C (-37%), and apoB levels (-36%), alongside improved FMD results.

Arterial stiffness: Two studies assessed carotid stiffness before and after initiating statin therapy (Table 5). The first study showed a non-significant tendency of increased AS after initiating fluvastatin (+0.017 %), suggesting that AS remained relatively unchanged after 2 years [23]. The second study, using rosuvastatin, showed a non-significant tendency of reduced carotid beta stiffness after 1 year of treatment. Nonetheless, the decrease was greater than the observed changes in an FH population treated solely with a low-cholesterol diet [28].

Intima-media thickness: The included studies reporting on IMT changes following statin treatment are listed in Table 6. A study evaluating IMT after 2 years of pravastatin therapy reported a slight reduction of 0.010 ± 0.048 mm/y in IMT [20]. Follow-up assessments conducted after 5, 10, and 20 years demonstrated continued improvement in IMT with prolonged statin treatment, eventually reaching a level comparable to unaffected siblings (+ 0.0056 ± 0.0005 mm/y, vs + 0.0057 ± 0.0008 mm/y) [14, 29, 30]. Rosuvastatin treatment also resulted in a notable reduction in the progression of increased IMT. After 2 years of treatment, there was almost no difference in carotid IMT compared to unaffected siblings (0.408 ± 0.043 mm, vs 0.402 ± 0.042 mm) [31]. However, a more recent study with rosuvastatin reported an insignificant decrease in carotid IMT after 1 year of therapy [28]. In another study with pravastatin, there was a nonsignificant increase in carotid IMT after 1 and 2 years of therapy, respectively (+ 0.02 ± 0.06 mm; + 0,01 ± 0.06 mm) [32]. A study with fluvastatin did not reveal any improvement in carotid IMT after 2 years of treatment [23].

Associated factors of vascular changes during statin treatment

In both FMD studies, elevated LDL-C levels were observed to adversely affect FMD results, with Ferreira et al. additionally noting that high fibrinogen levels had a detrimental impact [27]. When considering AS, van der

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Table 3: Summary of intima-media thickness in children and adolescents with familial hypercholesterolemia, treated with statins.

Author, publication year, (Ref.)	Participants		Statin			Mean LDL-C reduction (%)	Method	Main results
	At baseline	At follow-up	Type	Dose (mg)	Duration			
Wiegman, 2004 (20)	FH with statins (n = 106, 13 ± 3.0 yrs), FH with placebo (n = 108, 13 ± 2.9 yrs)	FH with statins (n = 104, 15 ± 3.0 yrs), FH with placebo (n = 107, 15 ± 2.9 yrs)	pravastatin	20-40	2 yrs	24.1	carotid IMT	Regression of IMT in adolescents after 2 years of pravastatin compared to those who got placebo.
Hedman, 2005 (32)	FH (n = 30, 10.1 ± 3.4 yrs)	FH (n = 30)	pravastatin	Oct-60	1 – 2 yrs	33.1	carotid IMT	Non-significant increase in the IMT after 1 and 2 years of pravastatin.
van der Graaf, 2006 (23)	FH (n = 84, 12.6 ± 2.1 yrs)	FH (n = 84, 14.6 ± 2.1 yrs)	fluvastatin	80	2 yrs	33.9	carotid IMT	No differences in IMT after 2 years of fluvastatin therapy.
Rodenburg, 2007 (30)	FH (n = 186, 13.7 ± 3.1 yrs)	FH (n = 186, 18.2 ± 2.6 yrs)	pravastatin	20-40	2 yrs	29.2	carotid IMT	Regression of IMT in adolescents after early initiation of pravastatin.
Kusters, 2014 (14)	FH (n = 194, 12.9 ± 0.5 yrs), unaffected sibling (n = 83, 13.0 ± 0.7 yrs)	FH (n = 19.4, 24.0 ± 0.5 yrs), unaffected siblings (n – 83, 23.8 ± 0.7 yrs)	pravastatin	20-40	10 yrs	27.1	carotid IMT	Increased IMT in FH compared to unaffected siblings at baseline. Same progression of IMT after 10 years of Pravastatin, but still significantly greater IMT.
Braamskamp, 2017 (31)	FH (n = 198, 12.1 ± 3.3 yrs), unaffected siblings (n = 65, 12.0 ± 3.5 yrs)	FH (n = 197), unaffected siblings (n = 65)	rosuvastatin	Oct-20	2 yrs	41	carotid IMT	Increased IMT in FH compared to unaffected siblings at baseline. Less progression of IMT in children with FH after 2 yrs Rosuvastatin.
Luirink, 2019 (29)	FH (n = 214, 13.0 ± 2.9 yrs), unaffected siblings (n = 95, 12.9 ± 2.9)	FH (n = 184, 31.7 ± 3.2 yrs), unaffected siblings (n = 77, 31.6 ± 3.0 yrs)	pravastatin	20-40	20 yrs	32	carotid IMT	Increased IMT in FH compared to unaffected siblings at baseline. Slowed progression of IMT after 20 years of Pravastatin.
			simvastatin	20-80				
			atorvastatin	Oct-80				
			rosuvastatin	May-40				
Hennig, 2020 (28)	FH (n = 57, 9.57 ± 3.26 yrs)	FH with diet only (n = 12), FH with statin (n = 20)	rosuvastatin	May-40	1 yr	34.4	Carotid IMT	Insignificant decrease in the IMT after 1 year of statin treatment.

Data are presented as mean ± standard deviation. ctr, control; FH, familial hypercholesterolemia; IMT, intima-media thickness; yrs, years

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Table 4: Flow-mediated dilation changes in adolescents with familial hypercholesterolemia treated with statins

	Statin			Placebo			Unaffected siblings		
Study	**Baseline (%)**	**End (%)**	**Mean change (%)**	**Baseline (%)**	**End (%)**	**Mean change (%)**	**Baseline (%)**	**End (%)**	**Mean change (%)**
de Jongh, 2002	11.7 (5.0)	15.5 ± 5.4	3.9 ± 4.3	11.6 ± 3.5	12.7 ± 4.9	1.2 ± 3.9	15.6 ± 6.8		
Ferreira, 2007	5.27 ± 4.67	12.94 ± 7.66	7.66 ± 8.58				15.05 ± 5.97		

Data are presented as mean ± standard deviation.

Table 5: Arterial stiffness changes in adolescents with familial hypercholesterolemia treated with statins

	Statin		
Study	**Baseline (%)**	**End (%)**	**Mean change (%)**
Van der Graaf, 2006	2.773 ± 0.0669	3.001 (0.0824)	0.017
Hennig, 2020			

Data are presented as mean ± standard deviation.

Table 6: Intima-media thickness changes in adolescents with familial hypercholesterolemia treated with statins

	Statin			Placebo			Unaffected control group		
Study	**Baseline (mm)**	**End (mm)**	**Mean change (mm/y)**	**Baseline (mm)**	**End (mm)**	**Mean change (mm/y)**	**Baseline (mm)**	**End (mm)**	**Mean change (mm/y)**
Wiegman, 2004	0.497 ± 0.055		- 0.010 ± 0.048	0.492 ± 0.045		+ 0.005 ± 0.044			
Hedman, 2005	0.42 ± 0.04		+ 0.01 ± 0.06						
van der Graaf, 2006	0.544 ± 0.005		no change						
Rodenburg, 2007	0.494 ± 0.047	0.547 ± 0.060							
Kusters, 2014	0.442 ± 0.007	0.480 ± 0.009	+ 0.039 ± 0.007				0.433 ± 0.009	0.469 ± 0.011	+ 0.037 ± 0.005
Braamskamp, 2017	0.397 ± 0.049	0.408 ± 0.043	+ 0.0054 ± 0.0024				0.377 ± 0.045	0.402 ± 0.042	+ 0.0143 ± 0.0049
Luirink, 2019	0.445 ± 0.008	0.555 ± 0.004	+ 0.0056 ± 0.0005				0.438 ± 0.008	0.551 ± 0.004	+ 0.0057 ± 0.0008
Hennig, 2020									

Data are presented as mean ± standard deviation.

Graaf et al. noted higher stiffness levels in boys [23], while Hennig et al. reported lower AS in younger patients [28]. Regarding IMT, Rodenburg et al. found that IMT increased by 0.003 mm for each year that statin therapy was delayed in children with FH [30]. This age-dependent effect was also observed in five other studies [14, 20, 29, 31]. Furthermore, three studies identified a higher baseline IMT in boys [23, 30, 33, 34]. Notably, Wiegman et al. highlighted the positive impact of a healthy lifestyle on atherosclerotic development, demonstrating a significantly lower increase in IMT in the placebo group due to strict adherence to a healthy lifestyle, which included a fat-modified diet, regular physical exercise, and abstention from smoking [33].

Discussion

This review provides an updated insight into the vascular effects of statin therapy, as measured by ultrasound, in adolescents with FH [35, 36]. Notably, most of these studies confirmed FH through genetic testing. Vascular investigations in childhood provide a unique advantage as treatment outcomes are less influenced by lifestyle factors, including smoking, unhealthy dietary habits, or comorbidities such as longstanding obesity, diabetes mellitus, or arterial hypertension [37]. The pediatric data corroborate findings in adults, emphasizing that the duration and potency of statin therapy are important predictors of improvement in FMD

and carotid artery wall thickness [38]. While FMD has been extensively studied in adults with FH, the pediatric literature includes only 2 studies. Both studies showed an increase in FMD after several months of simvastatin treatment, which concurrently resulted in an LDL-C reduction ranging from 37% to 39.8% [4, 27]. Conversely, the two studies examining AS using M-mode ultrasound produced conflicting results. One study with fluvastatin showed an insignificant increase in AS after 2 years of treatment (+ 0.017 %), while a significant decrease in carotid beta stiffness was observed after 1 year of rosuvastatin therapy. Notably, both studies reported an LDL-C reduction of approximately 33.9% to 34.4 % [23, 28]. These variations in AS results may suggest that factors beyond LDL cholesterol, such as physical activity, could influence longitudinal changes in this parameter [39]. Moreover, the interpretation of longitudinal studies in children is complicated by concurrent changes in arterial size and distensibility with growth. Technical differences should always be considered when comparing vascular studies. Therefore, we included only those studies using automated carotid artery IMT measurements. Despite the use of automated techniques, no or rather late reductions in IMT were observed during statin treatment, and these changes were examined at different moments, ranging from 1 to 20 years of treatment, and involving different statins. Changes in LDL-C also ranged from 24.1% to 41%. Furthermore, most studies did not account for changes in BMI or blood pressure. Consistent with findings in adults, younger age was associated with more favorable IMT changes during statin therapy in most studies [14, 20, 28-31]. The UK NICE FH guidelines recommend starting statin treatment at 10 years, a recommendation substantiated by the vascular changes observed in ultrasound assessments. The higher baseline IMT observed in boys with FH in several studies suggests a potential need for earlier statin treatment in male patients.

It is important to note that some vascular studies involving children may be considered low-confidence due to small sample sizes or a lack of control groups. Additionally, the results may be influenced by varying levels of patient adherence. Interoperator variability on interpretation should also be acknowledged, although it typically remains below 5% for most techniques. However, comparing results across different clinical laboratories employing various techniques remains challenging. None of the studies evaluated the potential impact of lowering Lp(a) concentrations or increasing HDL-C levels during statin treatment. Furthermore, there have been no direct comparative studies examining the effects of different statin types on vascular function. Additionally, it remains uncertain whether the improvement in vascular characteristics independently predicts risk reduction in FH, as recent meta-analyses have primarily focused on changes in lipid profiles [14, 33]. Nevertheless, future longitudinal vascular studies should consider changes in several parameters, including physical activity and blood pressure. Currently, the assessment of vascular function is not a standard criterion for initiating or adjusting statin therapy in FH, although integrating such assessments may contribute to improved therapies for children with FH.

Conclusion

Ultrasound studies focusing on superficial arteries provide compelling evidence for the utility of statin therapy in managing FH among adolescents, showcasing advantageous vascular improvements when initiated at a younger age. However, further research is essential to establish recommendations regarding the preferential use of the most potent statins as the initial treatment and to formulate precise target LDL-cholesterol levels for managing FH in adolescents.

Conflict of Interest Statement

All authors declare that they have no conflicts of interest.

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Author Contributions

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