Management of familial hypercholesterolaemia in childhood

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Purpose of review
All guidelines for the management of heterozygous familial hypercholesterolaemia in children and young people recommend statins to lower LDL-cholesterol (LDL-C) concentrations, to reduce the individual's adult risk of developing cardiovascular disease (CVD). Here, we review recent findings regarding the efficacy and safety of the use of stains in childhood.

Recent findings
As expected from their safety profile in adults, there is no evidence from short-term trials or long-term follow-up that statin use in children is associated with any adverse effects on growth, pubertal development or muscle or liver toxicity. Long-term follow-up indicates benefits with respect to lower CVD rates. Factors that influence adherence are discussed, as is the role of the underlying genetic causes for hypercholesterolaemia and of variation at other genes in determining the LDL-C-lowering effect.

Summary
Based on the good safety profile, and the expert opinion guidelines, clinicians should consider prescribing statins for children with hypercholesterolaemia from the age of at least 10 years (and earlier if CVD risk is particularly high in the family). Uptitrating statin dosage and the use of additional lipid-lowering therapies should be considered so that LDL-C concentrations are lowered to recommended targets.

Keywords
adherence, SCLO1B1 genotype, statin safety, treatment guidelines

INTRODUCTION

Familial hypercholesterolaemia (OMIM #143890) is an autosomal dominant disease which results in elevated concentrations of atherogenic LDL-cholesterol (LDL-C) in the blood from birth (or possible even *in utero*). Individuals with hypercholesterolaemia have a much higher risk of developing premature cardiovascular disease (CVD) than the general population. In a follow-up study of over 14 000 individuals with clinical characteristic of hypercholesterolaemia, matched with 42 500 UK general practice individuals (mean age 45 years), those with the characteristics of hypercholesterolaemia had a hazard ratio 13.5-fold higher for developing CVD over a 13.8 median years follow-up, than the nonhypercholesterolaemia group [1▪]. By contrast, in those with a formal diagnosis of hypercholesterolaemia in their notes and who were being treated with statin therapy, the CVD hazard ratio was 1.66. Data from the UK 'Simon Broome' hypercholesterolaemia register [2▪▪] has shown that compared with the general population of England and Wales, male patients with 'Severe' hypercholesterolaemia in the age range 20–39 years had a standardized mortality ratio (SMR) of over 1700, with the SMR in women of this age being twice as high (Fig. 1). For both men and women the SMR decreases with age but is always higher in women. Analysis of recent mortality data (2008–2016) has shown that with the availability of potent statins the overall (combing all ages) SMR [95% confidence interval (CI)] has fallen in men from the prestatin era (before 1992) of 356 (178–637) to 159 (91–258), whereas in women the fall has been much less 498 (215–982) to 350 (192–588). Overall these two articles confirm the significantly higher CVD and coronary heart disease (CHD) risk in untreated

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Curr Opin Pediatr 2020, 32:633–640
DOI:10.1097/MOP.0000000000000943

KEY POINTS

- For children with hypercholesterolaemia, statins should be used as the first line of therapy (in tandem with dietary and lifestyle advice).
- Consider statin use by the age of 10 years or earlier if CVD risk factors are present.
- As children approach the age of 14 years, consider to reduce LDL-C below 2.5 mmol/l, by uptitration of statin dose and/or adding other lipid-lowering agents.
- Healthcare professionals should have clear and informative discussions with both children and young people and their carers about the importance of managing their plasma lipid concentrations and their future CVD risk.
- Short-term trials of stains and long-term follow-up show no evidence of clinically significant side effects, no effect on growth or maturation and the expected reduction in CVD.

individuals with hypercholesterolaemia and in particular that risk in the younger age group and especially in women remains high even with the availability of potent statins.

Long-term placebo-controlled randomized controlled trials are neither ethical nor feasible in those with hypercholesterolaemia because of their high CVD risk. However, there is overwhelming evidence that children with hypercholesterolaemia have a markedly elevated risk of future morbidity and mortality from CHD because of their elevated LDL-C, and that early identification and treatment to lower their LDL-C will concomitantly reduce this risk. Based on the population prevalence of hypercholesterolaemia as ~1/250 [3], there are approximately 50 000 hypercholesterolaemia children under 18 years in the United Kingdom, ~260 000 in the USA and over 400 000 in the EU. Over recent years there have been many consensus and expert opinion-based guidelines for the management of children with heterozygous hypercholesterolaemia with the European Atherosclerosis society guideline published in 2014 [4] and a UK guideline in 2019 [5■■] All guidelines recommend that children identified with hypercholesterolaemia should receive clear healthy lifestyle advice, which should of course be also adopted by the whole family. This includes healthy diet choices as well as exercise and nonsmoking information. All guidelines also recommend the use of statin lipid-lowering therapy as a first-line

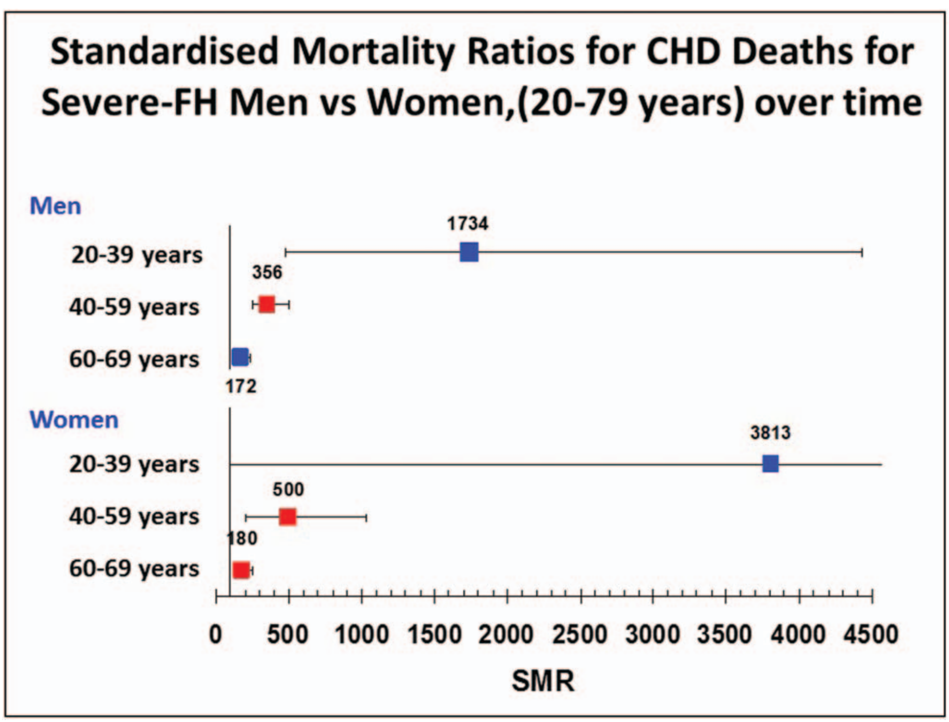

FIGURE 1. Standardized mortality ratios for coronary heart disease deaths of men and women with severe hypercholesterolaemia by age groups. Severe hypercholesterolaemia is diagnosed using criteria originally proposed by the International Atherosclerosis Society and are: if the patient has LDL-cholesterol more than 10 mmol/l, *or* LDL-cholesterol more than 8.0 mmol/l and one high-risk feature, or LDL-cholesterol more than 5 mmol/l and two high-risk features. High-risk features are age more than 40 years without treatment, smoking, male sex, lipoprotein(a) more than 75 nmol/l, hypertension, diabetes mellitus, family history of early coronary heart disease in first-degree relatives, chronic kidney disease and BMI more than 30 kg/m^2. Data from [2■■].

treatment, and this review focusses on the recommendations, safety issues and lifestyle and genetic determinants of response to statin therapy that have been published in the last 18 months for the treatment of children with heterozygous hypercholesterolaemia.

TREATMENT AND SAFETY

The UK consensus statement on the management of children and young people with heterozygous hypercholesterolaemia proposes management strategies for those identified by cascade testing when a parent is diagnosed with hypercholesterolaemia and for those diagnosed following incidental lipid tests, including those found as infants by universal screening [5▪▪]. All children should be seen in a child-friendly and child appropriate environment, by a healthcare professional (HCP) with expertise in managing children. Life-style dietary and exercise advice should be started in childhood, and should ideally be adopted by the whole family. The treatment strategy in three key age categories is shown in Fig. 2. In particular, in those under 10 years of age, if drug treatment is considered appropriate, aim for a 30–50% reduction in LDL-C from baseline or a level less than 3.5 mmol/l, while in those over 10 years aim for a 50% reduction in LDL-C from baseline or a level less than 3.5 mmol/l. Finally in those over 14 years, if there are additional comorbidities (e.g. type 1 diabetes) or a very strong family history of early coronary events in adults in their 2nd and 3rd decade, assuming compliance to statin therapy, the guideline suggests slowly increasing the statin dose and/or with the addition of ezetimibe 10 mg daily, aiming towards a target LDL-C concentration of less than 2.5 mmol/l over the next 3–5 years.

The guideline contains a clear statement that boys and girls both need to be considered for lipid-lowering therapy at the same age, and that initiation of treatment should not be delayed in girls. The increased risk of CVD in hypercholesterolaemia is the result of having an increased 'LDL-C burden' since even a modest elevation in LDL-C concentration accumulates over time and accelerates atherosclerosis. A recent study from Norway [6▪▪] indicates that this LDL-C burden may be greater in girls than in boys. Children and young people with hypercholesterolaemia (438 girls, 452 boys) not receiving lipid-lowering therapy, aged 0–19 years were

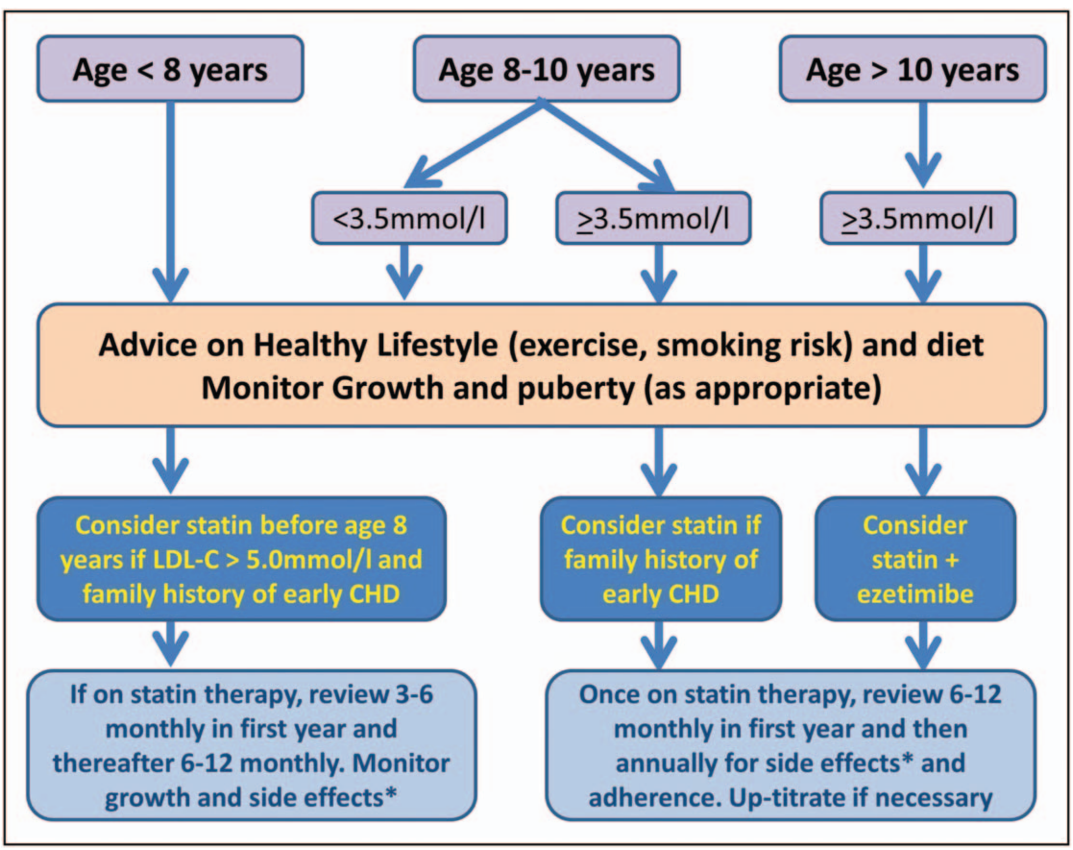

FIGURE 2. UK consensus guideline for clinical management of children and young people with hypercholesterolaemia. For all children with hypercholesterolaemia, dietary and lifestyle advice should be discussed at every visit. CHD, coronary heart disease. *Liver function tests annually and creatine kinase at baseline and thereafter as indicated. Adapted from [5▪▪].

included. Compared with boys, girls had significantly higher mean (95% CI) LDL-C concentrations with differences of 0.39 (0.19–0.59) mmol/l ($P < 0.001$). This estimate did not change after adjustment for age. This would contribute an additional ~7% to the total lifelong LDL-C burden in hypercholesterolaemia women, and with the addition of added burden due to statin cessation during pregnancy and breastfeeding, would help explain the high CVD risk in adult women with hypercholesterolaemia.

The largest study of children published to date is the IAS Register of more than 3000 children with hypercholesterolaemia recruited from eight countries in Europe [7■■]. Some countries such as Holland and Greece have mature hypercholesterolaemia paediatric programmes, whereas others (e.g. Austria) have only recently started systematic case-finding programmes. Not surprisingly the age of hypercholesterolaemia diagnosis in children varied significantly across the countries, as did the proportion of those more than 10 years being treated with statin and/or ezetimibe. Approximately a quarter of the treated children and almost three quarters of the untreated children older than 10 years still had LDL-C concentrations over the guideline recommended 3.5 mmol/l. These data suggest that many children with hypercholesterolaemia are not receiving the full potential benefit of early identification and appropriate lipid-lowering treatment according to recommendations. Data on use of ezetimibe as an adjunct to statin therapy was particularly relevant. Ezetimibe is recommended for adults with hypercholesterolaemia who are statin intolerant or who fail to reach target on statin alone and for children over the age of 10 years. Ezetimibe was used as an adjunct to statin therapy in all countries but at a low and varying frequency. This might have been caused by the relatively high price at the time of analysis and because of relatively limited evidence of its use in children. However, as expected, ezetimibe use lowered LDL-C significantly and more than 90% of children taking a statin and ezetimibe achieved LDL-C below 3.5 mmol/l, compared with only 53% of those on statin only.

One potential harm of the identification and treatment of children with hypercholesterolaemia would be if statin use at an early age (e.g. age 10 years) were associated with any long-term safety issues. Statins have been used in adults (with hypercholesterolaemia and in those in the general population) since the late 1980s, and in the ensuing 40 years no major long-term safety issue have been identified [8]. Studies in children have also found no long-term safety concerns. The 2019 Cochrane review update on the safety of statins in children [9] included 26 potentially eligible studies, which included nine randomized placebo-controlled studies (1177 participants). The magnitude of LDL-C lowering varied from study to study, most likely due to different statins and doses and possibly due to different definitions about true monogenic heterozygous hypercholesterolaemia. The review did not identify any clinically significant side effects with statins (i.e. abnormal liver transaminase or creatine kinase values). Sexual maturation was similar to normal population groups. The review concluded that while long-term safety remains unknown, statin use in childhood was safe in the medium term. This finding is fully supported by the UK Hypercholesterolaemia Children's Register [10] and by a study from France [11], both of which found no instances of clinically relevant safety issues and an equal growth rate in statin treated and nontreated children.

The issue of long-term safety has been recently examined in a 20-year follow-up study of statin therapy in children [12■■]. The individuals studied were hypercholesterolaemia child participants in a 1997–1999 placebo-controlled trial evaluating the 2-year efficacy and safety of pravastatin, who were now invited for follow-up, together with their 95 unaffected siblings. The new study showed that initiation of statin therapy during childhood slowed the progression of carotid intima–media thickness (CIMT) and reduced the risk of CVD in adulthood. Mean progression of CIMT over the entire follow-up period was 0.0056 mm/year in those with hypercholesterolaemia and 0.0057 mm/year in siblings, showing that treatment had reduced the progression of atherosclerosis in the carotid artery (and presumably also in the coronary arteries) to that of a nonhypercholesterolaemia individual. The cumulative incidence of CVD events and of death from CVD at 39 years of age was lower among the treated cohort than among their affected parents (1 vs. 26% and 0 vs. 7%, respectively). Crucially, there were no serious adverse events reported, including no cases of rhabdomyolysis, with no significant differences in liver function observed between those with hypercholesterolaemia and their unaffected siblings [12■■].

ADHERENCE/SUPPORT

One of the key issues in the decision as to whether, and when, to start or uptitrate statin treatment for a child, are the views of the parents/guardians about the risks associated with untreated hypercholesterolaemia and the potential benefit and concern about side effects of the medication prescribed. These issues have been reviewed in a qualitative

Table 1. Analytical and descriptive themes for treatment adherence

Analytical theme	Descriptive themes
Risk assessment	FH is a silent disease Family history modifies perception of FH-related threat to health FH is not as threatening to health as other conditions
Perceived personal control of health	FH is a manageable condition Individuals feel personally responsible for managing their FH FH medication is effective FH lifestyle treatment viewed as less important than medication
Disease identity	Importance of establishing that high cholesterol levels are not self-inflicted Receiving genetic diagnosis provides certainty
The influence of family	Desire to protect children Parental influence on treatment-related behaviours FH and its treatment become normalized within families
Informed decision-making	HCP interactions Inadequate and/or incorrect knowledge about FH and treatment
Incorporating treatment into daily life	FH and its treatment does not have big impact on life Balancing FH treatment with other competing priorities Lifestyle advice treatment is restrictive and difficult to follow Social implications of following FH treatment Desire for further support and guidance

FH, hypercholesterolaemia; HCP, healthcare professional. Adapted from [13].

evidence synthesis, based on a literature search which identified 24 articles reporting the findings of 15 population samples (264 individuals with hypercholesterolaemia and 13 of their family members) across eight countries [13]. Different themes were studied in relation to treatment adherence and as shown in Table 1, six key analytical themes were generated, each with specific descriptive themes. These were used to identify seven 'enablers' of treatment adherence, including other family members on treatment, commencement of treatment from a young age, receiving a formal diagnosis of hypercholesterolaemia and a positive relationship with the HCP. They also identified six barriers to adherence including mismatch between perceived and actual risk, prioritization of other life events and incorrect and/or inadequate knowledge of treatment advice. These give an important framework for the discussions HCPs should have with both children and young people and their carers about the importance of managing their plasma lipid concentrations and their future CVD risk.

Similar issues were reported in a series of in-depth interviews held with 17 families with a child or young person with a genetic diagnosis of hypercholesterolaemia [14]. Four main themes were common, including the need for undertaking early prevention, postponing treatment, parental concerns and the importance of the wider family context. Although the majority of parents supported genetic testing for hypercholesterolaemia in childhood some were supportive of following early treatment recommendations, whereas others expressed reluctance. Some parents were concerned that inappropriate information had been shared with their children and wished that more time could be allotted to discuss how, when and what to tell in advance. The authors concluded that additional research is needed to explore the long-term outcomes for children who undertake genetic testing and early treatment for hypercholesterolaemia, and to test different interventions that may improve the engagement, follow-up and support of children who are at risk, or diagnosed, with hypercholesterolaemia.

GENETICS AND RISK FACTORS

As well as treatment and lifestyle issues, the baseline LDL-C concentration (and thus LDL-C burden and future CVD risk) and to some extent the response to statin therapy and risk of side effects, is determined by the genetic makeup of the child. It is well known that individuals with an LDL-receptor gene (*LDLR*) 'negative' mutation (e.g. a partial gene deletion or a single base change that leads to a premature stop codon) have higher untreated LDL-C than those with an LDLR 'defective' mutation (e.g. a missense mutation which retains partial function of the LDLR). In addition, those with hypercholesterolaemia caused by a mutation in the LDL-C protein apolipoprotein B (*APOB*) have lower mean LDL-C concentrations and show a lower risk of CVD, whereas mutations in *PCSK9* cause a more severe hypercholesterolaemia phenotype. Recently it has also been identified that a particular mutation in the gene coding for apolipoprotein E, leading to the deletion of one amino acid [p.(Leu167del)], can also mimic the hypercholesterolaemia phenotype, with these subjects showing a greater LDL-C-lowering response to statin therapy than *LDLR*-FH patients [15■].

All guidelines recommend the utility of genetic testing to identify the particular underlying DNA cause for the hypercholesterolaemia phenotype to support statin treatment and for use in identifying carrier relatives [4,5■■,16]. The utility of genetic testing in hypercholesterolaemia has been exemplified by several publications. In a recent article [17], two patients from China were studied who were originally clinically diagnosed with homozygous hypercholesterolaemia (HoFH), with untreated total or LDL-C over 13 mmol/l. Often individuals with HoFH have a minimal response to statin therapy because they have little or no residual LDLR function that can be upregulated by statin treatment. However, after recording of the family history and genetic testing of the patients and parents, both were found to have a severe form of heterozygous hypercholesterolaemia. This was caused by different single nucleotide variants, which caused different changes at the same codon for tryptophan at amino acid 483 in *LDLR*, with the Trp383X mutation, resulting in a premature stop codon and Trp383Gly being a missense mutation. Both patients responded well to conventional statin and ezetimibe treatment, with LDL-C concentrations being reduced by 67 and 83%, respectively. This article demonstrates the clinical utility of having a DNA diagnosis of the underlying disorder and the way in which treatment response can be better predicted.

Even using the most sensitive next-generation sequencing approaches, many studies have shown that an *LDLR/APOB/PCSK9* mutation can be found in only ~40% of patients with a clinical diagnosis of hypercholesterolaemia. In the remaining ~60%, a 'Polygenic' cause is most likely to be the cause of the hypercholesterolaemia phenotype, due to the coinheritance of common LDL-C raising variants, which are spread throughout the genome, in genes involved in cholesterol metabolism. The clinical utility of a 12-SNP LDL-C 'SNP-Score' has been confirmed in samples of no-mutation hypercholesterolaemia adults and children from more than eight countries with European-white populations and most recently from Portugal [18■]. In a recent analysis of the data [19], it appears likely that in more than 80% of those with a clinical hypercholesterolaemia but with no detectable mutation, the polygenic explanation is the most likely cause of their hypercholesterolaemia. Guidelines now are being modified to take into account that only in families where the index case has a monogenic cause will it be cost effective to carry out cascade testing. However, finding a polygenic explanation supports a more conservative (less aggressive) treatment care pathway for adults and children with no mutation.

Satin safety is primarily related to differences in the amount of circulating statin in blood after a standard dose, known as the 'systemic exposure'. One of the major causes of differences in the systemic exposure is the uptake of statins by the liver, where they have their lipid-lowering action. The *SLCO1B1* gene, encoding the solute carrier organic anion transporter family member 1B1 protein, has a common functional variant (c.521T>C, rs4149056) which alters the valine amino acid at position 174 to alanine (Val174Ala), which affects the correct localization of the transporter on the basolateral membrane of the hepatocyte. The GnomAD database (https://gnomad.broadinstitute.org/) shows that the frequency of the 174Ala allele is ~16% in European populations and similar in East Asians, but is much lower in those from the Indian subcontinent (5%) and in those of African origin (3%). Thus in European subjects around 27% will be carriers and ~3% will have two copies of the 174Ala allele. This variant alters the function of the OATP1B1 protein such that those with the 174Ala allele have a much slower clearance of statins to the liver, resulting in higher blood statin levels for longer. Individuals homozygous for the 174Ala allele are known to have an ~17-fold higher risk of severe myopathy when given simvastatin, with carriers showing a ~4.5-fold higher risk [20].

An elegant series of articles has examined the role of the allelic variation in the gene coding for on simvastatin [21] pravastatin [22] and rosuvastatin [23■■] exposure in children and adolescents (8–20 years old) following administration with a clinically relevant dose. As shown in Fig. 3, while the absolute exposure is different with different stains, compared with those with two copies of the 174Val allele, 174Ala carriers have 1.4–2.5-fold higher systemic exposure, whereas Ala/Ala individuals have between 2.2 and 6.3-fold higher exposure. Simvastatin showed the greatest and rosuvastatin the smallest Val/Val vs. Ala/Ala differences. The authors point out that there is still a great deal of interindividual differences in exposure not explained by this variant, but the extent of this difference is least for rosuvastatin, suggesting that this agent may be more ideal for clinical use in children.

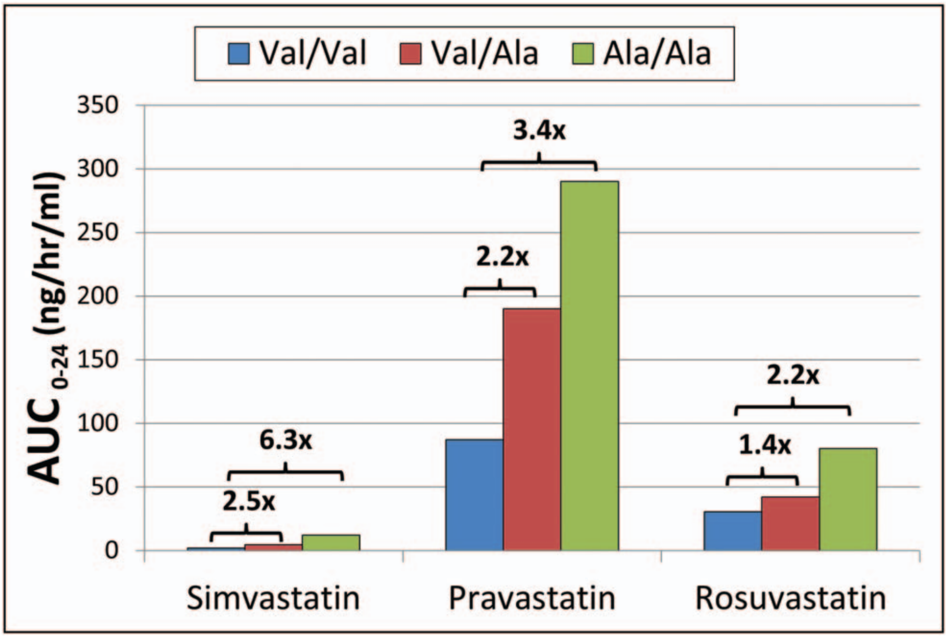

FIGURE 3. Cartoon showing relative area under the curve over 24 h for statin derivatives in the plasma of children given a standard dose of simvastatin, pravastatin or rosuvastatin, with different *SLCO1B1* rs4149056 genotypes. For full details of the methods used, and dosages of statins employed see the original references. Numbers of children for simvastatin/pravastatin/rosuvastatin with different genotypes were Val/Val (15/15/13) Val/Ala (15/15/13) and Ala/Ala (2/2/2). Data from [21,22,23■■].

CONCLUSION

All published paediatric hypercholesterolaemia guidelines recommend the use of genetic tests to confirm the monogenic diagnosis and that statins should be used as the first line of therapy (in tandem with dietary and lifestyle advice). Consensus among experts proposes consideration of statin initiation by 10 years of age, and particularly for children who have an LDL-C concentration above 3.5 mmol/l. The UK guideline proposes uptitration of statin dose or the addition of ezetimibe in young people over 14 years to lower LDL-C below 2.5 mmol/l. Short-term trials of stains show no evidence of clinically significant side effects and no effect on growth or maturation, and one long-term follow-up confirms both safety and the reduction in CVD in those treated as children as they grow into adulthood. When planned trials of novel LDL-C-lowering agents such PCSK9 antibody inhibitors have been completed [24■], these agents may also become available to add to the armoury of lipid-lowering therapies to reduce future CVD risk in children with hypercholesterolaemia.

Acknowledgements

The current work was cowritten by S.E.H. and U.R.

Financial support and sponsorship

The authors acknowledge support from the International Atherosclerosis Society (Pfizer number 24052829), the British Heart Foundation (BHF); HEART UK, Cardiac Network Coordinating Group Wales and the Royal College of Physicians. S.E.H. is an Emeritus BHF Professor and acknowledges funding by PG08/008, and by the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

Conflicts of interest

There are no conflicts of interest.

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■ of special interest
■■ of outstanding interest

1. Iyen B, Qureshi N, Kai J, *et al.* Risk of cardiovascular disease outcomes in
■ primary care subjects with familial hypercholesterolaemia: a cohort study. Atherosclerosis 2019; 287:8–15.

A retrospective cohort study of 14 097 UK subjects with clinical hypercholesterolaemia diagnoses matched to 42 506 subjects without hypercholesterolaemia by age, sex, general practice. During 13.8 years follow-up incidence rates [95% confidence interval (CI)] of cardiovascular disease (CVD) (per 1000 person-years) were 25.6 (24.8–26.3) in hypercholesterolaemia and 2.9 (2.8–3.1) in nonhypercholesterolaemia subjects. The risk of CVD was greater in those with hypercholesterolaemia characteristics who were in general untreated (hazard ratio 13.52, 95% CI 12.48–14.65) than those with clinical diagnoses who in general were statin treated (hazard ratio 1.66, 95% CI 1.42–1.93).

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Out of 2929 patients on the register 1982 (67.7%) patients met the severe hypercholesterolaemia definition. The standardized mortality ratio for coronary heart disease mortality was significantly ($P=0.007$) higher for severe hypercholesterolaemia [220 (184–261)] compared with nonsevere hypercholesterolaemia of 144 (98–203). Many of the patients with severe hypercholesterolaemia are likely to qualify for treatment with PCSK9 mAb inhibitors.

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Key points are children with heterozygous familial hypercholesterolaemia should be managed by paediatric health professionals with expertise in hypercholesterolaemia. Statin to be considered by the age of 10 years and use age appropriate target LDL-cholesterol (LDL-C) level in children with hypercholesterolaemia. Dietary and life style advice should begin in early childhood. From the age of 14 years, consider joint review with adult lipidologist in transition clinic with transfer to adult lipid clinic at 16–18 years.

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By the age of 20 years, the LDL-C burden (sum of the mean annual LDL-C $\times$ age) will be 7.7% higher in girls (121.2 mmol/l in girls and 112.5 mmol/l in boys). This compares with the LDL-C burden in non hypercholesterolaemia children of this age of $\sim$45 mmol/l.

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Comparison of baseline characteristics and pre and post treatment lipid concentrations in more than 3000 children with hypercholesterolaemia from eight countries (Norway, United Kingdom, The Netherlands, Belgium, Czech Republic, Austria, Portugal and Greece). Around 25% of the treated children and almost 75% of the untreated children older than 10 years still have LDL-C levels over 3.5 mmol/l, indicating that many children with hypercholesterolaemia are not receiving the full potential benefit of early identification and appropriate lipid-lowering treatment according to recommendations.

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Of the original cohort, 184 of 214 patients with hypercholesterolaemia (86%) and 77 of 95 siblings (81%) were seen in follow-up. The mean LDL-C concentration in the patients was reduced by 32% from baseline (from 6.13 to 4.16 mmo/l). The cumulative incidence of CVD events and of CVD deaths at age 39 years was lower in children than their affected parents (1 vs. 26% and 0 vs. 7%, respectively).

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On high-intensity statins, mean reduction in LDL-C significantly higher in 22 (Leu167del) carriers vs. 44 LDL-receptor (LDLR) hypercholesterolaemia ($-$52.1 vs. $-$40%, $P=0.040$). This higher lipid-lowering response to statins supports the use of genetics for a more efficient management of hypercholesterolaemia.

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731 Index patients (311 children and 420 adults) who met the Simon Broome diagnostic criteria. The 6-SN LDL-C genetic risk score for polygenic hypercholesterolaemia was used ($>$25th %ile = polygenic cause). An hypercholesterolaemia-causing mutation was found in 39% of patients (94% in LDLR, 5% apolipoprotein B and 1% PCSK9), with 29% with polygenic hypercholesterolaemia.

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