Evidence Synthesis

Number 141

Lipid Screening in Childhood and Adolescence for Detection of Familial Hypercholesterolemia: A Systematic Evidence Review for the U.S. Preventive Services Task Force

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
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Rockville, MD 20850
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Contract No. HHSA-290-2012-00151-I, Task Order No. 2

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AHRQ Publication No. 14-05204-EF-2
December 2015

This report is based on research conducted by the Kaiser Permanente Research Affiliates Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. Contract No. HHSA-290-2012-00151-I, Task Order No. 2). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project: Iris R. Mabry-Hernandez, MD, MPH, for project oversight on behalf of the Agency for Healthcare Research and Quality; current and former members of the U.S. Preventive Services Task Force who contributed to topic deliberations; Stephen R. Daniels, MD, PhD, Patrick McBride, MD, MPH, and Alpo Vuorio, MD, PhD for their expert reviews of the draft reports; David Grossman, MD, MPH, for his feedback on the research plan; Smyth Lai, MLS, for designing and conducting literature searches; Christel Kratohvil for research support and organization; So Man, PhD for providing additional trial data; Gabrielle Gundersen, BA; Brittany Burda, MPH; Caitlyn Senger, MPH; Tracy Beil, MS, and Aaron Scrol, MA.

Structured Abstract

Background. Familial hypercholesterolemia (FH) is an inherited disorder of lipoprotein metabolism characterized by highly elevated total cholesterol concentrations early in life, independent of environmental influences. Around 1 in 200 to 1 in 500 people in North America and Europe are estimated to have heterozygous FH. When untreated, FH is associated with a high incidence of premature clinical atherosclerotic cardiovascular disease.

Purpose. We conducted a systematic evidence review of the benefits and harms of screening children and adolescents for heterozygous familial hypercholesterolemia (FH). The purpose of this review is to assist the United States Preventive Services Task Force (USPSTF) in updating its previous recommendations on such screening.

Data Sources. We searched MEDLINE, the Cochrane Central Register of Controlled Trials, and PubMed from 2006 through July 2014 to locate relevant trials for all key questions (KQs) published since the previous reviews in support of prior recommendations. We supplemented these searches with reference lists from relevant existing systematic reviews, cohort studies, suggestions from experts, and Clinicaltrials.gov to identify ongoing trials.

Study Selection. Investigators independently reviewed 6,752 abstracts and 375 articles against a set of *a priori* inclusion criteria. Investigators also independently critically appraised each study using design-specific quality criteria based on USPSTF methods. We included fair- or good-quality studies that met the *a priori* criteria for each key question. We resolved discrepancies by consensus.

Data Extraction and Analysis. One investigator abstracted data from the 27 included articles into evidence tables, and a second reviewer verified the accuracy of the abstracted data. We qualitatively summarized the evidence for screening and the effects of treatments on health outcomes. Lipid concentrations and measures of atherosclerosis were expressed as percent change from baseline or as differences from baseline. For KQ6, the number of included studies was sufficient to permit meta-analysis. For the randomized trials of statins that reported means and standard deviations for percent change (k=6), we summarized the results using forest plots. We did not combine data across studies, given the variability in drug, dose, and intended duration in the included studies.

Results. We found no direct evidence for five KQs: the effectiveness of screening children and adolescents for FH in improving health outcomes (MI or stroke) in adulthood (KQ1) or intermediate outcomes (lipid concentrations and atherosclerosis) in childhood (KQ2), the harms of screening for FH in children and adolescents (KQ4), the effectiveness of treating children and adolescents with FH on health outcomes (MI or stroke) in adulthood (KQ5), and the association between intermediate outcomes in childhood and adolescence and the future incidence or timing of MI and stroke in adulthood (KQ8). Studies met inclusion criteria for three key questions:

Key Question 3: What is the diagnostic yield of appropriate screening tests for familial hypercholesterolemia in children and adolescents? (KQ1a: Selective screening based on family history; KQ1b: Universal screening).

Two studies provided data allowing determination of the diagnostic yield of pediatric FH screening programs. A statewide universal screening program screened over 80,000 10-to-11 year olds in West Virginia schools and reported a diagnostic yield of about 1.3 cases per 1,000 screened. In this study, "probable FH" was defined as a low-density lipoprotein cholesterol (LDL-C) concentration greater than 155 mg/dL or total cholesterol (TC) concentration greater than 260 mg/dL plus DNA evidence of a low-density lipoprotein receptor (LDLR) mutation in a first- or second-degree relative. A Danish school-based study of over 2,085 6-to-8 year olds used the ApoB:ApoA-1 ratio and reported a diagnostic yield of 4.8 per 1,000. We found no studies reporting diagnostic yield or effectiveness of selective screening for FH in youth (i.e., screening subjects with a family history or other targeting factor).

Key Question 6: Does treatment of familial hypercholesterolemia with lifestyle modifications and/or lipid-lowering medications in children and adolescents improve intermediate outcomes (i.e., reduce lipid concentrations or reverse or slow the progression of atherosclerosis) in childhood and adolescence?

Eight good-quality randomized controlled trials (RCTs) formed the evidence base for statin treatment of FH in youth. Studies of statins ranged from 6 weeks to 2 years long, with most shorter than 1 year. Treatment with statins lowered LDL-C and TC concentrations in the short-term in children and adolescents with FH, with most studies reporting that statins lowered LDL-C by 20 to 40 percent compared to placebo. The greatest effect on LDL-C was in a trial of rosuvastatin. Participants who received the highest dose (20 mg/day) experienced a 50-percent decrease (least mean squares) in LDL-C from baseline, compared to a one percent decrease among controls ($p<0.001$).

Eight studies reported the effect of statins on TC, all showing decreases of about 20 to 30 percent from baseline (compared to no change with placebo). The effect on high-density lipoprotein cholesterol (HDL-C) was minimal or null. A single study assessed the effect on a measure of atherosclerosis and found that pravastatin reduced carotid intima media thickness (CIMT) by 2.01 percent (compared to a 1.02-percent increase in the control group; $p=0.02$). There were no consistent differences in treatment effect among different statins, but the number of studies for any one drug was limited. The two studies that compared different doses of statins reported a dose response with pravastatin and rosuvastatin. In the 2010 rosuvastatin trial, the only statin study reporting how many subjects attained the target LDL-C concentration, only 12 to 41 percent of participants reached a target LDL-C of less than 110 mg/dL, with greater effect at higher doses.

Six studies of statins provided the necessary data to create a forest plot of mean difference across statins between percent change from baseline of TC, LDL-C, and HDL-C. Treatment effects on TC and LDL-C were statistically significant for all five drugs in these six studies (atorvastatin, lovastatin, pravastatin, simvastatin, and rosuvastatin), with overlapping 95% confidence intervals across drugs.

Five fair-to-good quality randomized controlled trials (RCTs) evaluated non-statin drugs in children and adolescents with FH. All trials reported decreases in LDL-C from baseline. Three RCTs studied bile sequestering agents. A good trial of colestipol found a mean reduction in LDL-C of 19.5 percent after 8 weeks of treatment, compared to a 1-percent decrease in the

control group. One fair-quality RCT of cholestyramine found an 18.6-percent reduction in LDL-C after 1 year compared to a 1.5-percent increase in the control group. One good 8-week RCT of colesevelam published after the 2007 USPSTF review found a least-squares mean decrease in LDL-C of 10 percent (standard error 2.1) at the higher of two doses, compared to a least-squares mean increase of 2.5 (SE 2.0) percent. A lower dose provided a smaller, non-significant reduction. Two good RCTs of ezetimibe were published after the 2007 USPSTF review. One reported that LDL-C decreased by a mean of 54.0 percent (SE 1.4) in participants who received of combination of ezetimibe and simvastatin, whereas the mean decrease was 38.1 percent (SE 1.4) in the simvastatin-only group at 33 weeks. The second found that, at 12 weeks, ezetimibe monotherapy decreased LDL-C by 28 percent (95% CI -31 to -25) from baseline, compared to a negligible change in the placebo group.

Key Question 7: What are the harms of treatment of familial hypercholesterolemia with medications in children and adolescents?

There is a fair-to-good body of evidence about the short-term harms of pharmacologic treatment of children and adolescents with FH. Most studies were conducted outside the United States but were applicable to U.S. primary care setting. Most studies were of short duration: 6 weeks to 2 years; the longest was 10 years. Statins were generally well tolerated, although reversible elevations of liver enzymes and/or creatine kinase (CK) concentrations were noted in some studies. One study found lower dehydroepiandrosterone sulfate (DHEAS) in men with FH treated with statins compared to unaffected siblings. Bile acid binding resins were commonly associated with adverse gastrointestinal symptoms and poor palatability. Long-term harms are unknown.

Limitations. Direct evidence for the impact of screening on intermediate or health outcomes is lacking. One of the two studies assessing the diagnostic yield of screening for FH may not be generalizable to a U.S. population, and the other provides few details as to the screening and confirmatory testing for FH. Evidence on the effectiveness of pharmacotherapy lacks long-term studies assessing the effect of lipid-lowering medications on intermediate outcomes in childhood and adolescence or on health outcomes in adults. Participants in the eight statin trials were patients at tertiary care centers; none of the studies were conducted in screening-detected populations. Few studies were conducted in non-white populations. Three statin trials included children as young as 8 years old; however, the age distribution of the statin studies as a whole is skewed to early adolescence. We found no studies comparing outcomes between groups of children or adolescents who initiated treatment at different ages. Long-term studies of harms of pharmacotherapy in youth are lacking. Finally, this review was limited to FH alone; other atherogenic dyslipidemias are addressed in a separate review.

Conclusions. We found no direct evidence of the effect of screening on intermediate or health outcomes. The evidence describing the diagnostic yield of screening for FH in children is minimal. There is good evidence of the effectiveness of statins in reducing LDL-C and TC concentrations in studies of up to 2 years long and limited evidence of a statin effect on measures of atherosclerosis. Statins were generally well-tolerated in the short term, although reversible elevations of liver enzymes and/or CK concentrations were noted in some studies and a decrease in DHEAS was noted in one study. Bile acid binding resins were commonly associated with adverse gastrointestinal symptoms and poor palatability. Long-term harms are unknown.

Randomized trials of screening for FH in U.S. youth are needed, as are longer-term treatment trials evaluating the benefits and harms of medications in children and adolescents with FH.

Abbreviations

ACTH	adrenocorticotropic hormone
AHRQ	Agency for Healthcare Research and Quality
AE	adverse effects
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BMI	body mass index
CAD	coronary artery disease
CARDIAC	Coronary Artery Risk Detection in Appalachian Communities (study)
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CHARON	hyperCholesterolaemia in cHildren and Adolescents taking Rosuvastatin OpeN label (study)
CHD	coronary heart disease
CIMT	carotid intima media thickness
CK	creatine kinase
CMS	Centers for Medicare and Medicaid Services
CoQ10	coenzyme Q10
CVD	cardiovascular disease
DHEAS	dehydroepiandrosterone sulfate
dL	deciliter
EPC	Evidence-based Practice Center
FH	familial hypercholesterolemia
HBA1c	hemoglobin A1C or glycosylated hemoglobin
HDL-C	high density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolemia
KQ(s)	key question(s)
LDL-C	low-density lipoprotein cholesterol
LDLR	low density lipoprotein receptor
mg	milligram(s)
MI	myocardial infarction
NHBLI	National Heart, Lung, and Blood Institute
non-HDL-C	TC minus HDL-C, a measure that includes LDL-C as well as other atherogenic lipoproteins (very low and intermediate density lipoproteins)
PBMC	peripheral blood mononuclear cells
PLUTO	Pediatric Lipid-redUction Trial of rOsuvastatin (study)
pmol	picomol
PPV	positive predictive value
RCT	randomized controlled trial
SD	standard deviation
SE	standard error
TC	total cholesterol
TS	Tanner stage
USPSTF	U.S. Preventive Services Task Force
VLDL	very low density lipoprotein cholesterol

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Chapter 1. Introduction

Scope and Purpose

The Agency for Healthcare Research and Quality (AHRQ) commissioned a systematic evidence review to support the United States Preventive Services Task Force (USPSTF) in updating its 2007 recommendation statement on screening for lipid disorders in children.

As noted in the 2007 review, pediatric dyslipidemias are a heterogeneous set of conditions that include several monogenic disorders as well as dyslipidemias caused by a variety of factors, both genetic and environmental. Based on public input on the draft review of the research plan, the USPSTF decided to conduct separate systematic reviews on screening for familial hypercholesterolemia (FH) and screening for multifactorial dyslipidemia. This review focuses on FH. This review assesses the benefits and harms of screening for and treatment of FH in children and youth aged 0 to 20 years. The separate systematic review to update the 2007 USPSTF recommendation on multifactorial dyslipidemia will address screening children and adolescents for other dyslipidemias involving elevated low-density lipoprotein cholesterol (LDL-C) or total cholesterol (TC) that are not FH. These two concurrent systematic reviews will allow the USPSTF to simultaneously consider both bodies of evidence to evaluate the preventive health benefits of screening children and adolescents for dyslipidemias involving elevated LDL-C.

Clinical Presentation and Diagnosis

Familial hypercholesterolemia is an inherited disorder of lipoprotein metabolism characterized by highly elevated total cholesterol concentrations early in life, independent of environmental influences. Tendon xanthomas (cutaneous deposits of cholesteryl ester-enriched foam cells in ligaments and tendons) may also be present, most commonly in the Achilles tendon.

Currently, no criteria for the diagnosis of FH are universally accepted. Studies of children with FH use several different diagnostic criteria, some of which are drawn from published definitions. The three most commonly cited diagnostic criteria are the Simon Broome criteria[1] from the United Kingdom (U.K.), the Dutch Lipid Clinic Network criteria[2] from the Netherlands, and the MEDPED criteria[3] from the U.S. All use a combination of elevated lipid concentrations, physical findings, family history, or genetic tests to establish the diagnosis. Further, combinations of diagnostic criteria are used to stratify diagnosis according to the probability of disease (i.e., definite, probable, possible FH) (**Appendix D**). The use of genetic diagnosis alone is complicated by incomplete penetrance of the genes that cause FH and by varying expressivity of clinical symptoms, especially in childhood and adolescence.[4, 5]

Etiology and Prevalence

Familial hypercholesterolemia is an autosomal-dominant disorder caused primarily by mutations in the low-density lipoprotein receptor (LDLR) gene.[6, 7] More than 80 percent of cases are attributed to 1 of 1,500 known deleterious mutations[8] in LDLR gene.[9] The remainder of cases reflect mutations in other genes (ApoB, PCKS9) or unknown mutations.

The prevalence of heterozygous FH is estimated to be 1 in 200 to 1 in 500 people in North America and Europe. It is higher (up to 1 in 100) for populations with known founder effects, including the Netherlands, South Africa's Afrikaner population, Quebec, and Lebanon.[9] Given population prevalence estimates, FH may be underdiagnosed, especially in children.[10, 11]

Homozygous FH, a more severe condition than heterozygous FH, is far less common, with a prevalence of about 1 in 1,000,000 births.[5] This evidence review focuses exclusively on the heterozygous form of the disorder. In the remainder of this evidence summary, we refer to heterozygous familial hypercholesterolemia simply as FH.

Natural History

Familial hypercholesterolemia is normally asymptomatic in childhood and is rarely associated with cardiovascular illness in the first two decades of life. The burden of FH is caused largely by premature cardiovascular events in adulthood that are associated with long-term exposure to elevated, and in some cases severely elevated, serum cholesterol concentrations and the associated atherosclerotic burden. Lifelong elevation of plasma concentrations of LDL-C leads to cholesterol deposition in the arteries, where it forms an atherosclerotic plaque that can begin early in life. Early atherosclerotic lesions in children, adolescents, and young adults have been related to higher antecedent concentrations of TC and LDL-C.[12-15] and mean carotid intima-media thickness (CIMT) values in young children (under age 8) with FH, which may be greater than those of their unaffected siblings.[16]

Untreated, FH is associated with a high incidence of premature clinical atherosclerotic cardiovascular disease. Before statins were in common use, FH was associated with a 1-in-6 cumulative incidence of ischemic heart disease events in men and a 1-in-10 incidence in women, by the age of 40.[17] By age 50, 25 percent of women and 50 percent of men with untreated FH will experience clinical cardiovascular disease (CVD).[18] In adults with untreated FH, coronary artery disease (CAD) occurs in 50 percent of men by age of 50 and in 30 percent of women by age 60.[19, 20] CAD-associated mortality is increased in people with FH under age 60. Among people surviving to age 60, the risk of CAD approaches that in the general population.[21] Deposition of LDL-C in other body tissues can manifest as clinical findings, mainly tendon xanthomas and corneal arcus.

Lipid Concentrations in Children and Adolescents

Lipid concentrations in healthy children vary with age, starting very low at birth, increasing slowly in the first 2 years of life, and then stabilizing until adolescence. TC and LDL-C concentrations subsequently decrease by 10 to 20 percent or more during adolescence, before rising again during late adolescence and young adulthood.[22-25] In children with FH, concentrations of TC, and LDL-C in early childhood will be two to three times as high as those in unaffected children.

Screening for Familial Hypercholesterolemia

Rationale for Screening

The rationale for screening for FH in childhood or adolescence is to identify pre-symptomatic children and to intervene with lipid-lowering agents before clinically significant atherosclerosis develops. Given the earlier onset and more severe clinical implications of FH compared to other dyslipidemias, the long pre-clinical disease course of atherosclerosis, and the availability of intervention for detected cases, FH may be a candidate for screening in primary care.

Laboratory Studies

Because elevated LDL-C concentrations are the primary abnormality associated with FH, all FH diagnostic criteria are based in part on serum concentrations of TC, LDL-C, or both. LDL-C may be calculated with the Friedewald formula:[26] LDL-C = TC – (Triglyceride / 5) – HDL. Because the calculation depends on TG, calculating LDL-C concentrations accurately requires blood to be drawn when the person is fasting. Direct LDL-C measurement does not require fasting[15]. Recent screening recommendations for childhood dyslipidemia have included guidelines for use of either LDL-C or non-high density lipoprotein cholesterol (non-HDL-C).[18, 27]

Screening Strategies

- Screening by clinical exam. Because only a few children have clinically detectable atherosclerotic deposits, such as xanthomas, by adolescence, detecting these deposits can aid in diagnosis but is not a useful screening marker for FH in children and adolescents.
- Selective screening based on family history. Targeted lipid screening of high-risk individuals aged 2 to 8 years has also been recommended, as well as screening in late adolescence and young adulthood (after lipid concentrations have once again risen).[18] Screening based on a family history of early CVD or hypercholesterolemia will identify only 30 to 60 percent of children with FH. The previous USPSTF review determined that having a parent or grandparent with CHD diagnosed before age 50 or 60 or a cholesterol concentration greater than 240 mg/dL was only 46 to 74 percent sensitive for identifying TC concentrations greater than 170 mg/dL or LDL-C concentrations greater than 130 mg/dL. A family history of a parent or grandparent having early CHD alone was only 46 percent sensitive for LDL-C concentrations above the 95th percentile.[15, 28-30]
- Universal screening. In universal screening, all children in a population undergo blood lipid screening based on age alone, regardless of other risk factors. Recent recommendations from the National Heart, Lung, and Blood Institute (NHLBI) have suggested universal screening at age 9 to 11 and again at age 17 to 21.[18] The National Lipid Association also recommends screening for FH at age 9 to 11 years.[27]
- Genetic screening. Only one FH diagnostic guideline (The Dutch criteria) currently recommends assigning a diagnosis of FH based on mutation status alone (**Appendix D**). Other schemes require other clinical or laboratory characteristics in addition to mutation status. In genetically homogeneous populations, population-based screening for genetic variants known to exist in the population may be a useful strategy. However, given the genetic heterogeneity of the U.S. population and the lack of validated genetic screening tests for this population, genetic screening is beyond the scope of this review.
- Cascade screening. Cascade screening involves case-findings among relatives with confirmed FH and often involves testing for genetic variants identified in the proband. Because implementing this approach in the U.S. would require new infrastructure, cascade screening is outside of the purview of U.S. primary care and beyond the scope of this review.

Current Clinical Practice in the United States

Beginning in the 1990s, organizations have recommended selective screening for childhood dyslipidemia based on the presence of risk factors, such as a family history suggesting inherited dyslipidemia (e.g., early CVD, early myocardial infarction [MI] or sudden death, or early

cerebrovascular disease) or a personal history of risk factors for CVD.[6, 31] A recent report from the NHLBI Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents recommended universal screening for children aged 9 to 11 and 17 to 21, as well as targeted screening of high-risk younger children and adolescents.[18] These recommendations are controversial, in part because of concerns about the lack of data on long-term efficacy and on the safety of lipid-lowering medications in children and adolescents.

Familial hypercholesterolemia screening in the U.S. In the U.S., there are no national screening programs, and FH identification falls to individual clinicians as a matter of differential diagnosis. At least one FH patient registry exists in the U.S.[32]

Familial hypercholesterolemia screening in other countries. Cascade screening is the most common screening strategy in other countries. The Netherlands has a known founder population with a high rate of FH, a subsidized health care system, and an infrastructure that supports a disease registry and so has a successful cascade screening program. In this program, relatives of FH patients are identified and screened with clinical exams, fasting lipid panels, and molecular testing for LDLR mutations. With a participation rate of more than 90 percent, it has been successful in detecting new cases, increasing coverage of lipid-lowering therapies, and is cost-effective in case-finding, although following up with children remains challenging.[33-36] These screening algorithms led to the Dutch Criteria described in this review. Norway and Wales have also implemented national cascade screening programs.[37] Several other countries have explored cascade screening programs or have begun implementation.[21, 38-41] U.K. public health authorities recommend cascade screening with identified FH patients using the clinically focused Simon Broome criteria.[42] Regional implementation suggests that cascade screening is feasible but has mixed results in identifying people with FH.[43-45] Currently, the U.S. does not have the necessary health infrastructure to support cascade screening.

Italy promotes a selective screening strategy based on family history to guide lipid testing.[36, 46] We are aware of at least one universal screening program, in Slovenia, but its impact is not yet known.

Treatment of Familial Hypercholesterolemia in Children

Interventions for correcting lipid aberrations in children and adolescents include lifestyle modification and pharmacotherapy.

Lifestyle: Current guidelines[27] recommend a low-fat, low-cholesterol diet and regular physical activity for children and adolescents with FH, although evidence for the effect of non-pharmacologic interventions in children with FH is limited. Some evidence indicates that low-fat, low-cholesterol diets are marginally effective in lowering lipid concentrations in children (over age 2 years) with certain conditions (including FH). The 2007 USPSTF review noted some uncertainty about whether these improvements would be sustained.[47] Exercise is associated with minimal, if any, improvement in lipids in children with any sort of dyslipidemia. The 2007 USPSTF review found no studies that assessed the effect of physical activity interventions in children with FH.[47]

Pharmacotherapy. Several lipid-lowering medications are used in children and adolescents with FH. Bile-acid-binding resins have been available for decades. Several HMG-CoA reductase inhibitors (statins)[48, 49] are FDA-approved for children with FH who are 10 years and older and (if female) are post-menarchal; one statin is approved for children as young as 8 years. A third class of lipid-lowering agents used in youth inhibits intestinal cholesterol absorption (e.g. ezetimibe).

Following the widespread adoption of statins to reduce LDL-C concentrations in adults with hypercholesterolemia (most of whom do not have FH), pediatric specialists have actively debated the appropriate age of statin initiation in youth with FH. Some experts in the field recommend waiting until after puberty—some suggesting as late as age 20[50]—to minimize potential adverse effects on growth and development. Others advocate starting statins in children with FH as young as 8 or 10 years.[27]

Previous USPSTF Recommendation

In 2007, the USPSTF found insufficient evidence to recommend for or against routine screening for lipid disorders in infants, children or adolescents up to age 20 (I recommendation).[15, 47] The 2007 recommendation referred to screening for all forms childhood and adolescent dyslipidemia, and no separate recommendation was made specifically regarding screening for FH. The 2007 evidence review found these evidence gaps relevant to screening children and adolescents for FH:

- Direct evidence on the impact of FH screening on intermediate and adult health outcomes;
- The diagnostic yield of screening for FH;
- The harms of screening; and
- The benefits and harms of long-term treatment of FH identified in childhood (noting that the long-term effectiveness of statins is a critical evidence gap).

Chapter 2. Methods

Overview

This systematic review was designed to complement the systematic review that supported the 2015 screening recommendation for multifactorial dyslipidemia in children and adolescents. For this review, we adapted the analytic framework for lipid screening from the 2007 USPSTF review to address the benefits and harms of primary care-relevant screening and treatment of children and adolescents with FH.

Key Questions and Analytic Framework

Using the USPSTF's methods (detailed in **Appendix A**), we developed an analytic framework (**Figure 1**) and eight key questions (KQs).

Screening Key Questions (1 to 4)

1. Does screening for familial hypercholesterolemia in asymptomatic children and adolescents delay or reduce the incidence of myocardial infarction (MI) or stroke in adulthood?
    a. Selective screening based on family history
    b. Universal screening
2. Does screening for familial hypercholesterolemia in asymptomatic children and adolescents improve intermediate outcomes (i.e., reduce lipid concentrations or reverse or slow the progression of atherosclerosis) in childhood and adolescence?
    a. Selective screening based on family history
    b. Universal screening
3. What is the diagnostic yield of appropriate screening tests for familial hypercholesterolemia in children and adolescents?
    a. Selective screening based on family history
    b. Universal screening
4. What are the harms of screening for familial hypercholesterolemia in children and adolescents?

Treatment Key Questions (5 to 7)

5. Does treatment of familial hypercholesterolemia with lifestyle modifications and/or lipid-lowering medications in children and adolescents delay or reduce the incidence of adult MI and stroke events?
6. Does treatment of familial hypercholesterolemia with lifestyle modifications and/or lipid-lowering medications in children and adolescents improve intermediate outcomes (i.e., reduce lipid concentrations or reverse or slow the progression of atherosclerosis) in childhood and adolescence?
7. What are the harms of treatment of familial hypercholesterolemia with medications in children and adolescents?

Outcomes Key Question (8)

8. What is the association between intermediate outcomes in childhood and adolescence and future incidence or timing of adult MI and stroke events?

In these key questions, intermediate outcomes include lipid concentrations (total and low-density lipoprotein cholesterol) and atherosclerosis markers (carotid intima–media thickness, calcium score, pathological findings).

Data Sources and Searches

We designed this review to extend the 2007 systematic review on screening in childhood lipids. In October 2013, we searched the following databases to identify systematic reviews on child lipid screening published since September 2005 (the date of the literature search for the previous USPSTF review on this topic): Agency for Healthcare Research and Quality, BMJ Clinical Evidence, Canadian Agency for Drugs and Technologies in Health, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment (Centre for Reviews and Dissemination), Institute for Clinical Systems Improvement, Institute of Medicine, MEDLINE and PubMed, and National Institute for Health and Clinical Excellence. We worked with a trained medical librarian to develop the appropriate search strategy for screening for childhood lipids (**Appendix A**). On February 12, 2014, we conducted our original search for this review, and the search was updated on June 13, 2014 and again on June 2, 2015.

For the published literature prior to September 2005, we searched all publications cited in the 2007 USPSTF review. Although that review did not specifically address diagnostic yield (KQ3 in this review), several of their key questions addressed various aspects of screening. We conducted a focused search of the studies cited in the 2007 USPSTF review to identify any that met our criteria for KQ3. Also, because the 2007 USPSTF review did not have a key question on the association between screening and intermediate outcomes (KQ2 in this review) nor on the association between intermediate outcomes in children and adolescents with FH and adult health outcomes (KQ8 in this review), we supplemented our search of the 2007 USPSTF citations with a search of the 2011 NHLBI Expert Panel Report[27] and publications from large published cohort studies with longitudinal data (**Appendix E**). To ensure the comprehensiveness of our search strategy, we reviewed the reference lists of included studies and relevant systematic reviews and meta-analyses to identify relevant articles that were not identified in our literature searches. We also supplemented our database searches with suggestions from experts and searched Clinicaltrials.gov to identify relevant ongoing trials (**Appendix B**).

Study Selection

Two investigators independently reviewed the title and abstracts of all identified articles to determine whether the study met the inclusion and exclusion criteria for design, population, screening, intervention, and outcomes (**Appendix A, Table 2**). Two reviewers then independently evaluated 375 full-text articles against the complete inclusion and exclusion criteria (**Appendix A, Table 1**). We resolved discrepancies through discussion and consultation with a third reviewer. Excluded studies and their reason for exclusion are listed in **Appendix C**. For screening studies (KQs 1 to 4), we included studies of asymptomatic children and adolescents age 0 to 20 years at the time of screening. Acceptable screening interventions were defined as a lipid panel (fasting or non-fasting lipid measurement, TC or LDL-C alone or in combination with HDL) delivered in a universal or selective screening strategy. We excluded screening studies that focused on genetic screening alone or cascade screening because those screening approaches are not relevant to screening for FH in primary care. We excluded screening studies of populations with known dyslipidemia, a diagnosis associated with secondary

dyslipidemia, or a documented family history of FH because these populations were not asymptomatic. Only screening studies that reported the number of children with probable or definite FH were included.

For treatment studies (KQs 5 to 7), we included interventions using lipid-lowering drugs or lifestyle interventions (including diet or exercise). We focused on interventions targeting people age 0 to 20 years who had a diagnosis of FH at the beginning of the intervention. We accepted any class of lipid lowering drug, including, but not limited to, statins and bile acid sequestrants. We excluded studies that focused on treating those with secondary dyslipidemia or monogenic dyslipidemia other than FH. We excluded treatment studies focusing on apheresis and revascularization, as those treatments are reserved for persons with homozygous FH. We included all reported clinical and laboratory harms associated with lipid lowing drugs.

We included studies with mixed dyslipidemic populations when the outcome data for subjects with FH were presented separately. We included studies where the author specifically identified subjects with FH using any specified and accepted criteria (**Appendix D**). We limited studies of efficacy or effectiveness to fair-to-good quality randomized trials that were conducted in countries with a high human development index (>0.9). Included intervention trials had to compare an intervention against a usual care or control group.

Consistent with current USPSTF methods, health outcomes (KQ1, KQ5 and KQ8) were defined as those experienced by the patient. We considered atherosclerosis or elevated lipid concentrations to be intermediate outcomes (KQ2 and KQ6). We included trials, cohort studies, and observational studies that reported clinical or laboratory harms but did not include case series or case reports.

Quality Assessment and Data Extraction

Two reviewers independently appraised all articles that met the inclusion criteria for this review. The appraisal criteria were adapted from USPSTF's design-specific quality criteria[51] (**Appendix A, Table 2**). Topic-specific quality criteria were designed with the assistance of clinical experts. The final quality rating recorded in the evidence tables was based on quality guidelines from the procedure manual for USPSTF reviews. We rated studies as good, fair, or poor quality. In general, a good study met all criteria well. A fair study did not meet, or it was unclear whether it met, at least one criterion but also had no known issue that would invalidate its results. A poor study had important limitations that made inference about a population difficult or unwarranted. We excluded poor studies from this review. Poor studies had severe limitations including one or more of the following risk of biases: lack of randomization, possibly biased assignment, unclear diagnostic criteria, unclear classification procedures, or no reporting of baseline characteristics. Excluded articles are listed in an excluded-studies table with reasons for exclusion (**Appendix C**). One reviewer extracted data from all included fair or good studies into a standard evidence table. A second reviewer checked the data for accuracy. The reviewers abstracted study characteristics (e.g., population, purpose, exposure, and outcomes of the study), study design elements (e.g., recruitment procedures, eligibility criteria, duration of follow-up, and attrition), randomized trial characteristics (e.g., setting, blinding, methods of measurement for outcome and exposure, duration, lipid concentrations), outcomes for screening studies (e.g., true positives, diagnostic yield, positive predictive value), intermediate outcomes (e.g. lipid concentrations, CIMT) and health outcomes (e.g., MI and stroke), and harms.

Data Synthesis and Analysis

The data are summarized in tables. Lipids and measures of atherosclerosis were expressed as the percent change from baseline or as the difference from baseline. One key question, KQ6, had sufficient included studies to permit meta-analysis. The results of RCTs of statins that reported means and standard deviations for percent change (k=6) were summarized in forest plots. Intervention effects for each study are presented as the mean difference between groups with 95% confidence intervals. When trials reported standard errors or confidence intervals for the primary outcome, we used the reported results to compute standard deviations. For one trial with three groups randomly assigned to different doses of a statin,[52] we used weighted means and standard deviations to combined reported results into a single intervention effect for the study. Results are displayed in a forest plot. We did not combine data across studies, given the variability in drug, dosage, and intended duration of treatment.

Expert Review and Public Comment

A draft research plan that included the analytic framework, KQs, and eligibility criteria, was available for public comment from January 23 to February 19, 2014. This draft research plan was broadly focused on dyslipidemia in childhood and adolescence, not specifically FH. Because of public comment, we decided to conduct two complementary reviews: screening for FH and screening for multifactorial dyslipidemia in children and adolescents. A draft version of the current report was reviewed by three invited content experts. Comments received during this process were presented to the USPSTF during its deliberation of the evidence and subsequently addressed, as appropriate, in the final version of this report.

USPSTF Involvement

The authors worked with USPSTF liaisons at key points throughout the review process to refine the inclusion criteria, to address methodological decisions on applicable evidence, and to resolve issues around the scope of the final evidence synthesis. The Agency for Healthcare Research and Quality (AHRQ) funded this research under a contract to support the work of the USPSTF. AHRQ staff oversaw the project and assisted in the external review of drafts of the evidence synthesis. AHRQ was not involved in study selection, quality assessment, or synthesis.

Chapter 3. Results

Literature Search

We reviewed 6,752 unique abstracts and excluded 6,378. We reviewed 375 full-text articles and excluded 333 (**Appendix C**). An additional 15 articles were reviewed for contextual questions and not included for any key questions. The remaining set of 27 articles is the included body of evidence for this review. We included 2 screening studies, 13 studies of drug treatment, and 18 studies (24 publications) of treatment harms. We did not find any relevant studies on adult health outcomes, intermediate outcomes, or harms of FH screening.

Results of Included Studies

KQ1: Does screening for familial hypercholesterolemia in asymptomatic children and adolescents delay or reduce the incidence of MI or stroke in adulthood?

a. Selective screening based on family history

b. Universal screening

No studies were identified.

KQ2: Does screening for familial hypercholesterolemia in asymptomatic children and adolescents improve intermediate outcomes (i.e., reduce lipid concentrations or reverse or slow the progression of atherosclerosis) in childhood and adolescence?

a. Selective screening based on family history

b. Universal screening

No studies were identified.

KQ3: What is the diagnostic yield of appropriate screening tests for familial hypercholesterolemia in children and adolescents?

a. Selective screening based on family history

b. Universal screening

Description of Included Studies

We identified two fair-quality studies of universal screening for FH in school settings (**Table 1**). The Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) Project was a West Virginia screening program aimed at identifying the prevalence of obesity, dyslipidemia, hypertension, glucose intolerance and other cardiac risk factors. While the program was not aimed at detection of FH, one publication from CARDIAC reports on children who met criteria

for FH.[53] The second study was a Danish screening study, also based in a school setting, that measured apolipoproteins as a screening test for FH.[54] No studies on selective screening for FH were identified.

Included Populations and Interventions

The West Virginia study was a statewide screening program conducted in schools in all 55 counties between 1998 and 2012. All 5th grade students (aged 10 to 11 years) were eligible for screening. Girls represented 53 percent of the children screened. The majority were White (93.2 percent), 2.9 percent were African-American, and there were less than one percent in other race and ethnic categories. Fasting lipid panels were drawn during the school day and sent to local hospitals or commercial laboratories for analysis, along with other serum chemistries. Procedures for obtaining family history are not described. Children with LDL-C concentrations greater than 155 mg/dL or TC concentrations greater than 260 mg/dL plus DNA evidence of an LDLR mutation in a first- or second-degree relative. were considered to have "probable FH." Parents of children with probable FH were asked to take them to a health care provider for additional testing. Results of this testing are not shown; the procedures are not well described. The CARDIAC screening program was embedded in a series of cardiovascular risk reduction activities in the schools and the larger community.

The Danish study took place in a school setting in Copenhagen, targeting children aged 6 to 8 years who were starting first grade. Screening consisted of measuring apolipoproteins in capillary blood, with follow up assessment of subjects and family members based on results. The initial questionnaire asked parents about the incidence and age of onset of chest pains or coronary occlusions in themselves or their relatives (parents, siblings, aunts, and uncles). A positive family history was defined as a report of angina pectoris or myocardial infarction (MI) in men under age 50 or in women under age 60. Questionnaire responses were not used to guide screening. All eligible children were offered screening, regardless of responses. The screening test consisted of a morning non-fasting capillary blood sample. The sample was dried at room temperature for 2 hours and transported to a laboratory within 6 hours.

Those children with an Apo B:A-1 ratio above 0.83, which was value marking the 97.5th percentile for the sample, had their capillary apolipoprotein ratios rechecked. Children with an Apo B:A-1 ratio above 0.83 on repeat testing had fasting TC, HDL-C, very low density lipoprotein cholesterol (VLDL-C), and triglyceride concentrations measured. Fasting lipid panels were obtained from this group of children and from all available first- and second-degree relatives. LDL-C was calculated as TC – (HDL-C + VLDL-C). If LDL-C was above the 95th percentile for age, an additional lipid profile analysis was obtained after at least 3 weeks, and physical and laboratory studies were performed to rule out causes of secondary hyperlipidemia.

Quality

The quality of the studies was fair. The West Virginia study provided inadequate information about family history screening, failed to report results of confirmatory testing, and lacked a control group. The Danish study gave a scant description of the recruitment and lipid screening of parents and data on nonparticipants, and lacked a control group.

Summary of Findings

The statewide universal screening program in West Virginia schools reported a diagnostic yield of about 1.3 cases per 1,000 screened, with a high threshold for FH.[53] The Danish study

identified 10 subjects with laboratory results and a family history consistent with FH from a sample of 2,085, for a diagnostic yield of 4.8 per 1,000.[54]

Detailed Results

Detailed results are available in **Table 2**. The statewide universal screening program in West Virginia schools used fasting lipid profiles.[53] In this fair-quality study, 42 percent of 81,156 eligible fifth-grade children were screened between 1998 and 2012, and 12,204 (25.7 percent of those screened) had at least one abnormal lipid value. The authors defined "probable FH" as having an LDL-C concentration greater than 155 mg/dL or TC concentration greater than 260 mg/dL plus DNA evidence of an LDLR mutation in a first- or second-degree relative. Results of confirmatory testing (second lipid panel and family history) are not shown. Based on the author's definition of FH, even without confirmatory testing information, we may consider the 107 screen-positive children to be true positives. This results in a diagnostic yield of about 1.3 cases per 1,000 screened. This rate of 0.13 percent is considerably lower than published estimates.

In the Danish study, questionnaires were sent to 3,025 families; 2,675 were returned, and 2,166 parents consented to their children's screening. Of these, successful blood testing and measurement of Apo B:A-1 ratio was obtained for 2,085 children. On initial screen, 47 children (2.2 percent) had an Apo B:A-1 ratio above 0.83; the ratio remained above 0.83 on repeat in 12 children (0.58 percent). Of the 12 children with a high ratio on the second screening, 11 had fasting lipid concentrations (TC and LDL-C concentrations) above the 95th percentile for age based on Danish norms. Almost all (10 out of 12) showed biochemical evidence of familial involvement (both the child and one parent) consistent with FH. Diagnostic yield for universal screening was 4.8 per 1,000, which was above the expected incidence of 2 to 3 per 1,000. This result suggests either a higher proportion of FH in the Danish population or the existence of a broader set of inherited dyslipidemias beyond FH because genetic mutation testing was not performed.

Lipid measurements in relatives of children with persistent Apo B:A-1 ratios greater than 0.83 identified 29 close relatives with previously undiagnosed hypercholesterolemia and were sufficient to establish an autosomal-dominant inheritance pattern of FH in 10 families. Physical examination and additional laboratory testing in subjects was unrevealing.

KQ 4: What are the harms of screening for familial hypercholesterolemia in children and adolescents?

No studies were identified.

KQ 5: Does treatment of familial hypercholesterolemia with lifestyle modifications and/or lipid-lowering medications in children and adolescents delay or reduce the incidence of adult MI and stroke events?

No studies were identified.

KQ 6: Does treatment of familial hypercholesterolemia with lifestyle modifications and/or lipid-lowering medications in children and adolescents improve intermediate outcomes (i.e., reduce lipid concentrations or reverse or slow the progression of atherosclerosis) in childhood and adolescence?

Description of Included Studies

Thirteen fair-to-good-quality treatment trials in children with FH met our inclusion criteria (**Table 3**). All 13 trials evaluated lipid-lowering medications. Eight were trials of statins, three were trials of bile-sequestering agents[55-57], and two were trials of ezetimibe, an inhibitor of intestinal cholesterol absorption.[58, 59] No studies meeting the inclusion criteria evaluated the effect of lifestyle modifications or dietary supplements on intermediate outcomes in children with FH.

Included Populations

The 13 trials included from 54 to 248 participants (**Table 3**). Trial participants' ages ranged from 6 to18 years. In eleven of these trials, mean ages of participants ranged from 12 to 15 years; two trials had a mean age of 8 years.[55, 59] Both girls and boys were well represented in included trials, 11 of which included both sexes. One study included girls only[60] and one included boys only.[61] Half (k=7) of included trials were conducted in two or more countries in Europe, North America, or Asia. [57-59, 61-65] Four of these multi-center trials had centers in four or more countries and three included at least one country outside our human development index-based inclusion criteria.[62, 63, 65] The remaining trials were conducted in the Netherlands (k=2),[52, 66] Norway (k=2),[55, 65] Canada (k=1)[67], and the United States (k=1).[60] Only seven trials reported race, and in these, 80 to 94 percent of subjects were White.[52, 57-59, 63, 64] All participants were patients at specialty lipid clinics. None of the studies reported identifying screening-detected participants. Only one study required participants to be treatment-naïve.[66]

Familial hypercholesterolemia was defined by elevated fasting lipid concentrations in combination with family history using various standard criteria. Genetic mutations were among the possible inclusion criteria in five studies; [55, 57, 58, 64, 66] some studies specified mutations in LDLR[56, 65] and apoB[65] genes. In one study, LDLR mutation was a required criterion for the diagnosis of FH.[65, 67] One ezetimibe trial[59] included youth who did not meet criteria for FH but whose LDL-C concentrations were between 160 and 400 mg/dL; these children accounted for 9 percent of participants in that trial and were analyzed together with the children with FH. Eleven trials used fasting LDL-C concentrations,[52, 58-67] and the other two used TC cut points.[55, 56] Fasting LDL-C or TC concentrations had to be elevated on at least two occasions in five trials.[55, 56, 61, 66, 67] Seven studies required that fasting LDL-C be elevated while the child or adolescent was on a low-fat diet, for a duration ranging from 4 weeks to 4 months.[52, 58, 59, 61, 65-67] LDL and TC cut points were based on age and were similar across studies.

Mean baseline TC ranged from 260 to 320 mg/dL. Mean baseline LDL-C ranged from 198 to 254 mg/dL. Mean baseline HDL-C ranged from 42 to 50 mg/dL. Mean baseline TG ranged from 62 to 110 mg/dL.

Five studies required participants to be at least at Tanner stage II or greater[58, 61-64] or required girls to be postmenarchal.[58, 62, 64] Three studies set a minimum weight or body mass index percentile for participation.[58, 60, 67]

For presumed safety reasons, four studies also excluded participants whose LDL-C was above a maximum cut point [60-62, 67] (400 mg/dL in two studies[60, 62]; 500 mg/dL in one[61]).

Individuals with elevated triglyceride concentrations were excluded from eight of these trials.[56, 59, 60, 63, 65-67] Most trials excluded participants with homozygous FH, secondary dyslipidemias, and use of medications that could affect lipid concentrations.

Included Interventions

Of 13 RCTs evaluating the effect of different lipid-lowering medications on dyslipidemia or atherosclerosis in children with FH (**Table 3**), statin medications were studied in 8 (N=1,071): pravastatin (N=286)[52, 66], simvastatin (N=236)[62, 67], and lovastatin (N=186)[60, 61] were each evaluated in 2 studies, and atorvastatin (N=187)[63] and rosuvastatin (N=176)[64] were each evaluated once. Dose ranges for the different statins were: pravastatin, 5 to 40 mg[52, 66]; simvastatin, 20 to 40 mg[62, 67]; lovastatin, 40 mg[60, 61]; atorvastatin, 10 mg[63]; and rosuvastatin, 5 to 20 mg.[64] Duration of the blinded, randomized trials ranged from 6[67] to 104 weeks.[66]

The three trials of bile-sequestering agents[55, 56, 65] evaluated cholestyramine at a dose of 8 g/day for 1 year[55], colestipol at a dose of 10 g/day for 8 weeks[56], and colesevelam at two different doses (1.875 g and 3.75 g/day) for 8 weeks[65]. There were two trials of ezetimibe, an inhibitor of intestinal cholesterol absorption. One trial assessed ezetimibe monotherapy (10 mg/day) compared to placebo for 12 weeks.[59] Another studied ezetimibe (10 mg/day) in combination with simvastatin (up to 40 mg/day) for 33 weeks.[58]

Retention was greater than 90 percent in seven studies,[52, 58-60, 63, 64, 66] 80 to 90 percent in three studies[56, 61, 65], 70 to 80 percent in two studies[62, 67], and 67 percent in one study.[55]

Quality

All trials were rated as fair-to-good. No trials were excluded for poor quality, although 32 studies were excluded for not being RCTs (**Appendix C**). We included 12 good-quality trials and one of fair quality.[55] The major limitation of the fair quality study was low patient retention.

Overall Results

Statins

Eight trials reported on the effects of statins on lipid concentrations. All trials reported decreases in LDL-C from baseline, with mean decreases ranging from 23 to 57 mg/dL. Effect sizes were similar across different statins (**Figure 3**). Two trials compared a range of doses, and both showed a dose-response effect on lipid concentrations for pravastatin[52] and rosuvastatin.[64] Of the 8 statin RCTs, 3 were longer than 6 months: two had 48 weeks of followup[61, 62], and one had 104 weeks.[66] The greatest effect on LDL-C was in a trial of rosuvastatin.[64] Participants who received the highest dose (20 mg/day) experienced a 50-percent decrease (least mean squares) in LDL-C from baseline, compared to a one percent decrease among controls ($p<0.001$).

Eight studies reported the effect of statins on TC, all showing decreases of 20 to 30 percent from baseline (compared to no change with placebo). The effects of statins on HDL-C were mixed, with some studies reporting small but equivocal improvement and others reporting no important changes. Six studies could be summarized in a forest plot **(Figure 2**, **Figure 3**, **Figure 4)** of mean differences across statins by percent change from baseline of TC, LDL-C, and HDL-C. Significant treatment effects on TC and LDL-C, with overlapping 95% confidence intervals, are seen for all five drugs in these studies: atorvastatin, lovastatin, pravastatin, simvastatin, and rosuvastatin. Mean differences for HDL-C include or come close to zero in all five studies.

Because of differences across studies, the forest plots include a range of treatment durations, from 12 to 48 weeks.

A single trial assessed the effect of pravastatin on measures of atherosclerosis, reporting a 2.01-percent decrease in CIMT, after 104 weeks, compared with a 1.02-percent increase in the control group.[66] Mean change between groups differed significantly (p=0.02). No study assessed the effect of statins on calcium score or pathologic findings.

Non-statin medications

Five fair-to-good quality RCTs of non-statins in children and adolescents with FH met our inclusion criteria: three of bile sequestering agents and two of ezetimibe. All trials reported decreases in LDL-C from baseline. There were three RCTs of bile sequestering agents. A good trial of colestipol found a mean reduction in LDL-C of 19.5 percent after 8 weeks of treatment, compared to a 1-percent decrease in the control group.[56] One fair RCT of cholestyramine found an 18.6 percent reduction in LDL-C after 1 year on treatment compared to a 1.5-percent increase in the control group.[55] One good 8-week RCT of colesevelam[65] published after the 2007 USPSTF review found a decrease in mean LDL-C of 10 (SE 2.1) percent at the higher of two doses compared to a mean increase of 2.5 (SE 2.0) percent in the control group. A lower dose resulted in a smaller non-significant reduction. One good RCT[58], also published after the 2007 USPSTF review, reported that LDL-C decreased by a mean (SD) of 54.0 (1.4) percent in participants who received ezetimibe and simvastatin compared to a decrease of 38.1 (1.4) percent in the simvastatin-only group at 33 weeks. A good RCT of ezetimibe monotherapy reported a 28 (95% CI 25, 31) percent reduction in TC in the treatment group compared to negligible change in the placebo group.[59]

Detailed results for statins

Effect on lipid concentrations

Eight good-quality RCTs of statins in children and adolescents with FH were included (**Table 4)**. Seven of these were included in the 2007 USPSTF review on this topic; one good-quality RCT[64] was published after that report. Details from these studies are discussed below.

Pravastatin

Two good-quality RCTs evaluated the effect of pravastatin on lipid concentrations in children with FH. The first[52] studied 72 children aged 8 to 16 years randomly assigned to one of four groups: a placebo group and three pravastatin groups receiving doses of 5, 10, or 20 mg/day. The authors do not report whether adherence was assessed. The intervention period lasted 12 weeks, at the end of which all three pravastatin arms had reductions in mean LDL-C relative to the control arm. There were greater reductions in TC and LDL-C concentrations in the group receiving 20 mg pravastatin compared to the groups receiving 5 or 10 mg of pravastatin. Changes in HDL-C and TG were not statistically significant. Detailed results are provided in **Table 4-a**.

The Dutch Pravastatin Trial, the longest of any statin trial in children[66], followed 214 children ages 8 to 18 years for 2 years. Children aged less than 14 years received pravastatin 20 mg/day; those age 14 years and older received 40 mg/day. The authors do not report whether adherence was assessed. At the end of the intervention period, the pravastatin group had

significant reductions in TC and LDL-C relative to the control group. Changes in HDL-C and TG were minimal and not statistically significant. Detailed results are provided in **Table 4-b**.

Simvastatin

Two RCTs evaluated the effect of simvastatin on lipid concentration in children with FH. The first was a good-quality trial[67] of 63 children aged 8 to 17 years randomly assigned in a 3:1 ratio to receive 20 mg/day of simvastatin or placebo for 6 weeks. Adherence was assessed by pill count but was not reported. At the end of the intervention period, the simvastatin group had significant reductions in TC and LDL-C relative to the control group. Detailed results are provided in **Table 4-c**. Data for this RCT were extrapolated from a figure.

A multi-center, good-quality study[62] randomly assigned 173 children in a 3:2 ratio to receive simvastatin or placebo. Simvastatin was started at 10 mg/day for the first 8 weeks, increased to 20 mg/day for the second 8 weeks, and to 40 mg/day for the last 8 weeks of the 24-week trial. The authors do not report whether adherence was assessed. At the end of the intervention period, the simvastatin group had significant reductions in TC and LDL-C relative to the control group. HDL-C changes were minimal, and TG changes were not statistically significant. Detailed results are provided in **Table 4-d**.

Lovastatin

Two RCTs examined lovastatin[60, 61] with a combined sample size of 186, and both showed a decrease in LDL-C.

The first trial[61] compared lovastatin to placebo in 132 boys aged 10 to 17 years (mean 13.2 years). This trial was rated good-quality. Lovastatin was started at 10mg/day and doubled every 8 weeks to a maximum dose of 40 mg/day. Adherence was assessed by pill count but was not reported. At the end of the 48-week intervention period, the lovastatin group had significant reductions in TC and LDL-C relative to the control group. Changes in HDL-C and TG were minimal and not statistically significant. The authors report that the U.S. Food and Drug Administration requested that subjects who had not reached Tanner stage II at entry discontinue the trial. This request resulted in the discontinuation of 8 subjects, 7 in the placebo group and 1 in the lovastatin group. Detailed results are provided in **Table 4-e**.

The second lovastatin trial[60] enrolled 54 girls aged 11 to 18 years (mean, 15 years) and randomly assigned them to lovastatin or placebo. In this good-quality trial, lovastatin was administered at 20 mg for the first 4 weeks and then increased to 40 mg for the duration of the 24-week trial. Adherence was assessed by pill count but was not reported. At the end of the intervention period, the lovastatin group had significant reductions in TC and LDL-C relative to the control group. Changes in HDL-C and TG concentrations were not statistically significant. Detailed results are provided in **Table 4-f**.

Atorvastatin

One good-quality trial of atorvastatin randomly assigned 187 children aged 10 to 17 years (mean 14.1 years) to receive 10 mg/day atorvastatin or placebo over 26 weeks.[63] The authors do not report whether adherence was assessed. At the end of the intervention period, the atorvastatin group had significant reductions in TC and LDL-C relative to the control group. There were small increases in HDL-C concentration and small decreases in TG concentration; both were statistically significant. Detailed results are provided in **Table 4-g**.

Rosuvastatin

The one RCT published after the 2007 USPSTF report, the PLUTO (Pediatric Lipid-redUction Trial of rOsuvastatin) study[64], was a good-quality trial that randomly assigned 176 children and adolescents aged 10 to 17 years (mean, 14.5 years) to 5, 10, or 20 mg/day of rosuvastatin or placebo. Pill counts indicated that 90 percent of participants were at least 80 percent compliant with the protocol. At 12 weeks, all three intervention groups had marked decreases in mean LDL-C and TC. The 20-mg dose group had the greatest reduction in LDL-C among the eight statin trials reviewed here. Fewer than half the participants who received rosuvastatin reached the target LDL-C concentration of less than 110 mg/dL: 12 percent, 41 percent, and 41 percent in the 5-mg, 10-mg and 20-mg groups, respectively. No subject reached this target in the control group. HDL-C and TG changes were neither clinically nor statistically different from the control group. Detailed results are provided in **Table 4-h**.

Effect on Atherosclerosis Markers

Only the 2-year pravastatin trial[66] reported the effect of a statin (pravastatin) on a measure of atherosclerosis (CIMT) (**Table 5**). Study details are described above, along with the effect on lipid concentrations. One experienced sonographer, blinded to treatment status, measured CIMT on all B-mode ultrasonograms. After 2 years of treatment with 20 mg, then 40 mg of pravastatin daily, mean (SD) CIMT declined marginally in the pravastatin group (−0.010 [0.048] mm; p=0.049), compared to a trend toward progression in the placebo group (+0.005 [0.044] mm; p=0.28). Expressed as a percent change from baseline, CIMT decreased by 2.01 percent in the pravastatin group and increased by 1.02 percent in the control group (calculated). The mean (SD) change in CIMT between the two groups, 0.014 (0.046) mm, was significant (p=0.02).

Detailed Results for Non-Statin Medications

Bile sequestering agents

A good-quality RCT evaluated colestipol (10 g/day) in 66 children and adolescents aged 10 to16 years (mean age, 13.1 years) with FH.[56] Adherence was 68 percent in the colestipol group and 76 percent in the placebo group. After 8 weeks, the colestipol group had significant reductions in TC and LDL-C relative to the control group. Changes in HDL-C were not significant. Detailed results are provided in **Table 4-i**.

One fair-quality study examined the effect of cholestyramine in 72 children aged 6 to 11 years (mean age, 8.4 years) with FH.[55] The intervention group received 8 g/day of cholestyramine for 1 year. Adherence was assessed but not reported. At the end of the 12 month intervention period, the cholestyramine group had significant reductions in TC and LDL-C relative to the control group. HDL-C did not change appreciably in either group. Detailed results are provided in **Table 4-j**.

A single trial of bile sequestering agents included in this review was published after the 2007 USPSTF review on child lipids. This good-quality, multisite RCT evaluated colesevelam in 194 children and adolescents aged 10 to 17 years (mean, 14.1 years).[65] Participants were randomly assigned to three groups: 1.875 g/day (low dose), 3.75 g/day (high dose), or placebo for 8 weeks. Adherence (assessed by pill count) was greater than 85 percent in all groups, and 89.2 percent of participants who were randomized completed the study. At the end of the 8-week intervention period, the colesevelam groups experienced greater reductions in LDL-C and TC than the placebo group, with more pronounced reductions in the high-dose group. The treatment goal of

LDL-C<110 mg/dL was achieved by 3.2 percent (n=2) in the low-dose group and by 7.9 percent (n=5) in the high-dose group. Detailed results are provided in **Table 4-k**.

Ezetimibe

There were two studies of ezetimibe, an intestinal cholesterol absorption inhibitor. One good-quality RCT compared the effectiveness of ezetimibe, an intestinal cholesterol absorption inhibitor, plus simvastatin to simvastatin alone in 248 children and adolescents aged 10 to 17 years (mean, 14.2 years).[58] In this six-group trial, three received ezetimibe (10 mg/day) and three received placebo. All six groups received simvastatin, with three different doses for the first 6 weeks (10, 20, or 40 mg/day), but the same dose (40 mg/day) for the next 27 weeks. The last 20 weeks of the trial were open label (both medications). The six groups were combined into two groups for analysis: ezetimibe plus simvastatin and placebo plus simvastatin. The authors do not report whether adherence was assessed. At the end of the 33-week intervention period, the ezetimibe plus simvastatin group had significant reductions in TC and LDL-C relative to the placebo plus simvastatin. Detailed results are provided in **Table 4-l**.

One good-quality RCT compared the effectiveness of a 12-week course of ezetimibe to placebo in 138 children aged 6 to 10 years (mean, 8.3 years).[59] Children in this trial either met criteria for FH (n=125, 91%) or did not meet criteria but had LCL-C greater than or equal to 160 mg/dL. The study groups were analyzed together regardless of diagnosis status. Participants were randomized to receive ezetimibe (10 mg/day) or placebo in a 2:1 ratio. At the end of the 12-week intervention period, the ezetimibe group had significant reductions in TC and LDL-C relative to the placebo group. Maximum effect was achieved at 2 weeks. HDL-C changes were not significant. Detailed results are provided in **Table 4-m**.

The number of studies of non-statin medications was too small to explore heterogeneity or publication bias.

KQ 7: What are the harms of treatment of familial hypercholesterolemia with medications in children and adolescents?

Description of Included Studies

We identified 24 publications (18 trials) that met criteria for KQ7. Several of these publications have overlapping study populations (**Table 6**). Twelve RCTs (7 with statins and 5 with non-statins) were included in both KQ6 and KQ7. Twelve articles were published before 2007 that fit our inclusion criteria: 9 of statins[52, 60-63, 66, 68-70], two of bile sequestering agents[55, 56], and one of a bile sequestering agent co-administered with a statin.[71] We identified an additional 12 articles published since 2007 with relevant data on harms: nine of statins,[64, 72-79] one of a bile sequestering agent[65], and two of a selective inhibitor of intestinal cholesterol absorption (ezetimibe).[58, 59] Most studies were less than 2 years long. One study reported 10-year follow up data of statin use.[67]

Included populations

The 18 included trials ranged in size from 6 to 248 children or adolescents with FH. Specific information on recruitment of subjects was not available for many studies; however, in most of those studies for which this was reported, subjects had already been diagnosed with FH and were often drawn from a specialty clinic population. Age at baseline ranged from 6 to 18 years; mean age ranged from 6 to 16 years. All but two studies included between 31 percent and 65 percent

female subjects; the remaining two included exclusively female subjects[60] or male subjects.[61] Four studies (8 publications) were conducted in the Netherlands[52, 66, 70, 72, 74, 76-78] two studies (2 publications) were conducted in Norway,[55, 56] and one study each was conducted in the U.S.,[60] Canada [71], Finland[68], Austria[69], and France.[73] Nine studies were conducted at multiple sites in two or more countries in North America, Europe, Africa, and/or Australia.[58, 59, 61-65, 75, 79] Identified countries involved in these studies include the U.S. (6 studies), Canada (6), the Netherlands (4), Norway (4), Israel (2), South Africa (2), Australia, Austria, Belgium, Colombia, Costa Rica, the Czech Republic, France, Greece, Hungary, Italy, New Zealand, Slovakia and Spain (1 each). In these studies, the percentage of Caucasian subjects ranged from 80 percent to 100 percent. A case definition of FH was provided for all but one[63] study. Specific diagnostic criteria for FH varied from study to study, but in all cases included either genetic testing or clinical criteria identical or similar to one of the three most-commonly cited diagnostic criteria (**Appendix D**).

Included interventions

Among the statin trials, there were five trials of pravastatin: two RCTs[52, 66] (6 publications), two observational trials of pravastatin[68, 73] and one randomized crossover trial of combination therapy with colestipol and pravastatin.[71] There were two RCTs of lovastatin[60, 61] and one RCT (2 publications) of simvastatin.[62, 70] Two statins, atorvastatin,[63, 75] and rosuvastatin[64, 79] each had two trials, an RCT and an open-label trial. Finally there was one observational cohort study of various statins.[69] The longest follow-up periods for statin studies were reported in a 48 week lovastatin RCT,[61] a 2 year open-label rosuvastatin trial,[79] and the Dutch Pravastatin Trial (a 2-year RCT with follow up at 10 years).[66]

Studies evaluating harms of non-statin medication included three RCTs of bile sequestering medications: colesevelam[65], cholestyramine[55], and colestipol[56]. There were two trials of ezetimibe: one RCT of co-administration of simvastatin with ezetimibe[58] and an RCT of ezetimibe monotherapy.[59] The longest of these non-statin studies were two year-long RCTs: the cholestyramine trial and trial of ezetimibe with simvastatin.

Two studies included for assessment of harms involved a statin and a non-statin. The trial of pravastatin vs. placebo (in youth treated with colestipol)[71] is discussed in the section on statins. The trial of ezetimibe vs. placebo (in youth treated with simvastatin)[58] is discussed in the section on non-statin medications.

Quality

All included studies were fair-to-good quality. Among studies of statins, eight studies (13 publications) were good- quality and five studies (6 publications) were fair-quality. The quality issues most often found in the fair-quality studies were lack of a control group, inadequate description of methods, and a followup of less than 90 percent. Four good-quality and one fair-quality studies assessed harms of non-statin medication treatment. The primary concern with the fair-quality papers being a low rate of followup. The two studies of combination therapy with a statin and a non-statin medication were both of good quality.

Summary of Findings

The 18 studies included 2,210 children and adolescents, 2,197 of whom had FH.

Statins

There were 13 studies (19 publications) on harms of statins, including 1,492 children and adolescents. The shortest intervention durations were 8 to 12 weeks (four studies) and the longest was two years (one RCT). Few studies conducted follow up assessments beyond the intervention period. One study (the two year RCT) provided the longest follow up data (10 years) for a group almost all of whom were treated with statins for much for the 10-year period. Dosage varied within and between studies, with some including an open-label phase with all subjects on active medication.

Most studies reported data on clinical adverse events (AEs) and laboratory abnormalities, and several studies of statins monitored growth and pubertal development. In many studies, reporting of harms assessment did not mention which harms were assessed, only those that were noted to have occurred. Statins were generally well-tolerated. There was no evidence of a consistent association between a particular subjective harm and statin use in general (**Table 8** and **Table 9**).

Serious AEs were rare. In controlled studies with a placebo group, the frequency of reported AEs usually did not differ significantly from those in placebo. The most common AEs were otorhinolaryngologic (mostly nasopharyngitis) gastrointestinal (predominantly abdominal pain, nausea/vomiting and diarrhea), respiratory (mostly respiratory infection and influenza); and neurological (predominantly headache). Statins were well-tolerated with 98.5 percent of young adults still taking statin medications 10 years after beginning a clinical trial.[78] In this same study, adherence was good, with 78.7 percent reporting taking more than 80 percent of their medications. Most studies did not report on statistical significance of difference in rates for individual AEs between study groups. Those that did generally reported no significant associations. The most frequently reported AEs (**Table 9**) were generally not believed to be associated with medication use. Systemic, immunologic, and pain-related AEs were reported only sporadically in these studies (fewer than ten reports per study).

In one small, uncontrolled study of statins in six professional athletes with FH (mean age 16.8; SD 2.6 years) , three subjects reported muscle pain on all five statins tried, and three reported muscle pain on three of the five statins tried.[69] However, musculoskeletal pain was infrequently reported in other studies, occurring in only 4.8 percent (56 of 1,018) of subjects taking statins in studies that reported this data. Musculoskeletal pain, myalgia and muscle pain were reported as adverse events in 10 statin studies. The incidence ranged between 0 and 10 percent for those on statins (and between 0 and 6.2% for those in the placebo groups). The incidence of musculoskeletal pain, myalgia and muscle pain was not reported as being significantly different from control subjects in any studies for which this information was available.

All but two of the 13 statin studies assessed liver transaminases and creatine kinase (CK) concentrations as part of their safety assessment. Concentrations were checked at baseline and conclusion; many studies also included checks at scheduled intervals during treatment. Five of the 13 studies reported no abnormalities of either CK or transaminases. In the eight that did, the abnormalities were usually transient, with concentrations usually resolving either spontaneously or after temporary withdrawal of the medication (**Table 8**).

Ten statin studies also assessed the impact of treatment on growth and pubertal development in children or adolescents, either through physical examination and measurement, laboratory screening, or both.[52, 60-64, 66, 72, 73, 76] No studies suggested an important association between statin use and abnormalities in any of these outcomes.

Ten-year follow-up of the Dutch Pravastatin Trial measured sex hormones in young men and women (mean age 24 years) with FH who had participated in the initial 2-year pravastatin trial, followed by continued use of pravastatin and other statins over the intervening years. Compared to their brothers without FH, the young men with FH in this study treated with statins had lower mean dehydroepiandrosterone sulfate (DHEAS), although values were still within the normal range. These elevations are of unclear clinical significance.

Bile sequestering agents

Three RCTs evaluated the harms of monotherapy with three different bile sequestering agents, colesevelam[65], cholestyramine[55], and colestipol,[56] in a total of 332 children and adolescents with FH. Two were 8-week trials and one lasted one year. The most common drug-related AEs were gastrointestinal. Abdominal pain, diarrhea, nausea, or vomiting were reported by 7 to 10 percent (calculated from reported data) of subjects in the two studies that reported data from the placebo-controlled period. However, these rates were similar to those reported in the placebo groups (4.6 to 5 percent, calculated).[55, 65] The studies on colestipol and cholestyramine both note that unpalatability was a marked problem and caused 14 subjects to withdraw from the cholestyramine study. However, unpalatability was also often reported in the placebo group in the same study, in which 10 subjects withdrew.

The most notable laboratory abnormalities were decreased vitamin D concentrations in treated subjects (compared to placebo) in the cholestyramine study and, to a lesser extent, in the colestipol study. Folate concentrations were lower in subjects treated with colestipol than in those on placebo, and homocysteine was increased in subjects treated with cholestyramine, concentrations of which were negatively correlated with folate concentrations at baseline and at 1 year.[55, 56] No marked laboratory abnormalities were reported in the colesevelam trial, although it is not clear which safety factors were measured.

Ezetimibe

Two RCTs evaluated harms of ezetimibe in 373 children and adolescents with FH. One was a 12-week trial of monotherapy and the other a 52-week trial of ezetimibe co-administered with simvastatin.[58] In the year-long study,[58] alanine aminotransferase (ALT) elevations occurred in 5 percent of participants in the simvastatin plus ezetimibe group and 2 percent of those in the simvastatin only group. Laboratory values normalize with interruption of discontinuation of treatment. Most AEs and their rates were similar between groups; gastrointestinal symptoms, elevated transaminase concentrations (that resolved following interruption of therapy), and myalgia without associated CK elevation. The 12-week ezetimibe monotherapy trial[59] found no significant difference in AE distribution between study groups and no serious AEs in either group.

Detailed Results

Studies are listed here by class and drug, then chronologically by date of the publication of the original study. All publications for a given study are considered together.

Statins

Pravastatin

Four trials evaluated harms of pravastatin use in children with FH including the Dutch Pravastatin Trial that produced five publications that addressed harms with up to 10 years follow up. A fifth trial used a randomized crossover design to evaluate pravastatin in children treated with colestipol.[71]

In a 12-week good-quality RCT, 72 children aged 8 to 16 years with FH in the Netherlands were randomly assigned to placebo or to one of three pravastatin doses (5 mg, 10 mg, or 20 mg daily).[52] Physical exams were performed at the beginning and end of the study, and fasting blood samples (hematology, ALT, aspartate aminotransferase [AST], CK, alkaline phosphatase, urinalysis, thyroid-stimulating hormone, cortisol, and adrenocorticotropic hormone [ACTH]) were measured monthly. The incidence of laboratory abnormalities did not differ significantly between groups. The most common AEs were gastrointestinal symptoms and headache; both these and other sporadic complaints (rash, fatigue, epistaxis, myalgia) were equally distributed between the placebo and treatment groups. None was believed to be medication-related. (Note: This trial was conducted in the Netherlands, however, we use the shorthand term "Dutch Pravastatin Trial" to refer to a separate study by Wiegman and colleagues—described below—which was a larger trial with longer follow up.)

In a good-quality randomized crossover trial of colestipol combined with pravastatin,[71] 36 youth aged 9 to 18 years received either colestipol alone (10 g/day) or low-dose colestipol (5 g/day) in combination with pravastatin (10 mg/day). This Canadian study consisted of an 8-week period without lipid-lowering medication followed by two, 18-week treatment periods. Subjects crossed over to the alternate regimen after the first treatment period. Serum chemistries and blood counts were assessed at baseline, 2 weeks, 8 weeks, and 18 weeks into each treatment period. Alkaline phosphatase concentrations were significantly decreased in both treatment regimens at 2 and 8 weeks, but the decrease was significant only in the colestipol-only regimen at 18 weeks. The absolute reduction in ALT concentrations from baseline was significantly greater in the colestipol-only group than in the combination group at 8 and 18 weeks. No significant changes or differences between regimens were reported for CK, AST, other blood chemistries, or hematologic values. Increases in weight, height, and body mass index did not differ significantly between groups. Subject-reported AEs were more common on the higher-dose colestipol-only regimen than on the combination regimen: constipation occurred in 21 percent on colestipol-only versus 3 percent on combination; bloating/gas in 15 percent versus 3 percent; stomach ache in 21 percent versus 0 percent, headache in 14 percent versus 3 percent, and muscle ache in 6 percent versus 3 percent, respectively.

One fair-quality, prospective observational study examined the pharmacokinetics and pharmacodynamics of pravastatin in Finnish children with FH.[68] Twenty children with FH aged 4 to 15 years received 10 mg pravastatin daily for 8 weeks. Subjects indicated AEs (gastrointestinal symptoms, headache, skin reactions, sleep disturbance, muscle/tendon tenderness, and pain) each day on a home questionnaire, and laboratory values (creatinine, ALT, CK) were measured at baseline, 4 weeks, and 8 weeks. Laboratory values did not increase during the study. Other AEs were rare: four reports of headache, two reports of sleep disturbance, and one report each of abdominal pain, loose stool, muscle tenderness at rest, and muscle tenderness with activity.

The Dutch Pravastatin Trial was the largest RCT of a statin in youth with FH and also the single trial in this review with the longest follow up (10 years). In this RCT, 214 children with FH aged 8 to 18 years were randomly assigned to receive either placebo or pravastatin (20 mg daily for children under 14 years of age, 40 mg daily for those 14 years and older) for 2 years.[66] Subjects were evaluated by a physician every 6 months. Sex steroids, gonadotropins, and pituitary-adrenal axis markers were measured at baseline and at 1 and 2 years into the study; developmental and maturation indices were measured at the same times: growth (height, weight, body mass index, body surface area), pubertal development (Tanner staging, menarche, testicular volume), and academic progress (school records). Muscle and liver enzymes (ALT, AST, CK) were measured at baseline, at 3 month intervals in year 1, and at 6 month intervals in year 2. CK concentrations were increased by more than a factor of four in four subjects in the intervention group and in three subjects in the placebo group; however, at the end of the trial, the groups had no relevant differences in CK or transaminase concentrations. Groups also did not differ in measures of endocrine function or in the aforementioned growth and maturation markers, and academic performance was not affected.

At the end of 2 years, all participants in the Dutch Pravastatin Trial, the intervention and control groups were combined and all participants were treated with pravastatin (20 to 40 mg daily) and followed for varying periods (duration of statin therapy ranged from 2.1 years to 7.4 years). Of the 186 subjects included in this fair quality study,[76] 83 percent were still using pravastatin at the time of follow up. No serious laboratory abnormalities were noted on follow up. Two subjects had CK concentrations greater than ten times normal. However, these elevations were considered to be associated with extreme fitness regimens, and they resolved without discontinuing treatment. Myalgia without CK elevation occurred in four subjects. Four subjects (three male, one female) had mildly elevated follicle-stimulating hormone concentrations, three had decreased DHEAS concentrations, and two had mildly elevated ACTH concentrations. None of these changes were thought to be related to statin use.

The authors assessed Dutch Pravastatin Trial participants for harms at 10 years post-randomization and published findings in three papers.[72, 77, 78] In the main 10 year adherence and tolerability analysis, 205 patients were available for follow up (mean age 24 years).[78] Tolerability was 98.5 percent over the 10 years; 3 out of 205 had discontinued medications due to side effects (gastrointestinal, muscle and joint pain or headache). There were 55 side effects were reported over 10 years by 40 subjects (19.5 percent) mainly consisting of: muscle complaints and gastrointestinal symptoms. There were no reports of rhabdomyolysis or elevation of liver enzymes. By 10 years, 17 participants had had discontinued lipid lowering medications due to pregnancy, lactation, and/or the advice of a physician, and 19 participants had chosen to discontinue the medication on their own. Among the 169 participants still taking lipid lowering medications, 99 percent were on various statins and 36 percent were on ezetimibe. Most (78.7 percent of) subjects reported adherence of greater than 80 percent in the previous month.

The last two papers from the Dutch Pravastatin Trial included the 214 patients with FH and 95 unaffected siblings who had been recruited at the conclusion of the 2-year RCT. One[72] of these two sibling comparison studies evaluated 194 participants (91 percent follow up) and 83 siblings (87 percent follow up) 10 years after randomization. All participants were aged 18 to 30 years at that time. In this study, 163 subjects were still using lipid-lowering medications at 10 years (31 percent pravastatin; 15 percent simvastatin; 27 percent rosuvastatin; 27 percent atorvastatin). Growth, maturation, level of education, history of AEs, liver transaminases, CK, glomerular filtration rate, and C-reactive protein were assessed. Subjects and unaffected siblings

did not differ remarkably on any outcomes (except for extremely elevated CK concentrations in two unaffected siblings). Three subjects discontinued statin therapy because of unspecified AEs. No serious major AEs were reported.

Comparison with these siblings also formed the basis of a study[77] examining the possible effects of statin on sex hormones, including testosterone, estradiol, LH, FSH, and DHEAS concentrations after 10 years. There were 88 participants with FH and 62 siblings available for this analysis. The only significant difference between siblings and those with FH was for DHEAS, which was significantly lower in the males with FH (8.4 micromol/L; SD 3.0) than in their brothers without FH (12.9 micromol/L; SD 4.9; $p < 0.001$). The authors note that despite this difference, the mean DHEAS concentration in the FH group was still within the normal range.

The final pravastatin study was an observational analysis of the medical records of 185 French children up to age 18 years with FH (mean age 11 years) who were being treated with pravastatin at varying doses.[73] Subjects were followed for 3 months to 7 years. Of the 185 patients, 24 (13 percent) experienced AEs: 4 reported muscular pain that resolved after changing to a new statin; 3 others had muscle pain not apparently associated with treatment; and 12 had musculoskeletal pain (2 with associated moderate CK elevation) that resolved spontaneously. Other AEs included asymptomatic CK elevation (eight subjects), transient headache (one), and gynecomastia with normal hormone concentrations (one). No subjects had elevated transaminase concentrations, and no instances of growth problems, early maturation, or delayed puberty were observed.

Lovastatin

Two good-quality RCTs evaluated harms of lovastatin in children with FH.

One trial, conducted in the U.S. and Finland, randomly assigned 132 boys aged 10 to 17 years with FH to either placebo or daily lovastatin (initially at a dose of 10 mg, titrated after 8 and 16 weeks to 20 mg and 40 mg, respectively, then maintained at 40 mg for the remaining 32 weeks of the study).[61] Adverse events were reported by 70.1 percent of subjects in the lovastatin group and by 73.8 percent in the placebo group. Adverse events reported in the lovastatin group included gynecomastia (1.5 percent); respiratory tract infection (47.8 percent); abdominal pain (10.4 percent); ear, nose, and throat infection (10.4 percent); skin disease (9.0 percent); gastroenteritis (7.5 percent); lymphadenopathy (3.0 percent); myalgia (4.5 percent); diarrhea (1.5 percent); and arthropathy (1.5 percent). The frequencies of these AEs did not differ significantly from those in the placebo group. Both the lovastatin and placebo groups had a statistically significant increase in ALT at 48 weeks; however, ALT concentrations did not differ significantly between the two groups. No sustained changes in AST or CK were noted in either group, although non-sustained CK elevations (greater than five times the upper limit of normal) were noted in three subjects in the lovastatin group and in one subject in the placebo group. These elevations were reported to be associated with vigorous or unusual exercise. Participants reported no associated muscle pain. Indices of growth and development did not differ between groups.

In the other, a U.S. study, 54 postmenarchal girls (aged 11 to 18 years) were randomly assigned to receive placebo or lovastatin 20 mg or 40 mg daily for 24 weeks.[60] Just over two-thirds of the girls in both the lovastatin and placebo groups reported AEs; among these, the most common were upper respiratory infection (29 percent of girls on lovastatin, 47 percent of girls on placebo), headache (20 percent and 21 percent), and pharyngitis (17 percent and 11 percent, respectively); 11 percent of lovastatin subjects also reported an influenza-like disease. Three

girls (9 percent) in the lovastatin group had AEs believed to be treatment-related: two girls (6 percent) with abdominal pain, one with diarrhea, one with nausea, and one with headache. All treatment-related AEs resolved spontaneously while patients continued on study medication. The only laboratory AE reported was a decrease in hemoglobin and hematocrit in one subject taking 40 mg of lovastatin. This AE was believed to be unrelated to treatment. Luteinizing hormone concentrations decreased in those on placebo but were unchanged in those on lovastatin. No significant between-group differences or changes from baseline were noted for other hormones (follicle-stimulating hormone, cortisol, estradiol, DHEAS), AST, ALT, CK, height, weight, body mass index, or vital signs (except a small decrease in systolic blood pressure in the placebo group).

Simvastatin

One good-quality RCT (two publications) evaluated the safety of simvastatin for treating children with FH in the Netherlands. This trial randomly assigned 173 children aged 10 to 17 years with FH to receive simvastatin or placebo.[62] Simvastatin dose in the first phase was 10 mg/day for 8 weeks, with subsequent increase to 20 mg for 8 weeks and then to 40 mg for 8 weeks. Subjects then continued at a dose of 40 mg/day for an additional 24 weeks. Drug-related laboratory AEs occurred in 2 subjects on simvastatin and in 1 on placebo during the first phase of the trial, and in 2 simvastatin and 1 placebo subjects during the second phase. These AEs included two cases of transaminase elevations greater than three times the upper limit of normal (one of which improved after a 10-day interruption in therapy; the other of which occurred in a child with infectious mononucleosis), and three cases of elevated CK concentrations. One of these three children was on concurrent erythromycin therapy and had CK levels greater than 10 times the upper limit of normal, which resolved after completing antibiotic therapy. The other two children had CK levels greater than five times the upper limit of normal, which returned to normal on repeat testing. Clinical AEs reported during the study included headache (in 4 subjects on simvastatin), abdominal pain (3 subjects on simvastatin), and myalgia (2 subjects on simvastatin). Other AEs (1 subject on simvastatin each) included chest pain, flatulence, weight gain, sleep disorder, and pruritus. Fewer subjects on placebo reported clinical AEs (5 subjects) than did those on simvastatin (10 subjects); however, none of the differences between the placebo and simvastatin groups in either phase of the study was statistically significant. There were small but statistically significant between-group differences in the absolute change of DHEA concentrations in both boys and girls at 24 and 48 weeks, but no associated growth or pubertal development abnormalities (no significant differences between groups on growth, body mass index, cortisol and hormone concentrations, or pubertal development).

A fair-quality subanalysis of this simvastatin RCT assessed harms in 50 children with FH aged 9 to 18 years to receive either placebo or simvastatin 10 mg/day for 8 weeks, then 20 mg/day for 8 weeks, and then 40 mg for 8 weeks.[70] Safety assessment included measuring AST, ALT, and CK and a physical examination. Laboratory values did not differ substantially between the simvastatin and placebo groups. The authors stated that no AEs were reported; no data were shown.

A different RCT[58] evaluated ezetimibe in children with FH being treated with simvastatin and is discussed in the section on ezetimibe below.

Atorvastatin

Two studies evaluated harms of atorvastatin used to treat FH in children. One good-quality RCT conducted in the U.S., Canada, Europe and South Africa, randomly assigned 187 youth

(aged 10 to 17 years with FH or severe hypercholesterolemia) to receive atorvastatin 10 mg/day or placebo daily for 26 weeks, followed by an additional 26 weeks during which all subjects received 10 mg atorvastatin daily.[63] During the RCT phase, the dose of atorvastatin could be titrated to 20 mg/day at week 4 for subjects not achieving target LDL-C levels. Adverse events occurred in 63 percent of the treatment group during the blinded phase and in 62 percent of the placebo group. Among subjects in the treatment group, AEs included infection (19%), accidental injury and headache (9% each), pharyngitis and flu syndrome (6% each), abdominal pain (4%); and fever (1%). All of these AEs occurred in the placebo group as well; the incidence did not differ significantly between groups. During the RCT phase, 7 percent of AEs in the atorvastatin group were judged to be treatment-related, compared to 4 percent in the placebo group. Adverse events were mostly mild or moderate; one subject in the atorvastatin group experienced increased depression that was thought to be possibly treatment-related, and this subject discontinued treatment. Marked laboratory abnormalities were noted in 29 percent of atorvastatin subjects and in 34 percent of placebo subjects during the RCT phase. Two subjects on atorvastatin had AST elevations (three times the upper limit of normal), and one had an ALT elevation, none of which required treatment modifications. No such abnormalities occurred in the placebo group. Indices of growth and sexual development did not differ significantly between groups, nor did the incidence or severity of treatment-related AEs increase in the second phase of the study.

One fair-quality, open-label, 8-week study assessed the tolerability of atorvastatin in 15 children aged 6 to 10 years (Tanner stage [TS] 1) and in 24 children aged 10 to 17 years (Tanner stage [TS] ≥2) with FH in Greece, Norway and Canada.[75] Initial doses were 5 mg/day for younger children and 10 mg/day for older children. Doses were doubled after 4 weeks if the target LDL-C concentration was not achieved. Indices of safety and tolerability did not differ between the younger and older groups, and no serious AEs were observed. At least one AE was reported by 9 of 15 subjects in the younger group and by 13 of 24 in the older group. The only AEs reported by more than one subject were viral upper respiratory infection (3 subjects in TS1 group), nasopharyngitis (1 subject in TS1; 2 subjects in TS≥2), headache (2 subjects in TS1, 1 in TS≥2), and increased ALT (2 subjects, both in TS≥2). Only four subjects (two from each group) reported AEs that were believed to be treatment-related. These AEs included one instance each of headache, abdominal pain, nausea, and vomiting in the younger group, and the two aforementioned subjects with ALT elevations in the older group (at the end of the study, ALT concentrations returned to normal in one subject, and were only slightly elevated in the other.) Data on vital signs, electrocardiogram, urinalysis, hematology, and biochemistry tests (including CK) were obtained at baseline and 8 weeks. The only abnormality was a moderate but transient increase in CK that was not believed to be related to treatment in one 9-year-old child.

Rosuvastatin

Two good-quality trials (three publications) evaluated the safety of rosuvastatin for treating FH in children. Authors of the first of these also published a separate analysis of a subset of trial participants.[74] The PLUTO trial conducted in 20 centers in North America and Europe was a good quality RCT that randomly assigned 176 participants with FH (aged 10 to 17 years) to receive placebo or rosuvastatin at a dose of 5 mg, 10 mg, or 20 mg daily for 12 weeks. This period was followed by a 40-week, open-label phase in which dosing for all subjects was titrated to achieve target LDL-C concentrations (maximum dose 20 mg/day).[64] Safety assessment included monitoring of growth, pubertal development, solicitation of AEs, and laboratory screening (consisting of CBC, albumin, total protein, liver enzymes, bilirubin, CK, blood urea

nitrogen, creatinine, calcium, glucose, electrolytes, thyroid-stimulating hormone, HbA1c, and urinalysis). During the first phase of the study, AEs occurred in between 50 percent and 64 percent of subjects on rosuvastatin (varying by dose) and in 54 percent of subjects on placebo. The most common were headache (in 6 to 9 subjects in rosuvastatin groups and in 9 subjects on placebo), nasopharyngitis (3 to 7 in rosuvastatin groups, 5 on placebo), influenza (0 to 2 in rosuvastatin groups, 4 on placebo), myalgia (1 to 2 in rosuvastatin groups, 0 on placebo), and nausea (0 to 2 in rosuvastatin groups, 2 on placebo). Blurred vision occurred in one subject on placebo, and vesicular rash occurred in one subject on rosuvastatin during the open-label period. Overall changes in AST and ALT were similar between groups, although transaminase concentrations were elevated (greater than three times the upper limit of normal) in three rosuvastatin subjects on doses of 10 mg or 20 mg during the first phase and in one rosuvastatin subject in the second phase. Overall changes in CK were also similar between groups, although CK was elevated (greater than ten times upper limit of normal) in four rosuvastatin subjects on doses of 10 mg or 20 mg during the first phase and in four during the open-label phase. Myalgia was reported by four rosuvastatin subjects during the first phase and five during the second phase. In all subjects, transaminase concentrations, CK, and myalgia returned to normal during treatment or remained normal after treatment was restarted.

Another publication from the PLUTO trial addressed a potential harm of statins, hypothesized based on the role of HMG-CoA reductase in the synthesis of coenzyme Q10 (CoQ10). CoQ10 serves both as an electron carrier in adenosine triphosphate (ATP) synthesis and as an important cellular antioxidant. For this reason, inhibition of HMG-CoA reductase activity in the course of statin treatment could reduce endogenous CoQ10 synthesis, thus impairing mitochondrial energy metabolism and cellular antioxidant capacity. A sub-study of PLUTO (conducted in the Netherlands) reports on CoQ10 concentrations in peripheral blood mononuclear cells (PBMCs) and plasma (at baseline and end of study) in 29 PLUTO participants and mitochondrial respiratory chain-driven ATP in PBMCs in 17 of these 29 subjects.[74] During rosuvastatin treatment, mean (SD) PBMC CoQ10 concentrations dropped, from 89 (59) pmol/mg to 63 (21) pmol/mg. At the end of the study, CoQ10 concentrations (corrected for baseline concentrations) differed significantly between the 5-mg and 10-mg groups but not between other treatment groups, and no dose-related effect of rosuvastatin on PBMC CoQ10 concentration was found. Although the differences were statistically significant, they were of unclear clinical significance. Proportion of participants with CoQ10 concentrations below the reference range did not change with rosuvastatin treatment. PBMC ATP synthesis did not change. Mean plasma CoQ10 concentration also decreased significantly; however, although concentrations differed between the 10-mg and 20-mg groups, they did not differ between other treatment groups, and the rosuvastatin dose at the end of the study was not associated with plasma CoQ10 concentration. Ratios of plasma CoQ10/TC and CoQ10/LDL-C remained equal during treatment. The authors concluded that the observed 32% decrease in PBMC CoQ10 level did not perturb mitochondrial respiratory chain–driven ATP synthesis in these participants.

The second rosuvastatin trial was CHARON (hyperCholesterolaemia in cHildren and Adolescents taking Rosuvastatin OpeN label), a 2-year single-arm open-label trial conducted in several sites in Europe and North America. 198 children and adolescent ages 6 to 17 (mean 11.6, SD 3.3) years received 10 or 20 mg daily of rosuvastatin (depending on age). Incidence and severity of adverse events (AEs) and serious AEs, rates of discontinuation due to AEs and abnormal serum laboratory values were recorded. Laboratory assessments included AST, ALT, urine protein:creatinine ratio and CK. Most participants (86 to 89 percent across age groups)

reported at least one treatment-emergent AE during the study period. The most common AEs were nasopharyngitis, headache, influenza and vomiting. There were 29 AEs that were considered to be possibly related to the study medication, including gastrointestinal disorders, myalgia, increased serum CK and skin disorders. Myalgia was reported in none of the 6-to-9 year olds, 7 percent of the 10-to-13 year olds and 10 percent of the 14-to-17 year olds. Arthralgias were reported in 3 percent of the 6-to-9 year olds, 10 percent of the 10-to-13 year olds and 5 percent of the 14-to-17 year olds. No serious treatment-related AEs were reported. Three of 198 participants discontinued rosuvastatin due to AEs (nausea, migraine and paresthesias).

Various statins

One Austrian study included youth treated with different statins. This fair-quality prospective clinical follow up study of 22 professional adolescent and young adult athletes with FH investigated the possibility that the frequency of harms associated with statin use in athletes (muscle pain in particular) may be greater than in non-athletes with FH. Six of these subjects were aged 20 years or less, and FH had been diagnosed between 4 and 10 years earlier.[69] Safety outcomes included muscle pain, CK concentrations, and liver enzymes. The six subjects were started on the lowest available dose of either pravastatin or lovastatin and subsequently switched to an alternate statin if AEs developed or target values were not met. Three of the six did not tolerate any of the five statins tried (pravastatin, lovastatin, simvastatin, fluvastatin, atorvastatin), and muscle pain developed in all six 2 to 18 days after the start of treatment with at least one of the medications. Two of the six experienced CK elevations while on certain statins (one subject while on pravastatin and lovastatin, one while on pravastatin, simvastatin, and atorvastatin). Muscle pain developed in all six subjects while on pravastatin and simvastatin, in five while on lovastatin, in four while on atorvastatin, and in three while on fluvastatin. Concentrations of liver enzymes did not change in any patient. Symptoms disappeared in less than a week after drug withdrawal in most patients, and within 3 weeks in all patients.

Non-statin medications

Bile sequestering agents

Three RCTs evaluated harms of bile sequestering medications in children and adolescents with FH. A different study (a randomized crossover trial of combination pharmacologic therapy with colestipol and pravastatin) is described above in the section on statins.[71]

One good-quality RCT with a follow-up open-label period randomly assigned 66 adolescents with FH aged 10 to 16 years to receive colestipol 10 mg daily (10 mg once a day or 5 mg twice a day) or placebo for 8 weeks. Those in the placebo group then received colestipol 10 mg daily for 1 year, and the other groups continued at their originally assigned doses for 1 year total treatment.[56] Of the 42 subjects completing 1 year of colestipol treatment, 8 reported AEs, including constipation (2 subjects), intermittent nausea (2 subjects), and 1 subject each for dyspepsia, flatulence, temporary reduction in appetite, and abdominal pain. Both constipation and abdominal pain improved with dose reduction. One subject lost one kilogram or more during the study, a boy with initial body mass index of 24.5 kg/m^2. Folate concentrations decreased in the colestipol group (compared to the placebo group) during the initial 8-week phase and remained decreased after 1 year (although they were still above the laboratory's lower reference point in all but three subjects. The authors note that this decrease might be attributable to sexual maturation because the 1-year findings were not controlled. Vitamin E and carotenoid

concentrations also decreased in the colestipol group during the initial 8-week phase; however, this decrease was proportionate to the decrease in cholesterol. Vitamin D concentrations did not change significantly during the initial 8-weeks, but after 1 year, vitamin D concentrations tended to be lower in the subset of subjects who took more than 80 percent of the prescribed colestipol dose than in others (p=0.07). Vitamin D, vitamin A, and vitamin-E-to-cholesterol ratio all remained above the laboratory's lower reference point in all subjects after 1 year. As with cholestyramine, poor palatability was a frequent complaint for colestipol; only 21 percent "liked the taste" of the medication.

One fair-quality, double-blind RCT evaluated harms of cholestyramine treatment in children aged 6 to 11 years with FH.[55] The 96 children enrolled were instructed to follow a low-fat, low-cholesterol diet for 1 year. At that point, 72 with elevated LDL-C concentrations and a family history of premature cardiovascular disease who agreed to continue were randomly assigned to receive cholestyramine 8 g or placebo daily for 1 year. Of the 48 completing the study, 22 were in the cholestyramine group and 26 were in the placebo group. Vitamin D concentration decreased from baseline by 30.9 percent (calculated) in the cholestyramine group and decreased by 20 percent (calculated) in the placebo group (p<.04). None of the subjects whose vitamin D concentrations decreased below the reference range were taking daily multivitamins. Total homocysteine was increased in the cholestyramine group and was negatively correlated with folate concentrations at baseline and 1 year. One subject with an increased homocysteine concentration became folate-deficient. No differences in liver enzymes or hemoglobin were noted between groups. Height velocity and weight were not adversely affected, and no other nutritional deficiencies were observed. Carotenoid concentrations did decrease significantly (as expected with a decrease in cholesterol). Other AEs were enumerated but not statistically compared between groups. Those who completed the study reported sporadic gastrointestinal symptoms. Nausea, loose stool, or abdominal pain were reported by 1 to 2 subjects each on cholestyramine; one subject withdrew because of vomiting after taking two packets; one subject withdrew after 2 months because of headaches; and one subject who had undergone appendectomy 3 months before had an intestinal obstruction after two doses of cholestyramine. However, the frequency of AEs was similar to that in the placebo group. Three subjects on placebo reported intermittent abdominal pain. One withdrew due to vomiting for three weeks, and one developed appendicitis. Unpalatability (unpleasant enough to cause withdrawal from the study) was the most common report in the 14 cholestyramine subjects; however, 10 subjects in the placebo group also reported unpalatability.

One good-quality RCT evaluated harms of colesevelam treatment in children and adolescents with FH (including both statin-naïve subjects and those on a statin regimen).[65] This study measured changes in vital signs, physical examination findings, and laboratory values (blood chemistry, including lipids, hematology, selected hormone concentrations, vitamins A and E, clotting factors, and high sensitivity C-reactive protein and urine analysis) in 194 subjects (aged 10 to 17 years) who were randomly assigned to placebo, low-dose, or high-dose colesevelam treatment for 8 weeks, followed by open label use for 18 weeks. Adverse events were reported by 34.5 percent of subjects during the initial 4-week period, during which all subjects received only placebo (plus their usual statin, if any). This percentage increased to 42.8 during the blinded period (with a similar distribution in all three groups), and to 50.5 percent during the open-label period, when all subjects received colesevelam (again with their usual statin, if any). Drug-related AEs were reported by 9.3 percent of subjects in the blinded period (by 6.3 percent of those on high-dose colesevelam, 10.8 percent of those on low-dose colesevelam, and 10.8

percent of those on placebo), and medication was stopped in one subject on high-dose and in three subjects on low-dose therapy. The most common drug-related AEs were gastrointestinal (diarrhea, nausea, vomiting, abdominal pain) and occurred in 7 percent of those on colesevelam and in 4.6 percent of those on placebo. During the open-label period, 6.0 percent of subjects reported drug-related AEs; the most common again being gastrointestinal symptoms (occurring in 4.3 percent). The AEs most commonly reported during the open-label period were headache (7.6 percent), nasopharyngitis (5.4 percent), and upper respiratory infection (4.9 percent). Five patients reported serious treatment-emergent AEs, but none was believed to be drug-related. Clinically meaningful changes were not found in safety laboratory measurements, vital signs, or physical findings, and changes in heart rate, blood pressure, body weight, and height velocity were similar for both groups.

Ezetimibe

Two good-quality RCTs evaluated ezetimibe, one in co-administration with simvastatin[58] and the other as monotherapy.[59] One good-quality RCT evaluated co-administration of ezetimibe with simvastatin in 248 subjects aged 10 to 17 years with FH.[58] Subjects were randomly assigned to receive varying doses of simvastatin plus either 10 mg/day ezetimibe or placebo for 6 weeks, followed by higher-dose (40 mg) simvastatin plus either 10 mg/day ezetimibe or placebo for 27 weeks, followed by an open-label regimen of lower-dose simvastatin (10 or 20 mg) plus 10 mg/day ezetimibe for 20 weeks. The study was not powered to detect differences between groups on safety endpoints. However, at the end of the second phase of the trial, 83 percent of the simvastatin-plus-ezetimibe group and 84 percent the simvastatin-plus-placebo group reported AEs. The most frequent AEs were reported at the same rates (nasopharyngitis in 27 subjects in each group, and headache in 16 subjects in each group). The only AEs that were noted in at least twice as many subjects in the ezetimibe group as in the placebo group occurred rarely: myalgia (7 subjects vs. 1 subject), diarrhea (9 vs. 3 subjects), nausea (8 vs. 4 subjects), abdominal pain (6 vs. 3 subjects), pharyngolaryngeal pain (6 vs. 3 subjects), and ALT increased to three times upper limit of normal on consecutive checks (6 vs. 3 subjects, respectively). Among the eight subjects with myalgia, CK concentrations were unremarkable. Persistently elevated transaminase concentrations returned to normal in all affected subjects after interrupting or discontinuing therapy. Three percent of participants discontinued treatment due to AEs. No clinically important AEs on growth, sexual maturation, or steroid hormones were reported.

The ezetimibe monotherapy RCT was conducted in 29 international sites and randomized 138 youth ages 6 to 10 (mean 8.3, SD 1.6) years to 10 mg ezetimibe or placebo for 12 weeks. Clinical harms assessed included rhabdomyolysis, myopathy, hypersensitivity, cholecystitis, cholelithiasis, and pancreatitis. Laboratory harms assessed included consecutive increases in ALT or AST greater than 3 times the upper limit of normal (ULN), consecutive increases in creatine phosphokinase greater than 5 ULN with clinical muscle symptoms or creatine phosphokinase greater than 10 times ULN. There were no significant differences in AE distribution across the treatment groups. There were no serious drug-related AE in either group. Three members of the ezetimibe group (3.3 percent) and none in the placebo group discontinued treatment because of AE (2 drug related, 1 serious): 1 elevated ACT, 1 prurigo, 1 epileptic event.

KQ 8: What is the association between intermediate outcomes in childhood and adolescence (lipid concentrations or atherosclerosis markers) and the future incidence or timing of adult MI and stroke events?

No studies were identified.

Chapter 4. Discussion

Summary of Evidence

Screening

Consensus in the current debate regarding screening for dyslipidemia in children and adolescents is that the primary benefit of screening is identifying children with FH.[27, 80, 81] Identifying children with mild or moderate elevations in LDL-C is a cited as a secondary benefit of such screening, but experts disagree on its relative importance and even whether it represents a net benefit.[17, 80-84] Dyslipidemia screening to identify LDL-C elevations not caused by FH is addressed in a separate USPSTF evidence review (citation when available).

Potential benefits of screening for FH include early identification of children and adolescents with FH, prompt initiation of treatment including pharmacotherapy and low fat, low cholesterol diet, slowing the progression of atherosclerosis and reducing the incidence or delaying the onset of CHD and stroke. In addition, identifying a child or adolescent with FH could accelerate identification of affected family members. Although most experts agree that the benefits of statin treatment likely outweigh the harms in persons with definite FH, the long-term benefits and harms of lipid-lowering medications in children and adolescents remain poorly understood.

In our review, we sought evidence about both universal and selective screening in studies published both before and since the 2007 USPSTF review. Consistent with that USPSTF review, we found no direct evidence that selective or universal screening programs improves intermediate or health outcomes in children or adolescents with FH. The few studies from which diagnostic yield could be determined for pediatric screening programs addressed only universal screening. The statewide universal screening program in West Virginia schools[53] found a diagnostic yield of 0.13 percent, a rate considerably lower than published estimates. The Danish study[54] of universal screening in first-graders used a lipid-screening approach, Apo B:A1 ratio, which to our knowledge is not commonly used. The authors reported a (calculated) diagnostic yield of 0.48 percent.

We found no studies reporting diagnostic yield or effectiveness of selective screening for FH in youth (i.e., screening focused on children with a family history of FH or other targeting factor). The 2007 review found 16 studies on the diagnostic accuracy of using family history to target screening for dyslipidemia in childhood. The quality of the overall body of evidence on this topic was rated "good." Studies include a range of family history definitions (e.g., whether grandparents or second-degree relatives were included) and definitions of risk (parental history of heart attack, other parental risk factors for dyslipidemia, age of onset of early CHD). The evidence suggested that, across different family history definitions, using family history as a tool for targeting screening missed substantial numbers of children with elevated lipid concentrations—as many as 90 percent overall, but ranging from 30 percent to 60 percent in most studies. The 2007 USPSTF Recommendation Statement on this topic noted that for children with familial dyslipidemia, the group most likely to benefit from screening, use of family history in screening may be inaccurate because of variability of definitions and unreliability of information.[47] It went on to point out that serum lipid levels are accurate screening tests for childhood dyslipidemia, although many children with multifactorial types of dyslipidemia would have normal lipid levels in adulthood.

A 2009 evidence report commissioned by AHRQ on the ability of family history to impact health outcomes (risk of stroke and CVD), although not focused exclusively on children, reached

conclusions similar to those mentioned above.[85] The review also determined that across disease types, specificity (unaffected family members correctly reported) was consistently high, and sensitivity (affected family members correctly reported) was consistently much lower. No factors were clearly associated with reporting accuracy in relatives and affected people, including demographics, race, type of disease, insurance status, type of relative, and time since diagnosis. The studies had high risks for selection, verification, and masking biases that may have overestimated accuracy.[85]

Two recent reports also support the findings of the 2007 USPSTF report and the 2009 AHRQ Evidence Report. In the Project Heartbeat! study, a longitudinal study tracking CVD risk factors in children in Texas, the accuracy of family history in predicting TC, LDL, and HDL-C concentrations was low. Sensitivity ranged 38 percent to 43 percent, and specificity from 64 percent to 65 percent.[86] Similarly, the recent report from the CARDIAC school-based screening program in West Virginia cited above[87] found that family-history screening did not accurately predict either dyslipidemia warranting pharmacologic treatment (specificity, 63 percent; sensitivity, 20 percent) nor the presence of any dyslipidemia (specificity, 30 percent; sensitivity, 63 percent).[87]

Thus, studies included in the previous USPSTF review, supplemented by several intervening systematic reviews and studies, consistently suggest that family history alone has low sensitivity for identifying children to be screened for FH. This approach should not be confused with "cascade screening" of all relatives (including children) of index cases with known FH, as has been recommended to improve early detection in several countries.[11, 88] The U.S. health system does not have the infrastructure to support cascade screening. Therefore, cascade screening was considered to be out of scope for this review.

We found no studies of the harms of screening children and adolescents for FH. The 2007 USPSTF review found that harms of screening for childhood dyslipidemia in general were poorly reported, but none of the studies in that review met our criteria because they were not focused on screening for FH in particular. There are some potential harms of screening for FH in children and adolescents. Screening asymptomatic populations for FH using TC or LDL-C norms carries the risk of false positives. As covered in the separate review on multifactorial dyslipidemia, at least some of these identified individuals may never experience clinically relevant lipid concentrations. Such "non-disease" can result in subtle harms, such as labelling a child as "sick" or causing parent or child anxiety, or unnecessary or even harmful treatment. In some cases, screening for FH may lead to unnecessary or even harmful treatment.

Treatment

We found no direct evidence for the effectiveness of treating children and adolescents with FH on health outcomes in adulthood; that is, reducing the incidence or delaying the onset of MI or stroke. However, the evidence is fair-to-good for the effectiveness of pharmacologic treatment of children and adolescents with FH on intermediate outcomes. Eight RCTs were of statins and five were of other drug classes. Studies of statins ranged from 8 weeks to 2 years in duration, with most being shorter than 1 year. Statins lowered LDL-C and TC concentrations in the short term, with most studies reporting that statins lowered LDL-C by 20 percent to 40 percent and as much as 50 percent compared to placebo. The greatest effect on LDL-C was in a trial of rosuvastatin[64]; participants who received the highest dose (20 mg/day) experienced a 50 percent decrease (least mean squares) in LDL-C from baseline, compared to a one percent decrease among controls ($p<0.001$). The effect on HDL-C was minimal or none.

A single study found that pravastatin reduced CIMT by 2 percent in the treatment group whereas CIMT increased by 1 percent in the control group. There were no consistent differences in treatment effects among different statins, but the number of studies for any one drug was limited. The two studies that compared different doses of statins reported a dose response with pravastatin[52] and rosuvastatin.[64] In the 2010 rosuvastatin trial,[64, 65] the only statin study in which attainment of LDL-C treatment targets were reported, only 12 to 41 percent of participants reached the target LDL-C concentration of less than 110 mg/dL, with greater effects at higher doses. Our findings are consistent with a recent systematic review[48] on the effectiveness of statins in children and adolescents with FH. Evidence is insufficient to allow comparison among different statins.

The three RCTs of bile-sequestering agents lasted from 8 weeks to 1 year. These drugs had more modest effects on LDL-C and TC than did statins. The study of colesevelam[65] showed a dose response. In the only non-statin study reporting attainment of LDL-C treatment targets[65], only 3.2 to 7.9 percent of participants reached a target LDL-C of 110 mg/dL or less, with a greater effect at the higher dose of colesevelam.

One additional drug, ezetimibe—an inhibitor of intestinal cholesterol absorption—was studied in two RCTs. In a trial of combination therapy with simvastatin, ezetimibe reduced LDL-C concentrations by 54 percent, 16 percent more than the 38 percent achieved by simvastatin alone.[58] In a 12-week RCT of ezetimibe monotherapy, LDL-C decreased by 28 percent from baseline, compared to a negligible change in the placebo group.[59]

Most participants in whom lipid-lowering medications have been studied are children and adolescents with FH, as opposed to those with other, generally milder dyslipidemias. Most of these trials have been conducted in tertiary clinic populations, not screen-detected individuals. Therefore, subjects in these trials may not accurately represent the spectrum of children and adolescents that would be identified from a screening program.

The earlier USPSTF review found that dietary counseling and exercise (in the absence of medication) had limited effect in reducing LDL in children and adolescents with probable or definite FH. We found no new studies of lifestyle (diet or exercise) treatment for FH in youth. Neither did we find new studies of dietary supplements in children or adolescents with FH that met our inclusion and quality criteria. All medication trial protocols included a low fat, low cholesterol diet.

When the aim of pharmacologic treatment is reducing disease risk (rather than treating disease), only a low risk of harm is acceptable. The evidence about the short-term harms of pharmacologic treatment of children and adolescents with FH is fair to good. Most studies were conducted outside the United States but were applicable to U.S. primary care settings. Most studies were short, only 6 weeks to 2 years long. Statins were generally well-tolerated, although reversible elevations of liver enzymes and/or CK concentrations were noted in some studies. Ten year follow-up of the Dutch Pravastatin Trial found lower DHEAS in individuals with FH treated with statins compared to unaffected sibings.[77] Clinical significance of this difference is unknown. No severe, permanent harms of statins were reported. Bile acid binding resins were commonly associated with adverse gastrointestinal symptoms and poor palatability. Long-term harms are unknown. Ezetimibe, represented in only two studies, was well tolerated in the short term. Reports of a small increase in cancer risk among adults treated with ezetimibe[89] emphasizes the importance of long-term follow-up studies when treatment is being initiated in children and adolescents.

Outcomes

We found no evidence in individuals with FH to quantify the association between intermediate outcomes (such as lipid concentrations or measures of atherosclerosis) in children or adolescents and MI and stroke in adults. The previous USPSTF review did not examine the evidence related to health outcomes in adulthood.

The Simon Broome Register provides some of the first estimates of the increased mortality risk conferred by FH. This tertiary clinic-based UK registry found excess CHD mortality in individuals with FH compared to the general population, with markedly elevated standardized mortality ratios in the 20 to 39 year age group.[1] These data establish the severe natural history of FH among adults referred to lipid clinics; they do not allow direct estimation of the association between lipid concentrations or atherosclerosis in youth and CHD in adulthood.

Children and adolescents with severely elevated LDL-C have pathologic signs of atherosclerosis at earlier ages than do those with normal LDL-C concentrations of the same age[14, 90] but these signs have not been directly related to the probability of CHD in adulthood. Elevated LDL-C in adults predicts MI and stroke.[5, 20] However, no direct evidence supports a link between lipid concentrations or measures of atherosclerosis in children and adolescents with FH and health outcomes in adulthood.

Optimal Age of Statin Initiation (Contextual Question)

The rationale for screening for FH depends on the availability of safe and effective interventions that alter the course of disease for screen-identified cases compared to other methods of diagnosis.[70] One benefit of screening youth for FH would accrue if beginning statin treatment in childhood or adolescence improved health outcomes over those obtained if treatment for FH were begun in young adulthood. Several lines of evidence have promoted interest in treatment at younger ages. An analysis of adults with FH in the Simon Broome Register compared standardized mortality rates in the pre-statin and statin eras and found that the advent of statins coincided with a reduction in fatal CHD in young adults, most of it ascribed to primary prevention.[91] This finding raises hopes that earlier statin initiation could reduce young adult mortality, although the authors note that addressing this possibility would require expansion of the cohort.) The evidence in adults with elevated LDL-C concentrations (not FH) suggests that achieving lower LDL-C concentrations leads to more benefit.[92-94] Aggressive treatment in adults with FH suggests that it is possible to slow, and even reverse, the progression of atherosclerosis.[95]

Motivated by such evidence, experts have raised the question at what age to initiate statin therapy in youth with FH.[50] Answering this question would require a randomized trial in which statin treatment in children or adolescents would begin at different ages and that lasted long enough to measure cardiovascular events or intermediate outcomes in adulthood (such as LDL-C, CIMT, or calcium score). Such a trial has not been undertaken, and indeed, available trials of statin treatment in FH still have relatively short follow ups. Comparing the long-term incidence of MI or stroke in adults identified and successfully treated for FH from an earlier age with those identified in early or middle adulthood might also be informative. In 14 well-known cohort studies in children or adolescents (see **Appendix E** for list), we found no such evidence.

The best evidence of statin exposure longer than 2 years in childhood comes from one study: the Dutch Pravastatin Trial.[66, 72, 76] Although the initial RCT[66] was included as primary evidence for efficacy of treatment (KQ6), the followup studies[72, 76] were designed as cohort studies, so were included only for harms (KQ7). As described above (see Results), this study began as a 2-

year RCT of pravastatin compared to placebo (n=214; mean age, 13 years) and found a beneficial effect of pravastatin on LDL-C and CIMT.[66] Subsequently, the trial was converted to a cohort study, with all FH patients treated with pravastatin and a group of non-FH siblings enrolled as controls. Two publications from this later phase of the Dutch Pravastatin Trial[72, 76] provide observational data to inform this age of initiation question. The first follow-up of the Dutch Pravastatin Trial cohort was at a mean of 4.5 years after baseline.[76] Younger age at treatment initiation and longer duration of statin exposure independently predicted favorable CIMT values.[76] The other publication from the Dutch Pravastatin Trial that sheds light on age of statin initiation reports on CIMT in 91 percent of the original RCT population and 87 percent of the original sibling control group at 10-year follow-up.[72] The progression of CIMT was similar in both FH and sibling groups but began higher in the FH group at baseline and remained higher at follow up. As in the other follow up study, younger age at statin initiation was associated with thinner CIMT at 10 years.[72]

These observational findings from the Dutch Pravastatin Trial represent the best evidence to date on the benefits of earlier treatment of FH in youth. Thus, despite considerable trial and observational data in adults, and a biologically plausible pathway through which long-term statin treatment beginning in childhood could reduce or delay the occurrence of cardiovascular events in adulthood through the persistent reduction in atherosclerotic burden, the evidence to assess these benefits is limited. In the absence of RCT data comparing adult CHD outcomes in youth stated on statins at different ages, the optimal age of statin initiation in children and adolescents with FH remains unclear.

Limitations of the Review

One limitation of this review was by design: based on strong advice received during the public comment period, we restricted the key questions to FH alone and addressed other atherogenic dyslipidemias in a separate review (citation when available). Thus, all findings here are limited to screening for and treatment of FH.

The literature has several limitations. No published studies met our inclusion criteria for several key questions in this review. Direct evidence for the impact of screening on intermediate or health outcomes is lacking. Evidence for the effectiveness of pharmacotherapy lacks data from long-term studies assessing the effect of lipid-lowering medications on intermediate outcomes in childhood and adolescence or on health outcomes in adulthood. Of the eight trials of statins that evaluated effects on lipid concentrations, only one (short-term) study of the effect of pravastatin on atherosclerosis (as measured by CIMT) met our inclusion criteria.[66] Participants in the eight statin trials were patients at tertiary care centers; none of the studies were conducted in screen-detected populations. Few studies were conducted in non-white populations.

Only two studies reported the percent of participants achieving target LDL-C. Two statin trials included children as young as 8 years; however, the age distribution of the statin studies as a whole is skewed to early adolescence, with a mean age of 12 to 15 years. Thus, the bodies of evidence on screening (ages 6 to 8 years) and on statin treatment (largely adolescent subjects) are not aligned. We found no updated evidence on lifestyle interventions for FH or any trials comparing initiation of statins at different ages. The body of evidence on harms of pharmacotherapy also lacks long-term studies.

Future Research Needs

Randomized trials are needed to assess the benefits and harms of FH screening programs in children and adolescents. Future studies should describe the screening programs in detail, including the follow-up and laboratory testing of children who screen positive and all screening as well as diagnostic criteria used to establish FH, as well as reporting the number of true positives. Standard genetic mutation testing of FH cases diagnosed by elevated lipid concentrations and family history alone could help confirm the utility of genetic tests in the multi-ethnic U.S. population. Reports of such studies should also describe efforts to educate parents about interpreting screening tests because this knowledge is an important component of screening programs that can affect adherence (e.g., participation in screening and parental adherence to recommendations for follow-up of positive screens). Future studies of screening approaches should also describe any decision support for providers caring for children and adolescents who test positive for FH because this information may be important for ensuring appropriate care.

Long-term trials of statin treatment are needed to assess harms as well as effectiveness in improving both intermediate outcomes (lipid concentrations and measures of atherosclerosis in youth) and, ideally, health outcomes in adulthood. More pharmacotherapy studies should be conducted in racially and ethnically diverse U.S. populations. Treatment studies in screen-detected FH cases are essential in the absence of randomized controlled trials of screening programs. Further consideration of genetic mutation status in treatment response and outcomes for FH patients may provide important data for personalizing treatment. Studies examining benefits and harms of lipid-lowering medication are needed in children with FH younger than 10 years. Long-term studies to assess harms are needed. Treatment studies should systematically reports AEs of treatment.

Our understanding of outcomes in FH would be furthered by studies examining longitudinal data on persons with FH to better understand the association between intermediate outcomes in childhood and adolescence and MI and stroke in adulthood.

Some experts have advocated for the inclusion of Mendelian randomization studies in systematic evidence reviews of pediatric dyslipidemia. The Mendelian study takes advantage of the random assortment of alleles in reproduction and uses an observational design to infer causality. This study design has been used to examine the association between different loci (LDLR[96, 97] and Apolipoprotein B mutations[98-101]) and CHD. Some studies provide evidence of an association between LDL-C concentration over long periods of time and CHD based on Mendelian randomization. However, experts have pointed out a number of limitations of this study design.[102] There is a need for a better understanding of the appraisal of Mendelian data and its integration into systematic reviews.

Past pediatric recommendations on screening for FH have generated controversy, much of which has centered on the advisability of accepting indirect evidence from relatively short-term trials that lack outcomes beyond lipid concentrations.[80, 82-84, 103, 104] Some experts have expressed skepticism that long term RCTs of statins in children and adolescents with FH could be feasibly and ethically conducted,[105] while others have called for the conduct of RCTs as a public health priority.[50, 106] Reaching agreement on any acceptable surrogate endpoints, such as CIMT and other measures of atherosclerosis,[106] may increase the feasibility of such a trial, allowing a shorter time-frame, provided such endpoints are predictive of CHD.

Conclusions

We found no direct evidence of the effect of screening on intermediate or health outcomes. Evidence describing the diagnostic yield of screening for FH in children is minimal. Evidence of the effectiveness of statins to reduce LDL-C and TC concentrations is good in studies up to 2 years long. Evidence that statins affect measures of atherosclerosis in youth is limited. Statins were generally well-tolerated in the short-term. Some studies reported reversible elevations of liver enzymes or CK concentrations and one study reported lower DHEAS concentrations at 10 years in men treated with statins starting in childhood or adolescence. Bile acid binding resins were commonly associated with adverse gastrointestinal symptoms and poor palatability. Long-term harms are unknown. Randomized trials of screening for FH in U.S. youth are needed, as are longer-term treatment trials to evaluate benefits and harms of medications in children and adolescents with FH.

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Glossary of Terms

Familial hypercholesterolemia: A heterozygous genetic disorder that limits the body's ability to remove LDL-cholesterol from the blood and can result in atherosclerosis at an earlier age.

Secondary dyslipidemia: dyslipidemia caused by one or more of the following: renal disease (chronic renal disease, hemolytic uremic syndrome, nephrotic syndrome); infection (acute viral or bacterial infections, HIV, hepatitis); hepatic disease (obstructive liver disease, cholestasis, biliary cirrhosis, Alagille syndrome); inflammatory disease (systemic lupus erythematosus, juvenile rheumatoid arthritis); storage disorder (glycogen storage disease, Gaucher's disease, cystine storage disease, Tay-Sachs, Niemann-Pick); or other conditions (Kawasaki disease, anorexia nervosa, cancer, previous solid organ transplantation, progeria, idiopathic hypercalcemia, Klinefelter syndrome, Werner's syndrome).

Health outcomes: Symptoms and conditions that patients can feel or experience, such as visual impairment, pain, dyspnea, impaired functional status or quality of life, and death. In this review, myocardial infarction and stroke are considered health outcomes.

Intermediate outcomes: Pathologic and physiologic measures that may precede or lead to health outcomes. In this review, intermediate outcomes are lipid concentrations (total cholesterol, LDL cholesterol) and atherosclerosis markers (carotid intima medial thickness, calcium score, and pathologic findings).

Screening: Methodically administering an instrument to patients to detect a disease or condition in an asymptomatic population. This report specifically focuses on universal screening and selective screening based on family history, which are defined below.

Universal screening: Administering an instrument to a defined population to detect a disease or condition or the prevalence of a disease or condition in an asymptomatic population.

Selective screening based on family history: Administering an instrument to a subpopulation with a previously identified family history of FH.

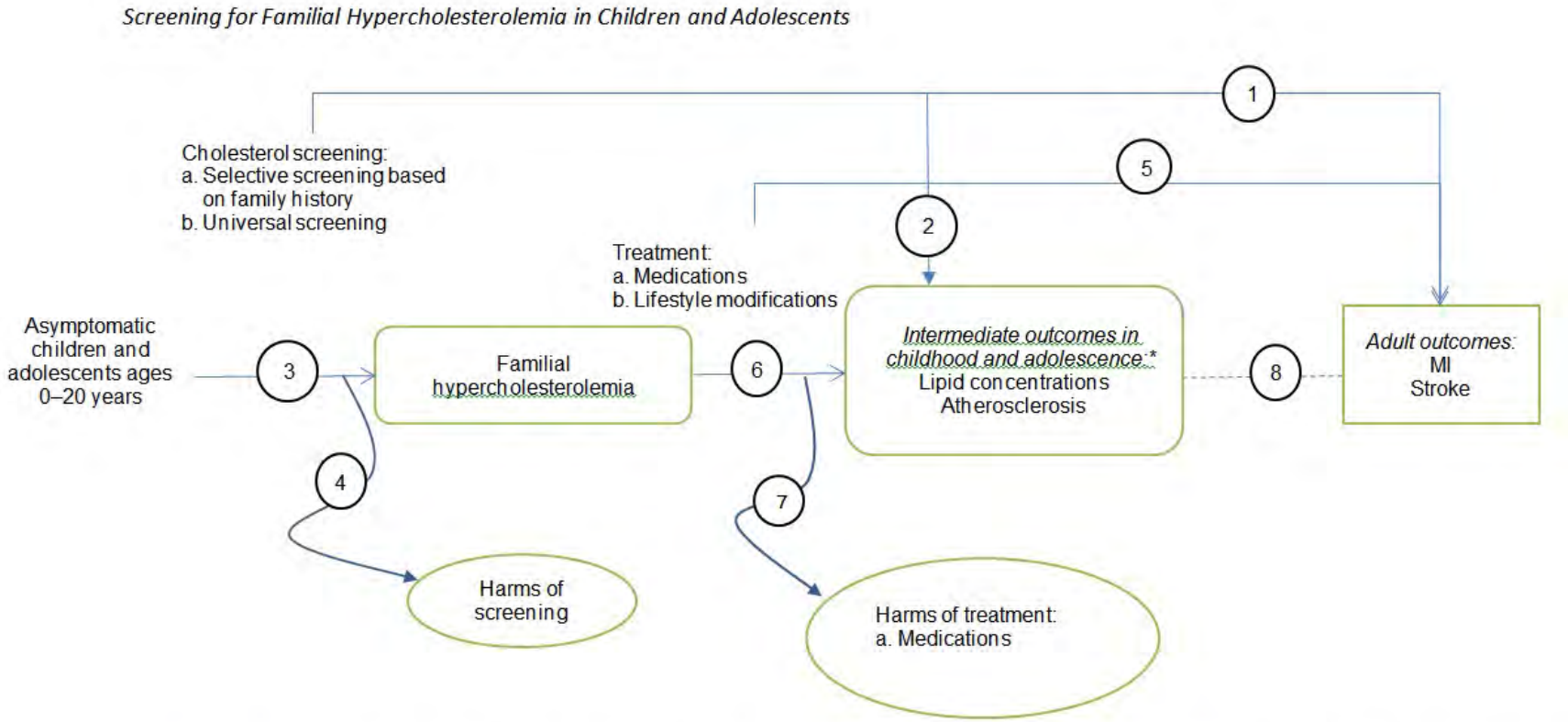
Diagnostic yield: The percentage of cases with a definitive diagnosis identified through screening, computed as true positives divided by total number screened.

Positive predictive value: The percentage of screen-positive individuals who are true positives.

Lifestyle modification: Behavioral interventions that attempt to change an individual or a group's dietary, activity, sleep, or other daily behavior.

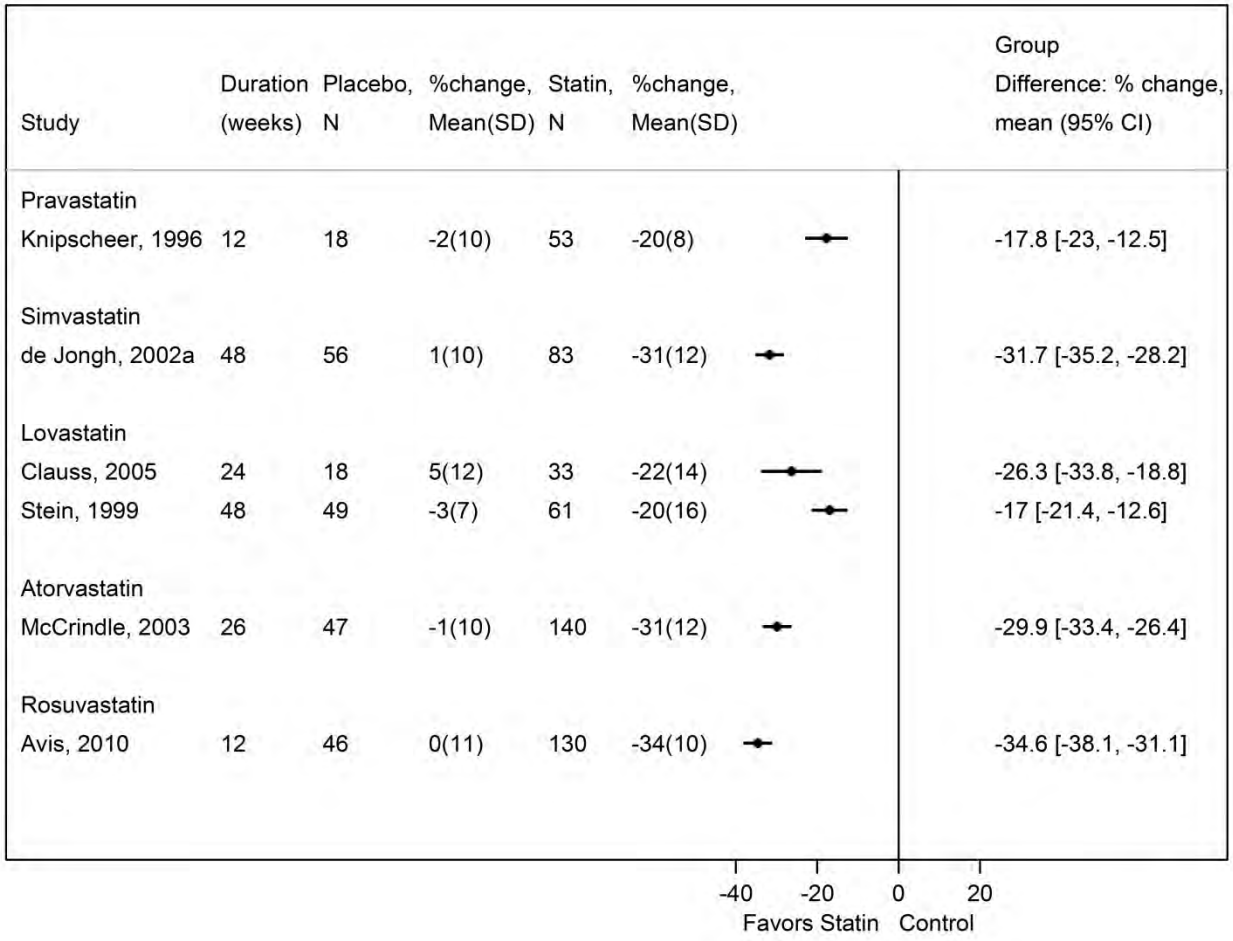
Lipid-lowering medications: Medications and compounds prescribed to interrupt physiological pathways with the intent of decreasing lipid concentrations in the blood stream.
Statins: HMG-CoA reductase inhibitors, a class of drugs used to lower cholesterol concentrations by inhibiting the HMG-CoA reductase enzyme.

Figure 1. Analytic framework



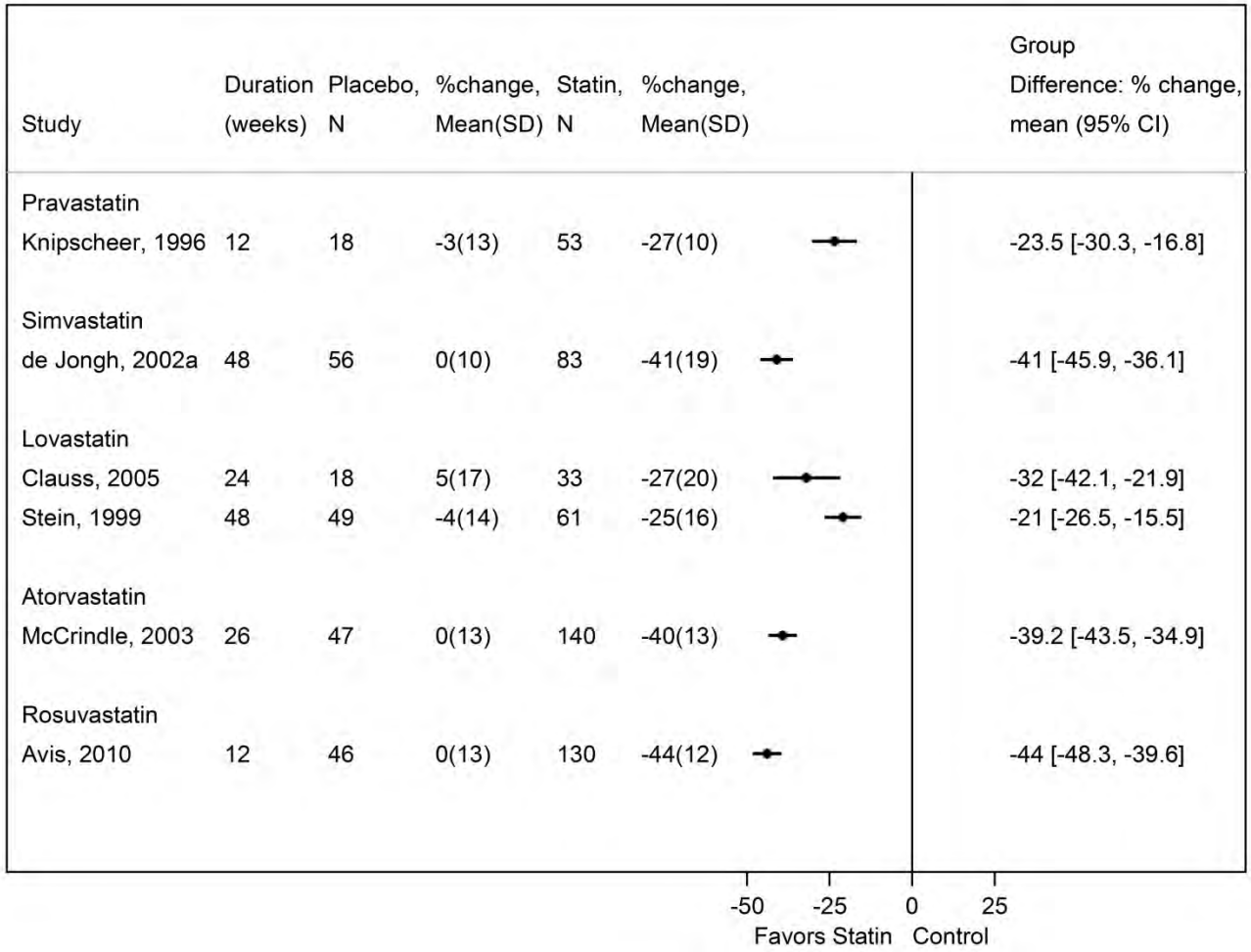
Abbreviations: MI=myocardial infarction

Figure 2. Effect of statins on mean percent change of total cholesterol



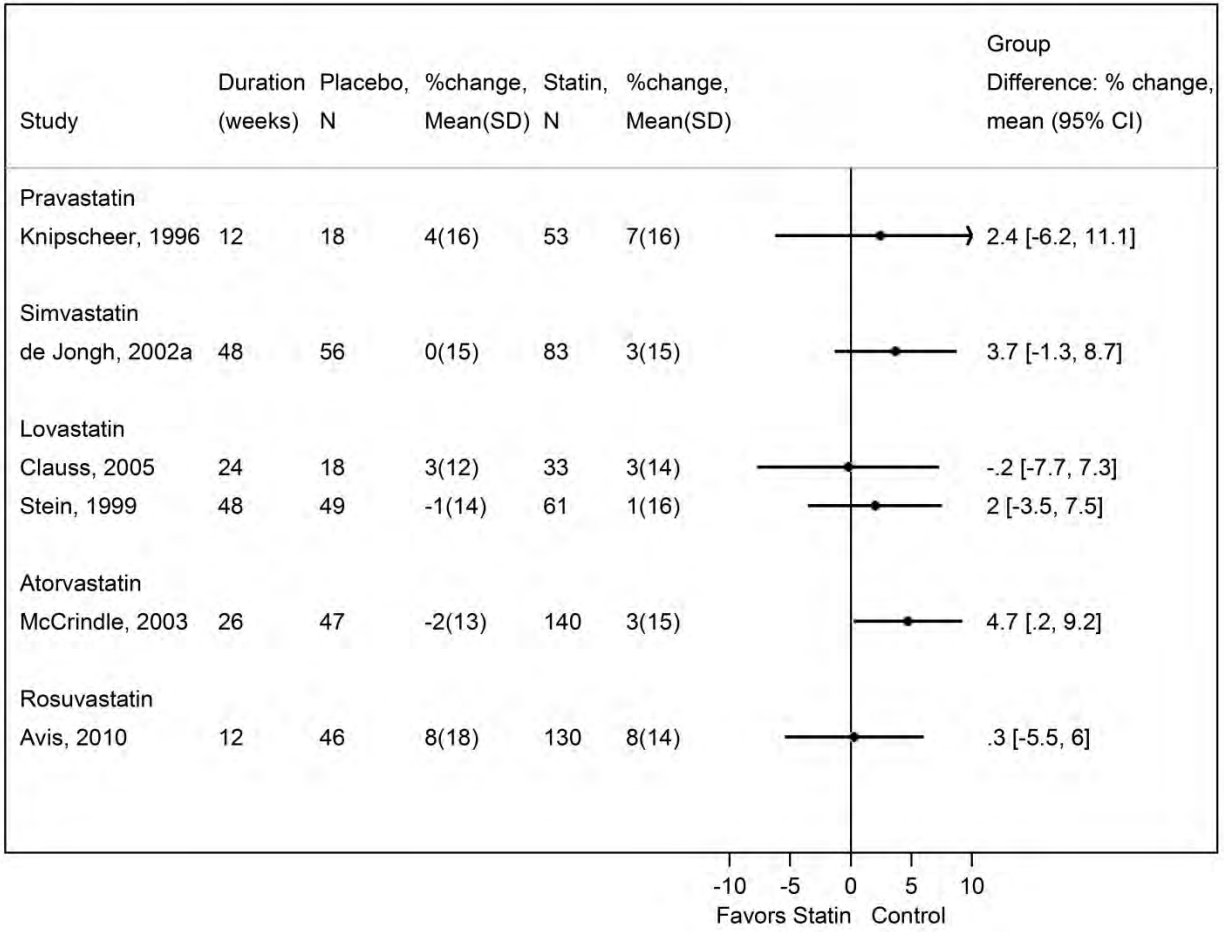
Abbreviations: SD=standard deviation, CI=confidence interval

Figure 3. Effect of statins on mean percent change of LDL-C



Abbreviations: SD=standard deviation, CI=confidence interval

Figure 4. Effect of statins on mean percent change of HDL-C



Abbreviations: SD=standard deviation, CI=confidence interval

Table 1. Included screening studies

Study, year Quality County	N	N with FH	Age, mean (SD), years	Age range, years	Percent female	Race	Population	Years of data collection
Skovby, 1991[54] Fair Denmark	2,085	10	NR	6 to 8	NR	NR	3,025 families with children age 6 to 8 years in Copenhagen schools	1987
Cottrell, 2013[53] Fair U.S.	81,156	107	NR	10 to 11*	53.0	93.2% White 2.9% African American 2.3% Bi-racial 0.4% Asian 0.7% Hispanic 0.5% Other	5th grade students in West Virginia at elementary schools screened annually	1998-2012

Abbreviations: FH = familial hypercholesterolemia, SD=standard deviation, NR = not reported

*Study composed of fifth grade students age range inferred from description

Table 2. Diagnostic yield of screening for FH

Author	Context	FH diagnosis criteria	Number screened	Number with probable FH (screen-positives), n	True positives, n	False positives, n	Diagnostic yield, %*	PPV, %†
Skovby, 1991[54] Fair Denmark	Copenhagen schools; all families with children starting first grade (age 6 to 8 years) were offered to participate in the pilot screening program	Apolipoprotein B concentration above the 99th centile and Apo B:A-1 ratio > 0.83	2,085	47	10	37	0.48	21.3
Cottrell, 2013[53] Fair U.S.	CARDIAC project, school-based screening in 5th grade students in 53/55 WV counties. All 5th graders eligible	TC>6.7mmol/L or LDL-C>4.0 mmol/L or LDLR mutation positive in FDR or SDR	81,156	NR	107‡	NR	0.13%	NR

Abbreviations: FH=familial hypercholesterolemia, PPV=positive predictive value, Apo B= apolipoprotein B, WV=West Virginia, CARDIAC=Coronary Artery Risk Detection in Appalachian Communities, TC=total cholesterol, mmol/L=millimoles per liter, LDL-C=low density lipoprotein cholesterol, LDLR=low density lipoprotein receptor, FDR = first degree relative; SDR = second-degree relative, NR=not reported

*Diagnostic yield is calculated as the number of true postives divided by the number of subjects screened
†Positive predictive value is calculated as the number of true positives divided by the number of screen positives
‡Paper describes 107 with probable FH, number of screen positive not reported

Table 3. Included treatment and harms of treatment studies (ordered chronologically by statin type and non-statin type)

Study, year Quality County	Drug name	Trial duration	N	N with FH	Age, mean (SD), years	Age range, years	Percent female	Race	Population	Years of data collection
TREATMENT *(KQ6: 13 studies. 12 report on harms and are included for KQ7)*										
KQ6 and KQ7 statins										
Knipscheer, 1996[52] Good Netherlands	Pravastatin	12 weeks	72	72	12.0 (NR)	8 to 16	65.3	91.7% white; 6.9% black 1.3% Asian	72 children with FH	NR
Wiegman, 2004[66] Good Netherlands Dutch Pravastatin Trial	Pravastatin	104 weeks	214	214	13.0 (3)	8 to 18	53.3	NR	214 children with FH age 8 to18 in the Netherlands	1997 - 2001
Couture, 1998[67]* Good Canada	Simvastatin	6 weeks	63	63	12.6 (2.3)	8 to 17	41.3	NR	63 FH patients enrolled at University Lipid Research Clinic with confirmed mutations in the LDLR gene	NR
De Jongh, 2002a[62] Good International multi center	Simvastatin	RCT: 24 weeks Extension: 24 weeks	173	173	14.2 (2.1)	10 to 17	43.3	NR	173 children with familial hypercholesterolemia	NR

Study, year Quality County	Drug name	Trial duration	N	N with FH	Age, mean (SD), years	Age range, years	Percent female	Race	Population	Years of data collection
Stein, 1999[61] Good United States; Finland	Lovastatin	48 weeks	132	132	13.2 (0.3)	10 to 17	0.0	NR	Boys aged 10 to 17 years old with FH; 14 pediatric outpatient clinics in the U.S. and Finland	1990-1994
Clauss, 2005[60] Good USA	Lovastatin	24 weeks	54	54	15.0 (2)	11 to 18	100.0	80.0% white; 20.0% not white	54 girls ages 10-18 with FH and at least 1 year postmenarche	1999 - 2000
McCrindle, 2003[63] Good U.S., Canada, Europe, South Africa	Atorvastatin	RCT: 26 weeks Open label: 26 weeks	187	187	14.1 (2.1)	10 to 17	31.0	92% White; 1.6% Black; 1.6% Asian; 4.8% other	187 children with FH or severe hypercholesterolemia	NR
Avis, 2010[64] Good Europe and North America	Rosuvastatin	RCT: 12 weeks Open label: 40 weeks	176	176	14.5 (1.8)	10 to 17	45.0	93.8% Caucasian	Patients ages 10-17 with FH recruited from 20 centers in Europe and North America	2006 - 2008
KQ6 and KQ7 non-statins										
Tonstad, 1996b[56] Good Norway	Colestipol	RCT: 8 weeks Open label: 52 weeks	66	66	13.1 (1.7)	10 to 16	43.5	NR	Adolescents previously referred to pediatric lipid clinic with elevated lipids	NR

Study, year Quality County	Drug name	Trial duration	N	N with FH	Age, mean (SD), years	Age range, years	Percent female	Race	Population	Years of data collection
Tonstad, 1996a[55] Fair Norway	Cholestyr-amine	52 weeks	72	72	8.4 (1.4)†	6 to 11	38.5	NR	Boys and girls 6 to 11 years with FH	NR
Stein, 2010[65] Good International multi center	Colesevelam	RCT:8 weeks Open label: 18 weeks	194	194	14.1 (2.0)	10 to 17	36.6	87.1% Caucasian; 3.1% black; 4.1% Asian; 5.2% multiple; 0.5% other	Children aged 10 to 17 with FH	2005 - 2007
van der Graaf, 2008[58] Good Netherlands, U.S., Canada	Ezetimibe and simvastatin	RCT: 33 weeks Open label: 20 weeks	248	248	14.2 (1.9)	10 to 17	42.7	81.9% Caucasian; 3.6% Asian; 1.6% Black or African American; 12.9% multiracial	Male and post-menarchal female adolescents age 10 to 17 with FH	2005 - 2007
Kusters, 2015[59] Good 9 countries	Ezetimibe	12 weeks	138	125	8.3 (1.6)	6 to 10	57%	80% white	138 children age 6 to 10 with diagnosed FH or LDL-C >160 mg/dL	2009 - 2012
HARMS OF TREATMENT ONLY *(KQ7: 9 studies)*										
KQ7 only - statins										

Study, year Quality County	Drug name	Trial duration	N	N with FH	Age, mean (SD), years	Age range, years	Percent female	Race	Population	Years of data collection
Hedman, 2003[68] Fair Finland	Pravastatin	8 weeks	20	20	10.3 (2.9)	4.9 to 15.6	65.0	NR	20 patients verified by LDLR mutation analysis or by lymphocyte test	NR
Rodenburg, 2007[76] Fair Netherlands Dutch Pravastatin Trial	Pravastatin‡	Mean duration of statin treatment: 4.5 years (range 2.1 to 7.4 years)	186	186	13.7 (3.1)	NR	51.0	NR	Children and adolescents with FH who were enrolled in a study at the Academic Medical Center in Amsterdam	1997 - 2003
Kusters, 2014[72] Good Netherlands Dutch Pravastatin Trial	Pravastatin†	10+ years	277	194	24.0 (95% CI 23.6-24.5)	NR	53.6	NR	Children enrolled in the Dutch Pravastatin Trial -- this follow-up describes outcomes for 194 members of the original cohort and 83 siblings	1997 - 2011

Study, year Quality County	Drug name	Trial duration	N	N with FH	Age, mean (SD), years	Age range, years	Percent female	Race	Population	Years of data collection
Braamskamp, 2015a[78] Good Netherlands Dutch Pravastatin Trial	Pravastatin	2 year (10 year followup)	Tolerability: 205 Adherence: 188	Tolerability: 205 Adherence: 188	At start of RCT: 13.0 (2.9) End of followup: 24.0 (3.2)	At start of RCT: 8 to 18 End of followup: 18 to 30	Tolerabilty (n = 205): 54% Adherence (n =188): NR	NR	Children enrolled in the Dutch Pravastatin Trial between 1997 and 1999	1997-2009
Braamskamp, 2015b[77] Good Netherlands Dutch Pravastatin Trial	Pravastatin	2 year (10 year followup)	150	88	FH at baseline: 12.8 (3.1) FH at 10 years: 23.9 (3.2) Siblings at 10 years (n = 62): 24.1 (3.0)	FH at baseline: 8 to 18 FH at 10 years: NR Siblings at 10 years: NR	24%	NR	Children enrolled in the Dutch Pravastatin Trial between 1997 and 1999 and their siblings	1997-2009
Carreau, 2011[73] Fair France	Pravastatin	Mean: 2 years and 2 months Range: 3 months and 7 years	185	185	11 (NR)	4 to 17	54.6	NR	Those identified from medical records at specialized French centers in Paris	2002 - 2009

Study, year Quality County	Drug name	Trial duration	N	N with FH	Age, mean (SD), years	Age range, years	Percent female	Race	Population	Years of data collection
De Jongh, 2002b[70] Fair Netherlands	Simvastatin	28 weeks	69	50	14.6 (2.5)[§]	9 to 18	47.8[§]	NR	50 heterozygous FH children plus 19 nonaffected controls. 28 in FH simvastatin group, 22 in FH placebo group, 19 non-FH controls.	NR
Gandelman, 2011[75] Fair Greece, Norway, and Canada	Atorvastatin	8 weeks	39	39	11.6 (3.0)	6 to 17	48.8	100% white	Tanner stage 1 and Tanner stage 2 children with genetically verified FH	2008 - 2009
Avis, 2011[74] Good Netherlands	Rosuvastatin	RCT: 12 weeks Open label: 40 weeks	29	29	14.4 (1.9)	10 to 17	48.3	NR	Children aged 10-17 with heterozygous FH Participating in Avis 2010 (PLUTO) trial	2006 - 2008
Braamskamp, 2015c[79] Good Netherlands, U.S., Canada, Belgium, Norway CHARON	Rosuvastatin	2 years	198	198	11.6 (3.3)	6 to 17	56%	NR	198 children with HeFH	2010-2013

Study, year Quality County	Drug name	Trial duration	N	N with FH	Age, mean (SD), years	Age range, years	Percent female	Race	Population	Years of data collection
Sinzinger, 2004[69]* Fair Austria	Various statins	8 years	22 (all subjects) 6 (in pediatric subgroup)	22 (all subjects) 6 (in pediatric subgroup)	16.8 (2.6) (all subjects)	13-35 (all subjects) 13-20 (pediatric subgroup)	40.0 (all subjects)	NR	Professional athletes with FH	NR
KQ7 only - nonstatins										
McCrindle, 2002[71] Good Canada	Colestipol and pravastatin	18 weeks	36	36	Median:14	9 to 18	30.6	NR	Children seen at the pediatric lipid disorder clinic at the Hospital for Sick Children (Toronto) and St. Joseph's Hospital (Hamilton)	NR

Abbreviations: KQ=key question, FH=familial hypercholesterolemia, SD=standard deviation, NR=not reported, LDLR=low density lipoprotein receptor, RCT=randomized controlled trial, LDL-C=low density lipoprotein cholesterol, PLUTO=Pediatric Lipid-redUction Trial of rOsuvastatin, HeFH=heterozygous familial hypercholesterolemia

* Couture 1998 only included for KQ6
† mean age for 96 subjects who entered the yearlong dietary phase
‡ Pravastatin was original drug prescribed to study cohort
§ Data represent only those with FH
** This review focuses on the 6 athletes that met our inclusion criteria (study reported individual-level data)

Table 4. Randomized controlled trials of medication in children and adolescents with FH: Effect of statins, BSAs and other drugs on lipid concentrations

Author, Year, Quality	N (IG/CG) Percent female	Mean age (SD), years Range, years	Drug RCT duration	Measure of change from baseline	TC	LDL-C	HDL-C	Triglycerides
STATINS								
Knipscheer,1996[52] Good Netherlands	72 (54/18) 65.3%	12.0 (NR) 8 to 16	Pravastatin 12 weeks	Mean (95% CI) % change	Mean % change 5mg: -18.2 (-21.9 to -14.2) 10mg: -17.2% (-21.1 to -13.1) 20mg: -24.6% (-28.1 to -21.0) CG: -2.3% (-6.7 to 2.4)	Mean % change 5mg: -23.3 (-27.9 to -18.4) 10mg: -23.8 (-28.5 to - 18.8) 20mg: -32.9 (-37.0 to -28.6) CG: -3.2 (-9.0, to -3.0)	Mean % change 5mg: +3.8 (-3.1 to 11.2) 10mg: +5.5 (-1.7 to 13.2) 20mg: +10.8 (3.4 to 18.8) CG: +4.3 (-2.7 to 11.8)	Mean % change 5mg: -1.7 (-15.4 to 22.2) 10mg: +6.6 (-12.0 to 29.0) 20mg: +3.3 (-14.3 to 24.5) CG: -11.7 (-26.6 to 6.1)
Wiegman, 2004[66] Good Netherlands	214 (106/108) 53.0%	13.0 (3) 8 to 18	Pravastatin 104 weeks	Mean (SD) difference	IG: -56.0 (43) CG: +2.0 (39)	IG: -57.0 (43) CG: 0.0 (36)	IG: +3.0 (10) CG: +1.0 (9)	IG:+12.0 (-35 to -16) CG: +1.0 (-20 to 22)
Couture,1998[67]* Good Canada	63 (47/16)	12.5 (2.4) 8 to 17	Simvastatin 6 weeks	Mean %change	IG: -29.5% CG: -5.8%	IG: -37.5% CG: -5.6%	NR by intervention group	NR by intervention group
De Jongh, 2002a[62] Good International multi center	173 (106/69) 43.3%	14.2 (2.1) 10 to 17	Simvastatin 24 weeks	Mean (SD) % change	IG: -28.3% (13.4) CG: -0.7% (9.5)	IG: -38.4% (16.0) CG: -1.2% (11.0)	IG: +4.9% (13.5) CG: +0.3% (15.5)	IG: -7.9 (-74.1 to 92.5) CG: -3.2% (-56.2 to 179.5)
Stein,1999[61] Good US and Finland	132 (67/65) 0.0%	13.2 (0.3) 10 to 17	Lovastatin 48 weeks	Mean (SE) % change	IG: -20.0% (2) CG: -3.0 % (1)	IG: -25.0% (2) CG: - 4.0% (2)	IG: +1.0% (2) CG: - 1.0% (2)	IG: +6.0% (6) CG: +8% (7)
Clauss, 2005[60] Good U.S.	54 (35/19) 100%	15.0 (2) 11 to 18	Lovastatin 24 weeks	Least mean square % change (SE)	IG: -21.8% (2.5) CG: +4.5% (2.9)	IG: -26.8% (3.4) CG: +5.2% (3.9)	IG: +2.5% (2.5) CG: +2.7% (2.9)	IG: -22.7% (6.8) CG: -3.0% (9.6)

Author, Year, Quality	N (IG/CG) Percent female	Mean age (SD), years Range, years	Drug RCT duration	Measure of change from baseline	TC	LDL-C	HDL-C	Triglycerides
McCrindle, 2003[63] Good US, Canada, Europe, South Africa	187 (140/47) 31.0%	14.1 (2.2) 10 to 17	Atorvastatin 26 weeks	Mean (SE) % change	Mean % change IG: -31.4% (1.0) CG: -1.5% (1.5)	Mean % change IG: -39.6 (1.1)% CG: -0.4% (1.9)	Mean % change IG: +2.8% (1.3) CG: -1.9 (1.9)	Mean % change IG: -12.0% (2.9) CG: +1.0% (6.2)
Avis, 2010[64] Good Europe and North America	176 (130/46) 45.0%	14.5 (1.8) 10 to 17	Rosuvastatin 12 weeks	Least squares mean % change	5mg: -30.0% 10mg: -34.0% 20mg: -39.0% CG: 0%	5mg: -38.0% 10mg: -45.0% 20mg: -50.0% CG: -1.0%	5mg: +4.0% 10mg: +10.0% 20mg: +9.0% CG: +7.0%	5mg: -13.0% 10mg: -15.0% 20mg: -16.0% CG: -7.0%
BSAs								
Tonstad,1996b[56] Good Norway	66 (33/33) 43.5%	13.1 (1.7) 10 to 16	Colestipol 8 weeks	Mean % change	IG: -14.0% CG: -1.0	IG: -19.5% CG: -1.0%	NR	NR
Tonstad,1996a[55] Fair Norway	72 (36/36) 38.5%	8.4 (1.4) 6 to 11	Cholestyramine 52 weeks	Mean % change	IG: -11.5% CG: +3.0%	IG: -18.6% CG: +1.5%	IG: +13.4% CG: +8.8%	NR
Stein, 2010[65] Good International multi center	194 (129/65) 36.6%	14.1 (2.0) 10 to 17	Colesevelam 8 weeks	LS mean percent change (SE)	3.75 g/d: -5.1% (1.58) 1.9 g/d: -0.9% (1.6) CG: +2.3% (1.6)	3.75 g/d: -10.0% (2.1) 1.9 g/d: -3.8% (2.1) CG: +2.5% (2.0)	3.75 g/d: +8.3 (1.6) 1.9 g/d: +4.5 (1.6) CG: +2.2% (1.6)	3.75 g/d: +17.4 (42.8) 1.875g/d: +18.5 (34.9) CG: +12.3 (36.2)
				Treatment difference	3.75 g/d: -7.4% (2.23) (p<0.01) 1.9 g/d: -3.2% (2.23)	3.75 g/d: -12.5% (2.92) (p< 0.001) 1.9 g/d: -6.3% (2.91) (p=0.031)	3.75 g/d: +6.1% (2.28) (p<0.01) 1.9 g/d: +2.4 % (2.3)	3.75 g/d: +5.1% (76.5) 1.875g/d: +6.4% (70.7) (p=0.47)
Other drugs								
van der Graaf,2008[58] Good Netherlands, USA,	248 (126/122) 42.7%	14.2 (1.9) 10 to 17	Ezetimibe (ezetimibe + simvastatin vs.	Mean (SD) % change	IG: -42.5% (1.2) CG: -29.3% (1.2)	IG: -54.0% (1.4) CG: -38.1% (1.4)	IG: +4.67% (1.3) CG: +3.68% (1.3)	IG: -20.0% (23.8) CG: -13.0% (39.0)

Author, Year, Quality	N (IG/CG) Percent female	Mean age (SD), years Range, years	Drug RCT duration	Measure of change from baseline	TC	LDL-C	HDL-C	Triglycerides
Canada			simvastatin) 33 weeks					
Kusters, 2015[59] Good 9 countries	138† (93/45) 57%	8.3 (1.6) 6 to 10	Ezetimibe 12 weeks	Mean % change at 12 weeks (95% CI)	IG: -21 (-23 to -18) CG: 0.2 (-3 to 3)	IG: -28(-31 to -25) CG: -0.95 (-4.9 to 3.0)	IG: 2 (-2 to 6) CG: 1 (-4 to 7)	IG: (geometic mean): -6 (-13 to 1) CG (geometic mean): 8 (-2 to 20)

Abbreviations: FH=familial hypercholesterolemia, BSAs=bile sequestering agents, IG=intervention group, CG=control group, SD=standard deviation, RCT=randomized controlled trial, TC=total cholesterol, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, NR=not reported, CI=confidence interval, mg=milligram(s), LS=least-squares, SE=standard error, g/d=grams per day

*For Couture 1998, data on TC and LDL-C were extrapolated from a figure
†13 non-FH participants (9 in treatment group, 4 in placebo group) were not analyzed separately)

Table 4-a: Data from Knipscheer 1996 (Pravastatin trial of 72 children aged 8 to 16 years)

Group	Baseline concentration, mean (range), mg/dL	Change from baseline concentration, mean % change (95% CI)	p-value*
Placebo			
TC	302 (216.0 to 516.8)	-2.3 (-6.7 to 2.4)	
LDL-C	247 (154.0 to 458.9)	-3.2 (-9.0 to 3.0)	
HDL-C	42 (30.9 to 54.0)	4.3 (-2.7 to 11.8)	
TG	71 (35.4 to 168.3)	-11.7 (-26.6 to 6.1)	
Pravastatin 5 mg			
TC	298 (227.6 to 397.3)	-18.2 (-21.9 to -14.2)	<0.05
LDL-C	240 (181.2 to 339.4)	-23.3 (-27.9 to -18.4)	<0.05
HDL-C	46 (34.7 to 65.6)	3.8 (-3.1 to 11.2)	
TG	62 (26.6 to 194.9)	1.7 (-15.4 to 22.2)	
Pravastatin 10 mg			
TC	294 (200.6 to 374.1)	-17.2 (-21.1 to -13.1)	<0.05
LDL-C	236 (138.9 to 304.7)	-23.8 (-28.5 to -18.8)	<0.05
HDL-C	42 (23.1 to 61.7)	5.5 (-1.7 to 13.2)	
TG	71 (35.4 to 186.0)	6.6 (-12.0 to 29.0)	
Pravastatin 20 mg			
TC	317.1 (216.0 to 513.0)	-24.6 (-28.1 to -21.0)	<0.05
LDL-C	259.1 (165.9 to 451.3)	-32.9 (-37.0 to -28.6)	<0.05
HDL-C	46.4 (30.9 to 69.4)	10.8 (3.4 to 18.8)	
TG	53.14 (26.6 to 115.1)	3.3 (-14.3 to 24.5)	

Abbreviations: mg/dL=milligrams per deciliter, CI=confidence interval, TC=total cholesterol, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, TG=triglycerides

*p-values apply to the difference in change from baseline between the treatment and control groups

Table 4-b: Data from Wiegman 2004 (Pravastatin trial of 214 children aged 8 to 18 years)

Group	Baseline concentration, mg/dL	Change from baseline concentration, mean (SD) difference, mg/dL	p-value*
Placebo			
TC	300 (47)	2 (39)	
LDL-C	237 (46)	0 (36)	
HDL-C	48 (11)	1 (9)	
TG	64 (46 to 90)	1 (-20 to 22)	
Pravastatin†			
TC	302 (56)	-56 (43)	<0.001
LDL-C	239 (53)	-57 (40)	<0.001
HDL-C	47 (10)	3 (10)	0.09
TG	70 (50 to 112)	-12 (-35 to 16)	0.21

Abbreviations: mg/dL=milligrams per deciliter, SD=standard deviation, TC=total cholesterol, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, TG=triglyceridesAll values are given as mean (SD) except for TG values, which are given as median (interquartile range)

*p-values apply to the difference in change from baseline between the treatment and control groups
†Children aged <14 years received 20 mg/day; those aged ≥14 years received 40 mg/day

Table 4-c: Data from Couture 1998 (Simvastatin trial of 63 children aged 8 to 17 years)

Group	Baseline concentration, mean (SE), mg/dL*	Change from baseline concentration, mean % change*†	p-value
Placebo			
TC	293 (13)	-5.8%	
LDL-C	228 (10)	-5.6%	
HDL-C	NR	NR	
TG	NR	NR	
Simvastatin 20 mg			
TC	286 (4)	-29.5%	NR
LDL-C	222 (4)	-37.5%	NR
HDL-C	NR	NR	NR
TG	NR	NR	NR

Abbreviations: mg/dL=milligrams per deciliter, SE=standard error, TC=total cholesterol, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, TG=triglycerides, NR=not reported

*Data from baseline and followup (Week 6) were extrapolated from a figure.
†Mean percent change from baseline was calculated from the extrapolated data

Table 4-d: Data from de Jongh 2002a (Simvastatin trial of 173 children aged 10 to 17 years)

Group	Baseline concentration, mg/dL	Change from baseline concentration, mean or median % change	p-value*
Placebo			
TC	279 (52)	-0.7 (9.5)	
LDL-C	212 (49)	-1.2 (11.0)	
HDL-C	47 (12)	0.3 (15.5)	
TG	90 (39 to 326)	-3.2 (-56.2 to 179.5)	
Simvastatin†			
TC	271 (44)	-28.3 (13.4)	<0.001
LDL-C	204 (42)	-38.4 (16.0)	<0.001
HDL-C	48 (9)	4.9 (13.5)	<0.05
TG	78 (42 to 279)	-7.9 (-74.1 to 92.5)	

Abbreviations: mg/dL=milligrams per deciliter, SD=standard deviation, TC=total cholesterol, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, TG=triglycerides

All values are given as mean (SD) except for TG values, which are given as median (range)
*p-values apply to the difference in change from baseline between the treatment and control groups
†The treatment group received simvastatin at 10mg/day for the first 8 weeks, 20mg/day for the second 8 weeks, and 40mg/day for last 8 weeks

Table 4-e: Data from Stein 1999 (Lovastatin trial of 132 male children aged 10 to 17 years)

Group	Baseline concentration, mean (SD), mg/dL	Change from baseline concentration, mean % change (SD)	p-value*
Placebo			
TC	315 (7)	-3 (1)	
LDL-C	250 (7)	-4 (2)	
HDL-C	44 (1)	-1 (2)	
TG	110 (6)	8 (7)	
Lovastatin†			
TC	318 (6)	-20 (2)	<0.001
LDL-C	251 (6)	-25 (2)	<0.001
HDL-C	45 (1)	1 (2)	
TG	112 (7)	6 (6)	

Abbreviations: mg/dL=milligrams per deciliter, SD=standard deviation, TC=total cholesterol, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, TG=triglycerides

*p-values apply to the difference in change from baseline between the treatment and control groups
†The treatment group received lovastatin starting at 10mg/day, doubling every 8 weeks to a maximum dose of 40 mg/day

Table 4-f: Data from Clauss 2005 (Lovastatin trial of 54 female children aged 11 to 18 years)

Group	Baseline concentration, mean (SD), mg/dL	Least mean squares percent change (SE) from baseline concentration	p-value*
Placebo			
TC	269 (41)	4.5 (2.9)	
LDL-C	199 (40)	-5.2 (3.9)	
HDL-C	45 (9)	2.7 (2.9)	
TG	103 (54)†	-3.0 (9.6)	
Lovastatin‡			
TC	289 (50)	-21.8 (2.5)	<0.001
LDL-C	218 (48)	-26.8 (3.4)	<0.001
HDL-C	49 (12)	2.5 (2.5)	
TG	106 (54)†	-22.7 (6.8)	

Abbreviations: mg/dL=milligrams per deciliter, SD=standard deviation, SE=standard error, TC=total cholesterol, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, TG=triglycerides

*p-values apply to the difference in change from baseline between the treatment and control groups
†Values are given as median (SE)
‡The treatment group received lovastatin starting at 20 mg/day for the first 4 weeks, increasing to 40 mg/day for the duration of the trial

Table 4-g: Data from McCrindle 2003 (Atorvastatin trial of 187 children aged 10 to 17 years)

Group	Baseline concentration, mean (SEM) mg/dL	Change from baseline concentration, mean % change (SEM)	p-value*
Placebo			
TC	298 (8)	-1.5 (1.5)	
LDL-C	230 (7)	-0.4 (1.9)	
HDL-C	46 (2)	-1.9 (1.9)	
TG	106 (8)	1.0 (6.2)	
Atorvastatin 10 mg			
TC	285 (4)	-31.4 (1.0)	<0.001
LDL-C	219 (3.6)	-39.6 (1.1)	<0.001
HDL-C	46 (1)	2.8 (1.3)	0.02
TG	103 (5)	-12.0 (2.9)	0.03

Abbreviations: mg/dL=milligrams per deciliter, SEM=standard error of the mean, TC=total cholesterol, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, TG=triglycerides

*p-values apply to the difference in change from baseline between the treatment and control groups

Table 4-h: Data from Avis 2010 (Rosuvastatin trial of 176 children aged 10 to 17 years)

Group	Baseline concentration, mean (SD), mg/dL	Least mean squares percent change from baseline concentration	p-value*
Placebo			
TC	293 (50)	0	
LDL-C	229 (43)	-1	
HDL-C	45 (11)	7	
TG	82 (57 to 124)	-7	
Rosuvastatin 5 mg			
TC	300 (60)	-30	<0.001
LDL-C	238 (55)	-38	<0.001
HDL-C	46 (12)	4	0.4
TG	80 (55 to 100)	-13	0.8
Rosuvastatin 10 mg			
TC	297 (49)	-34	<0.001
LDL-C	229 (45)	-45	<0.001
HDL-C	49 (10)	10	0.2
TG	81 (53 to 105)	-15	0.1
Rosuvastatin 20 mg			
TC	302 (49.9)	-39	<0.001
LDL-C	237 (47.9)	-50	<0.001
HDL-C	47.2 (13)	9	0.5
TG	81 (59 to 107)	-16	0.1

Abbreviations: mg/dL=milligrams per deciliter, SD=standard deviation, TC=total cholesterol, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, TG=triglycerides

All values are given as mean (SD) except for TG values, which are given as median (interquartile range)
*p-values apply to the difference in change from baseline between the treatment and control groups

Table 4-i: Data from Tonstad 1996b (Colestipol trial of 66 children aged 10 to 16 years)

Group	Baseline concentration, mean (SD), mg/dL	Change from baseline concentration, mean % change	p-value*
Placebo			
TC	297 (49)	-1.0	
LDL-C	237 (46)	-1.0	
HDL-C	43 (8)		
TG	85 (58)		
Colestipol 10 g			
TC	316 (57)	-14.0	p<0.01
LDL-C	254 (51)	-19.5	p<0.01
HDL-C	43 (10)		
TG	88 (54)		

Abbreviations: mg/dL=milligrams per deciliter, SD=standard deviation, TC=total cholesterol, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, TG=triglycerides

*p-values apply to the difference in change from baseline between the treatment and control groups

Table 4-j: Data from Tonstad 1996a (Cholestyramine trial of 72 children aged 6 to 11 years)

Group	Baseline concentration, mean (SD), mg/dL	Change from baseline concentration, mean % change	p-value*
Placebo			
TC	321 (47)	3.0	
LDL-C	NR	1.5	
HDL-C	44 (10)	8.8	
TG	84 (45)		
Cholestyramine 8 g			
TC	320 (51)	-11.5	<0.001
LDL-C	NR	-18.6	0.0001
HDL-C	49 (9)	13.4	
TG	69 (29)		

Abbreviations: mg/dL=milligrams per deciliter, SD=standard deviation,TC=total cholesterol, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, TG=triglycerides, g=gram(s)

*p-values apply to the difference in change from baseline between the treatment and control groups

Table 4-k: Data from Stein 2010 (Colesevelam trial of 194 children age 10 to 17 years)

Group	Baseline concentration, mean (SD), mg/dL	Treatment difference, mean % (SE)*	p-value†
Placebo			
TC	261 (47)		
LDL-C	197 (44)		
HDL-C	45 (9)		
TG	93 (40)‡		
Colesevelam 1.875 g			
TC	266 (45)	-3.2 (2.2)	
LDL-C	198 (44)	-6.3 (2.9)	<0.05
HDL-C	48 (12)	2.4 (2.3)	
TG	83 (46)‡	6.4 (70.7)	
Colesevelam 3.75 g			
TC	267 (51)	-7.4 (2.2)	<0.01
LDL-C	202 (50)	-12.5 (2.9)	<0.001
HDL-C	45 (10)	6.1 (2.3)	<0.01
TG	85 (55)‡	5.1 (76.5)	

Abbreviations: mg/dL=milligrams per deciliter, SD=standard deviation, SE=standard error, TC=total cholesterol, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, TG=triglycerides, g=gram(s)

*Treatment difference is calculated versus placebo
†p-values apply to the difference in change from baseline between the treatment and control groups
‡TG values given as median (±IQR)

Table 4-l: Data from van der Graaf 2008 (Ezetimibe trial of 248 children aged 10 to 17 years)

Group*	Baseline concentration, mean (SD), mg/dL	Change from baseline concentration, mean % change (SD)	p-value†
Placebo + Simvastatin			
TC	286 (4.1)	-29.3 (1.2)	
LDL-C	219 (3.9)	-38.1 (1.4)	
HDL-C	46 (0.8)	3.7 (1.3)	
TG	88 (38.8)‡	-13.0 (39.0)‡	
Ezetimibe + Simvastatin			
TC	292 (4.0)	-42.5 (1.2)	<0.01
LDL-C	225 (3.8)	-54 (1.4)	<0.01
HDL-C	46 (0.8)	4.7 (1.3)	0.58
TG	89 (49.3)‡	-20.0 (23.8)‡	<0.01

Abbreviations: mg/dL=milligrams per deciliter, SD=standard deviation, TC=total cholesterol, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, TG=triglycerides

*In this six-group trial, three received ezetimibe (10 mg/day) and three received placebo. All six groups received simvastatin, with three different doses for the first 6 weeks (10, 20, or 40 mg/day), but the same dose (40 mg/day) for the last 27 weeks of the trial. The six groups were combined into two groups for analysis: ezetimibe plus simvastatin and placebo plus simvastatin.
†p-values apply to the difference in change from baseline between the ezetimibe plus simvastatin group and the placebo plus simvastatin group
‡For triglycerides, median and standard deviation derived by (interquartile range)/1.075 are provided

Table 4-m: Data from Kusters 2015 (Ezetimbe trial of 138 children aged 6 to 10 years)

Group	Baseline concentration, mean (SD), mg/dL	Change from baseline concentration at 12 weeks, mean % change (95% CI)	p-value*
Placebo			
TC	290 (44)	0.2 (-3, 3)	
LDL-C	222 (45)	-0.95 (-4.9, 3.0)	
HDL-C	50 (12)	1 (-4, 7)	
Non-HDL-C	240 (48)	0.3 (-4, 4)	
TG	92 (61)	8 (-2, 20)†	
Ezetimibe 10mg			
TC	295 (48)	-21 (-23,-18)	<0.001
LDL-C	229 (46)	-28 (-31,-25)	<0.001
HDL-C	50 (9)	2 (-2, 6)	0.807
Non-HDL-C	245 (47)	-25 (-28, -22)	<0.001
TG	82 (30)	-6 (-13, 1)†	0.021

Abbreviations: mg/dL=milligrams per deciliter, SD=standard deviation, CI=confidence interval, TC=total cholesterol, LDL-C=low density lipoprotein cholesterol, HDL-C=high density lipoprotein cholesterol, non-HDL-C=non-high density lipoprotein cholesterol, TG=triglycerides

*p-values apply to the difference in change from baseline between the treatment and control groups
†For triglycerides, change from baseline presented as geometric mean

Table 5. Randomized controlled trials of medication in children and adolescents with FH: Effect on atherosclerosis

Study, year Quality County	N	N with FH	Mean age (SD)	Age range	Percent female	Race	Drug	CIMT* measurement at baseline (mm)	Change in CIMT measurement* from baseline (mm)
Wiegman, 2004[66] Good Netherlands	214	214	13.0 (3)	8 to 18	53.3	NR	Pravastatin 20-40 mg/day† vs. placebo 104 weeks	IG: 0.497 (0.055) CG: 0.492 (0.045)	IG: -0.010 (0.048) CG: 0.005 (0.044)

Abbreviations: FH=familial hypercholesterolemia, SD=standard deviation, CIMT=carotid intima media thickness, mm=millimeter(s), NR=not reported, mg=milligrams, IG=intervention group, CG=control group

*Measures reported are mean (SD)
† 20mg/day for those younger than 14; 40 mg/day for those 14 and older

Table 6. Overlapping study populations

Study	Author, year Quality County	Drug name	N	N with FH	Mean (SD) age, years range	Female, %	Years of data collection	Included for	Description
PLUTO: Pediatric Lipid-redUction Trial of rOsuvastatin	Avis, 2010[64] Good Europe and North America	Rosuvastatin	176	176	14.5 (1.8) 10 to 17	45.0	2006 - 2008	KQ6, KQ7	Parent study
	Avis, 2011[74] Fair Netherlands	Rosuvastatin	29	29	14.4 (1.9) 10 to 17	48.3	2006 - 2008	KQ7	Subset of PLUTO analyzing the effect of statin therapy on coenzyme Q10 and mitocondiral adenosine triphosphate synthesis
Dutch Pravastatin Trial	Wiegman, 2004[66] Good Netherlands	Pravastatin	214	214	13.0 (3) 8 to 18	53.3	December 1997 - November 2001	KQ6, KQ7	Parent study
	Rodenburg, 2007[76] Fair Netherlands	Pravastatin	186	186	24.0 (23.6-24.5)*	51.0	1997 - 2003	KQ7	4-7 yr follow-up of original RCT
	Kusters, 2014[72] Good Netherlands	Pravastatin	277	194	12.9 (NR) 12.5 to 13.4	53.6	1997 - 2011	KQ7	10 yr followup of original RCT
	Braamskamp, 2015a[78] Good Netherlands	Pravastatin	Tolerability: 205 Adherence: 188	Tolerability: 205 Adherence: 188	Start of RCT: 13.0 (2.9) 8 to 18 End of followup: 24.0 (3.2) 18 to 30	Tolerability (n = 205): 54% Adherence (n =188): NR	1997-2009	KQ7	10 yr followup of tolerability and adherence

Study	Author, year Quality County	Drug name	N	N with FH	Mean (SD) age, years range	Female, %	Years of data collection	Included for	Description
	Braamskamp, 2015b[77] Good Netherlands	Pravastatin	150 (includes 62 siblings)	88	FH at baseline: 12.8 (3.1) 8 to 18 FH at 10 years: 23.9 (3.2) NR Siblings at 10 years (n = 62): 24.1 (3.0) NR	24%	1997-2009	KQ7	10 yr followup reporting hormone concentrations
Dutch simvastatin trial†	De Jongh, 2002a[62] Good Multi center (n = 9)	Simvastatin	173	173	14.2 (2.1) 10 to 17	43.3	NR	KQ6, KQ7	Parent study
	De Jongh, 2002b[70] Fair Netherlands	Simvastatin	69	50	14.6 (2.5) 9 to 18	47.8	NR	KQ7	Subset of De Jongh 2002a aiming to determine whether simvastain improves endothelial function in children

Abbreviations: FH=familial hypercholesterolemia, SD=standard deviation, KQ=key question, RCT=randomized controlled trial, NR=not reported

* 95% confidence interval
†De Jongh 2002b is a subset of De Jongh 2002a, and the two populations have different age ranges

Table 7: Adverse Effects Reported in Studies of Statins, Bile-Sequestering Agents, and Other Drugs

Author, Year Quality Location	Drug	N with FH	Age range (years)	Study duration	Harms Assessed	Clinical Effects	Laboratory Effects
STATINS							
Knipscheer 1996 Good Netherlands	Pravastatin	72	8 to 16	12 weeks	Hematology, ALT, AST, CK, alkaline phosphatase, urinalysis, TSH, cortisol, ACTH	Clinical AEs equally distributed between treatment and placebo groups. Clinical AEs in treatment group included rash (n=1), nose-bleeding (n=1), headache (n=3), nausea/vomiting (n=3), and abdominal pain (n=2)	No significant difference between treatment and placebo groups for lab AEs. CK level abnormal in placebo (n=8), and pravastatin 5 mg/d (n=6), 10 mg/d (n=11), and 20 mg/d groups (n=8); cortisol level abnormal in placebo (n=2), and pravastatin 5 mg/d (n=2), 10 mg/d (n=5), and 20 mg/d (n=3) groups. For other lab effects, <5 participants had abnormal values in placebo group, as well as in all pravastatin groups combined.
McCrindle 2002 Good Canada	Pravastatin + Colestipol (PC) vs. Colestipol only (CO)	36	9 to 18	18 weeks	Height, weight, blood pressure, serum chemistries, blood counts	Clinical AEs more prevalent in CO group. Clinical AEs included constipation (PC 3%, CO 21%), bloating/gas (PC 3%, CO 15%) stomach ache (PC 0%, CO 21%), headache (PC 3%, CO 14%), and muscle aches (PC 3%, CO 6%)	No effects on CK, AST, other blood chemistries, or hematologic values. Alkaline phosphatase levels decreased significantly from baseline for CO group at 18 weeks. Absolute reduction in ALT level from baseline was significantly greater in CO group than PC group at 8 and 18 weeks
Hedman 2003 Fair Finland	Pravastatin	20	4 to 15	8 weeks	GI symptoms, headache, skin reactions, sleep disturbance, muscle/tendon tenderness, pain, creatinine, CK, ALT	Clinical AEs included abdominal pain (n=1), loose stools (n=1), headache (n=4), sleep disturbance (n=2), muscle tenderness or pain at rest (n=1), and muscle tenderness or pain associated with physical training (n=1)	No effects on serum ALT, CK, or creatinine levels
Wiegman 2004 Good Netherlands Dutch Pravastatin Trial	Pravastatin	214	8 to 18	104 weeks	Sex steroids, gonadotropins, pituitary adrenal axis markers, growth, sexual development, academic progress, AST, ALT, CK	No effects on growth, sexual development, or academic progress	No effects on muscle or liver enzyme levels (AST, ALT, CK), or on endocrine function

Author, Year Quality Location	Drug	N with FH	Age range (years)	Study duration	Harms Assessed	Clinical Effects	Laboratory Effects
Rodenburg 2007 Fair Netherlands Dutch Pravastatin Trial	Pravastatin	186	13.7 (mean age)	Mean duration of statin treatment: 4.5 years	Sex steroids, gonadotropins, pituitary adrenal axis markers, muscle and liver enzymes, growth, sexual development	Myalgia without CK elevation (n=4). No effects on growth or sexual development	No serious lab AEs reported; no subjects discontinued treatment due to lab AEs. Lab AEs included elevated CK likely associated with extreme exercise (n=2), mildly elevated FSH (n=4), decreased DHEAS (n=3), mildly elevated ACTH (n=2).
Kusters 2014 Good Netherlands Dutch Pravastatin Trial	Pravastatin	194	24.0 (mean age)	10+ years	Growth, sexual development, AST, ALT, CK, glomerular filtration rate, C-reactive protein, level of education, reported AEs	No effects on growth, sexual development, or education level; no reports of rhabdomyolysis or other serious major AEs. 3 subjects discontinued treatment due to unspecified AEs.	No effects on AST, ALT, CK, glomerular filtration rate, C-reactive protein. No differences between patients with FH and non-FH siblings for lab AEs.
Braamskamp 2015a Good Netherlands Dutch Pravastatin Trial	Pravastatin	205*	8 to 18 (start of RCT) 18-30 (end of followup)	2 year (10 year followup)	Adverse events and reasons for discontinuation assessed by questionnaire. Physical exam and blood sample taken at 10 year followup	3 subjects discontinued treatment due to side effects (GI, muscle/joint pain, headache). Over 10 years, 55 side effects reported by 40 subjects (19.5%), including muscle complaints (n=19), GI symptoms (n=14), fatigue (n=9), headache (n=4), skin reaction (n=4), other (n=5).§ No reports of rhabdomyolysis.	No reports of elevated liver enzymes or other major lab AEs
Braamskamp 2015b Good Netherlands Dutch Pravastatin Trial	Pravastatin	150	8 to 18	2 year (10 year followup)	Testosterone, estradiol, LH, FSH, and DHEAS	No reports of irregular menstrual cycle, hyperandrogenism, or involuntary childlessness	Compared with unaffected siblings, DHEAS was significantly lower in participants with FH (though still within normal range). No effects on testosterone, estradiol, LH, or FSH concentrations.

Author, Year Quality Location	Drug	N with FH	Age range (years)	Study duration	Harms Assessed	Clinical Effects	Laboratory Effects
Carreau 2011 Fair France	Pravastatin	185	4 to 17	2 years + 2 months (mean duration)	Growth, sexual development, CK, AST, ALT. AEs assessed by review of medical files	24 subjects (13%) reported AEs, including muscle pain that resolved after changing statins (n=4), muscle pain not attributed to treatment (n=3), musculoskeletal pain (n=12), and headache that resolved spontaneously (n=1). No reports of alopecia or problems related to growth or sexual development.	Asymptomatic CK elevation (n=8), pain with moderate CK elevation that resolved without changing treatment (n=2). No effects on AST or ALT.
Stein 1999 Good U.S., Finland	Lovastatin	132	10 to 17	48 weeks	Growth, sexual development, ALT, AST, CK, urinalysis, routine hematology, blood coagulation, thyroid function, blood nutrients, cortisol, DHEAS, FSH, LH, testosterone	No effect on growth or sexual development. AEs reported by 70.1% of subjects in treatment group and 73.8% in placebo group. Most common AEs in treatment group included respiratory tract infection (47.8%), abdominal pain (10.4%), ENT infection (10.4%), skin disease (9.0%), and gastroenteritis (7.5%). No significant difference between groups for any clinical AEs.	No effects on AST level; ALT level increased in placebo and treatment groups (no significant difference between groups); transient CK elevations in response to exercise (n=3 in lovastatin group, n=1 in placebo group); DHEAS increased (median increase 18% in treatment group, 5% in placebo group, p=0.03).
Clauss 2005 Good U.S.	Lovastatin	54 girls	11 to 18	24 weeks	ALT, AST, CK, creatinine, glucose, β-human chorionic gonadotrophin, hematology, urinalysis, sexual development, DHEAS, FSH, LH	No patients discontinued treatment due to AEs. No clinically meaningful differences between treatment groups in incidence of treatment-related AEs. Treatment-related AEs in lovastatin group included abdominal pain (n=2), diarrhea (n=1), nausea (n=1), headache (n=1). Blood pressure significantly lower in placebo group ($p<0.05$). No effects on growth or menstrual cycle length. No reports of myopathy or rhabdomyolysis.	Transient decreased hematocrit and hemoglobin (n=1), LH levels slightly decreased in placebo group ($p<0.05$, difference not clinically meaningful). No effect on ALT, AST, CK, DHEAS, FSH, cortisol, or estradiol.

Author, Year Quality Location	Drug	N with FH	Age range (years)	Study duration	Harms Assessed	Clinical Effects	Laboratory Effects
de Jongh 2002a Good International multi-center	Simvastatin	173	10 to 17	RCT: 24 weeks Extension: 24 weeks	Growth, sexual development, ALT, AST, CK, cortisol, DHEAS, estradiol, testosterone, LH, FSH, human chorionic gonadatropin	No statistically significant differences between placebo and simvastatin groups in period 1 or period 2. Clinical AEs in simvastatin group included: abdominal pain (n=3), chest pain (n=1), flatulence (n=1), myalgia (n=2), headache (n=4), sleep disorder (n=1), weight gain (n=1), and pruritus (n=1). No effect on growth or cortisol levels. No serious clinical AEs reported.	No statistically significant differences between placebo and simvastatin groups in period 1 or period 2. Lab AEs in simvastatin group included: increased ALT (n=3), AST (n=3), and CK (n=1) levels. No serious lab AEs reported; no participants discontinued treatment due to AE. DHEAS levels decreased (period 1) or remained stable (period 2) in the simvastatin group, compared to slight increases (periods 1 and 2) in the placebo group.
de Jongh 2002b Fair Netherlands	Simvastatin	50	9 to 18	28 weeks	Growth, blood pressure, ALT, AST, CK	No effects on BMI and blood pressure. No clinical AEs reported.	No significant effects on ALT, AST, and CK levels.
McCrindle 2003 Good U.S., Canada, Europe, South Africa	Atorvastatin	187	10 to 17	RCT: 26 weeks Open-label: 26 weeks	Blood pressure, physical exam, hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, AST, ALT, CK, alkaline phosphatase, blood urea nitrogen, creatinine, uric acid, albumin, total protein, glucose	No effect on sexual development. Most AEs were mild or moderate; no statistically significant differences between atorvastatin group and placebo group for any clinical AEs. Clinical AEs in atorvastatin group included abdominal pain (n=6), accidental injury (n=13), fever (n=2), flu syndrome (n=9), headache (n=13), infection (n=27) and pharyngitis (n=9).	Increase in AST levels (n=2) and ALT levels (n=1) in atorvastatin group. No participants withdrew or stopped medications as a result of increased transaminase levels

Author, Year Quality Location	Drug	N with FH	Age range (years)	Study duration	Harms Assessed	Clinical Effects	Laboratory Effects
Gandelman 2011 Fair Greece, Norway, and Canada	Atorvastatin	39	6 to 17	8 weeks	Growth, sexual development, hematology, biochemical tests, AST, ALT, CK, urinalysis, ECG, blood pressure and pulse	No difference in safety or tolerability between younger and older cohorts. No deaths, serious AEs or premature discontinuations. Clinical AEs in both cohorts combined included nasopharyngitis (n=3), viral upper respiratory tract infection (n=3), headache (n=3), gastroenteritis (n=2), abdominal pain (n=1), nausea (n=1), toothache (n=1), vomiting (n=1), and other**	No difference in safety or tolerability between younger and older cohorts. Increased ALT (n=2), with one of the participants returning to normal ALT during study period. Increased blood creatinine (n=1) attributed to reduced water intake.
Avis 2010 Good Europe and North America	Rosuvastatin	176	10 to 17	RCT: 12 weeks Open label: 40 weeks	Growth, sexual development, AE reports, blood count, albumin, total protein, liver enzymes, bilirubin, CK, blood urea nitrogen, serum creatinine, calcium, fasting glucose, TSH, urinalysis, phosphorus, potassium sodium, glycosylated hemoglobin	No effect on growth or sexual development. During RCT period, clinical AEs in rosuvastatin groups included headache (n=22), nasopharyngitis (n=17), influenza (n=4), myalgia (n=4), and nausea (n=4). During open-label period, clinical AEs in rosuvastatin groups included vesicular rash that progressed to cellulitis (n=1) and myalgia (n=5). Overall, safety profile of rosuvastatin was similar to that of placebo.	During RCT period, lab AEs in rosuvastatin groups included transaminase elevation (n=3) and CK elevation (n=4). Changes in ALT, AST, and CK were similar among groups. During open-label period, lab AEs in rosuvastatin groups included transaminase elevation (n=1) and CK elevation (n=4). For all patients, transaminase and CK elevations normalized while continuing treatment or remained normal after resuming treatment. No clinically meaningful renal abnormalities observed.
Avis 2011 Good Netherlands	Rosuvastatin	29	10 to 17	RCT: 12 weeks Open label: 40 weeks	PBMC CoQ10, plasma CoQ10, ATP synthesis	Not reported	Subjects taking rosuvastatin experienced a significant decrease in both PBMC CoQ10 concentrations in plasma CoQ10 concentrations, however, the changes are of unclear clinical significance. No change in ATP synthesis

Author, Year Quality Location	Drug	N with FH	Age range (years)	Study duration	Harms Assessed	Clinical Effects	Laboratory Effects
Braamskamp 2015c Good Netherlands, Canada, Belgium, Norway, U.S. CHARON	Rosuvastatin	198	6 to 17	2 years	Growth, sexual development, AE reports, AST, ALT, urine protein: creatine ratio, CK, ECG	No effect on growth or sexual development. Most commonly reported clinical AEs possibly related to treatment include GI disorders (8%), myalgia (2%), skin disorders (1%). Three patients experienced treatment-related AEs that led to discontinuation (nausea, migraine, paraesthesia). No cases of myopathy or rhabdomyolysis, and no deaths. No abnormal ECG or vital signs.	No clinically important changes in hematology, clinical chemistry, or hepatic, skeletal muscle, and renal biochemistries. Lab AEs included elevated CK levels without associated muscle symptoms (n=3), elevated creatinine (n=1), and elevated urine protein:creatinine ratio (n=7, 5 of whom returned to normal levels by study completion). No patients had abnormal eGFR.
Sinzinger 2004 Fair Austria	Various statins	6††	13-20††	8 years	Blood samples for CK and liver enzymes (GGT, AST, ALT) drawn at monitoring intervals	On average, subjects reported muscle pain in 80% of periods of statin therapy (mean time of onset was 6.2 days) ††	Elevated CK level in 2 subjects; no increase in liver enzyme levels††
NON STATINS							
Tonstad 1996b Good Norway	Colestipol	66	10 to 16	RCT: 8 weeks Open label: 52 weeks	Physical exam, growth, sexual development, nutrient levels	No effects on growth or sexual development; In colestipol group, subjects reported GI side effects (n=8) including constipation, nausea, dyspepsia, flatulence, decreased appetite, and abdominal pain	After 8 weeks, colestipol group experienced reduced serum folate, serum vitamin E and carotenoid levels (significant compared with placebo). After one year, vitamin D levels decreased more in subjects who took ≥80% of dose compared with subjects taking <80% of dose.
Tonstad 1996a Fair Norway	Cholestyramine	72	6 to 11	52 weeks	Physical exam, growth, sexual development, nutrient levels, hemoglobin, AST, ALT, TSH, free thyroxine, ferritin, erythrocyte	No effects on growth or sexual development; Clinical AEs reported in cholestyramine group include intestinal obstruction caused by adhesions (n=1), nausea (n=2), loose stools (n=2), and abdominal pain (n=2). Unpalatability, headaches, and vomiting were reasons for withdrawals	No effects on hemoglobin or liver enzyme levels. Compared with placebo group, cholestyramine group experienced significant decrease in vitamin D (among subjects not taking multivitamin) and significant increase in total homocysteine (which was negatively correlated with serum folate at baseline and 1 year).

Author, Year Quality Location	Drug	N with FH	Age range (years)	Study duration	Harms Assessed	Clinical Effects	Laboratory Effects
Stein 2010 Good International multi-center	Colesevelam	194	10 to 17	RCT: 8 weeks Open label: 18 weeks	Vital signs, physical exam, laboratory safety, chemistry, and hematologic studies, urinalysis, LH, TSH, FSH, testosterone, estradiol, fat-soluble vitamins, clotting factors, hsCRP	No effects on growth or sexual development. During RCT period, distribution of AEs was similar in all groups. Most common drug-related AE in colesevelam groups was GI symptoms (n=9) (including diarrhea, nausea, vomiting, abdominal pain). During open-label period, reported AEs included headaches (n=14), nasopharyngitis (n=10), and upper respiratory infection (n=9)	No clinically meaningful changes in safety lab measurements, hormones, vitamins, or clotting factors
van der Graaf 2008 Good Netherlands, U.S., Canada	Ezetimibe + simvastatin	248	10 to 17	RCT: 33 weeks Open label: 20 weeks	Physical exam, ECG, growth, sexual development, menstrual periods, AE reports, hormone assessments, thyroid function tests, blood chemistries, hematology, urinalysis	No effects on growth or sexual development. Clinical AEs in ezetimibe + simvastatin groups include nasopharyngitis (n=27), headaches (n=16), myalgia (n=7), diarrhea (n=9), nausea (n=8), abdominal pain (n=6), pharyngolaryngeal pain (n=6). AEs leading to discontinuation were myalgia (n=2), nausea (n=1) and muscle spasms (n=1).	CK elevation 10 times or greater than upper limit of normal without associated muscle symptoms (n=2); transaminase elevations at least 3 times upper limit of normal (n=6); No effects on steroid hormones. AEs leading to discontinuation were increased ALT (n=2) and increased CK (n=2).
Kusters 2015 Good 9 countries	Ezetimibe	138‡	6 to 10	12 weeks	Physical exam, ECG, ALT, AST, CK, nutrient levels, abnormal liver function, rhabdomyolysis or myopathy, hypersensitivity, cholecystitis/ cholelithiasis, pancreatitis	No notable differences between ezetimibe and placebo groups for any AEs, drug-related AEs, serious AEs, or AEs leading to discontinuation. No serious drug-related AEs reported. Minor AEs in ezetimibe group include headache (n=1), proteinuria (n=1), prurigo (n=1) and rash (n=1)	No notable differences between ezetimibe and placebo groups for any hematology, blood chemistry, or urinalysis measures assessed. Lab AEs in ezetimibe group included elevated ALT more than three times the upper limit of normal (n=1)

Abbreviations: FH=familial hypercholesterolemia, TSH= thyroid-stimulating hormone, ACTH = Adrenocorticotropic hormone, ALT=alanine transaminase, AST= aspartate transaminase, CK=creatine kinase, PC=pravastatin+colestipol group, CO=colestipol only group, AE = adverse effects, DHEAS=dehydroepiandrosterone sulfate, GI = gastrointestinal, FSH=follicle-stimulating hormone, LH=luteinizing hormone, ENT=ear, nose, and throat, GGT=gamma-glutamyl transpeptidase, hsCRP=high-sensitivity C-reactive protein, ECG=electrocardiogram, eGFR=estimated glomerular filtration rate, CoQ10=coenzyme Q10, ATP=adenosine triphosphate

*N=205 participants included for tolerability analysis. N=188 included for adherence analysis
†Age range of participants with FH at baseline. Age ranges for participants with FH and their siblings not reported at 10 years

‡13 non-FH participants (9 in treatment group, 4 in placebo group) were not analyzed separately
§Other = frequent urination (x2), weight reduction, hair loss, forgetfulness
**Other (n=1 each) includes pain, bronchopneumonia, ear infection, gastritis viral, influenza, lower respiratory tract bacterial infection, tonsillitis, viral rhinitis, hand fracture, arthralgia, musculoskeletal pain, pain in extremity, asthma, rhinitis allergic, and urticarial
††Sinzinger, 2004 study included 22 participants age 13-35. In this table, we report data from a pediatric subgroup of this population (n=6, age range 13-20)

Table 8. Laboratory harms reported in studies of medication in children and adolescents with FH (statins, BSAs and other drugs)

Author, Year	Exposure	N	Abnormal CK	Transaminase elevation*	Abnormal ALT	Abnormal AST	Liver function labs	Endocrine reproductive labs	Misc. labs
Pravastatin									
Knipscheer, 1996[68]	Pravastatin	72	+	+	+	+	+	-	NR
McCrindle, 2002[71]	Pravastatin + Colestipol	36	NR	NR	NR	NR	NR	NR	NR
Hedman, 2003[68]	Pravastatin	20	-	NR	-	-	NR	NR	NR
Wiegman, 2004[66]	Pravastatin	214	-	NR	-	-	NR	-	NR
Rodenburg, 2007[76]	Pravastatin	186	+	NR	NR	NR	NR	+	NR
Kusters, 2014[72]	Pravastatin	194	NR	NR	NR	NR	NR	NR	-
Braamskamp, 2015a[78]	Pravastatin	205†	-	-	-	-	-	NR	NR
Braamskamp, 2015b[77]	Pravastatin	150	NR	NR	NR	NR	NR	-	NR
Carreau, 2011[73]	Pravastatin	185	+	NR	NR	NR	NR	NR	NR
Lovastatin									
Stein, 1999[61]	Lovastatin	132	NR	NR	NR	NR	NR	NR	NR
Clauss, 2005[60]	Lovastatin	54	-	NR	-	-	NR	-	-
Simvastatin									
De Jongh, 2002a[62]	Simvastatin	173	+	+	+	-	+	-	-
De Jongh, 2002b[70]	Simvastatin	50	-	NR	-	-	NR	NR	NR
Atorvastatin									
McCrindle, 2003[63]	Atorvastatin	187	NR	+	NR	+	+	NR	NR
Gandelman, 2011[75]	Atorvastatin	39	NR	+	+	NR	+	NR	NR
Rosuvastatin									
Avis, 2010[64]	Rosuvastatin	176	+	+	NR	NR	+	NR	NR
Avis, 2011[74]	Rosuvastatin	29	NR	NR	NR	NR	NR	NR	+
Braamskamp, 2015c[79]	Rosuvastatin	198	+	-	-	-	-	-	+
Various statins									
Sinzinger, 2004[69]	Various statins	6‡	+	NR	NR	NR	-	NR	NR

Author, Year	Exposure	N	Abnormal CK	Transaminase elevation*	Abnormal ALT	Abnormal AST	Liver function labs	Endocrine reproductive labs	Misc. labs
BSAs									
Tonstad, 1996b[56]	Colestipol	66	NR	NR	NR	NR	NR	NR	NR
Tonstad, 1996a[55]	Cholestyramine	72	NR	NR	NR	NR	NR	-	-
Stein, 2010[65]	Colesevelam	194	+	NR	NR	NR	NR	NR	NR
Other									
van der Graaf, 2008[58]	Ezetimibe and simvastatin	248	+	+	+	NR	+	NR	NR
Kusters, 2015[59]	Ezetimibe	138	-	NR	+	-	+	NR	-

Abbreviations: FH=familial hypercholesterolemia, BSAs=bile sequestering agents, CK=creatine kinase, ALT=alanine transaminase, AST= aspartate transaminase, NR=not reported

*Transaminase elevation was considered if reported if the author specifically mentioned transaminase elevation.
†N=205 participants included in tolerability analysis. N=188 participants included in adherence analysis
‡Sinzinger, 2004 study included 22 participants age 13-35. In this table, we report data from a pediatric subgroup of this population (n=6, age range 13-20).

Table 9. Clinical harms reported in studies of medications in children and adolescents with FH (statins, BSAs and other drugs)

Author, Year	N	Loose stool / diarrhea	GI	Neuro Psych	ENT	Respir-atory	Derm	Musculo-skeletal	Endocrine	Immuno-logic	Systemic	Infection NOS	Pain NOS	Misc
Pravastatin														
Knipscheer, 1996[52]	72	NR	+	+	+	NR	+	NR	NR	NR	NR	NR	NR	NR
McCrindle, 2002[71]*	36	NR	+	+	NR	NR	NR	+	-	NR	NR	NR	NR	NR
Hedman, 2003[68]	20	+	NR	+	NR	NR	NR	+	NR	NR	NR	NR	+	NR
Wiegman, 2004[66]	214	NR	NR	-	NR	NR	NR	NR	-	NR	NR	NR	NR	NR
Rodenburg, 2007[76]	186	NR	NR	NR	NR	NR	NR	+	-	NR	NR	NR	NR	NR
Kusters, 2014[72]	194	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Braamskamp, 2015a[78]	205†	NR	+	+	NR	NR	+	+	NR	NR	NR	NR	NR	+
Braamskamp, 2015b[77]	150	NR	NR	NR	NR	NR	NR	NR	-	NR	NR	NR	NR	NR
Carreau, 2011[73]	185	NR	NR	+	NR	NR	NR	+	-	NR	NR	NR	+	NR
Lovastatin														
Stein, 1999[61]	132	+	+	NR	+	+	+	+	-	+	NR	NR	NR	NR
Clauss, 2005[60]	54	+	+	+	+	+	NR	NR	-	NR	NR	NR	NR	NR
Simvastatin														
De Jongh, 2002a[62]	173	NR	+	+	NR	NR	+	+	-	NR	+	NR	+	NR
De Jongh, 2002b[70]	50	NR	NR	NR	NR	NR	NR	NR	-	NR	NR	NR	NR	NR
Atorvastatin														
McCrindle, 2003[63]	187	NR	NR	+	+	+	NR	NR	-	NR	+	+	NR	+
Gandelman, 2011[75]	39	NR	+	+	+	+	NR	NR	NR	NR	NR	NR	NR	NR
Rosuvastatin														
Avis, 2010[64]	176	NR	+	+	+	+	+	+	-	NR	NR	NR	NR	NR
Avis, 2011[74]	29	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Braamskamp, 2015c[79]	198	NR	+	+	+	+	+	+	-	NR	+	+	NR	NR
Various statins														
Sinzinger, 2004[69]	6§	NR	NR	NR	NR	NR	NR	+	NR	NR	NR	NR	NR	NR

Author, Year	N	Loose stool / diarrhea	GI	Neuro Psych	ENT	Respir-atory	Derm	Musculo-skeletal	Endocrine	Immuno-logic	Systemic	Infection NOS	Pain NOS	Misc
BSA (colestipol)														
Tonstad, 1996b[56]	66	+	+	NR	NR	NR	NR	NR	-	NR	NR	NR	NR	NR
BSA (cholestyramine)														
Tonstad, 1996a[55]	72	+	+	+	NR	NR	NR	NR	-	NR	NR	NR	+	NR
BSA (colesevelam)														
Stein, 2010[65]	194	+	+	+	+	+	NR	NR	-	NR	+	NR	NR	NR
Ezetimibe														
van der Graaf, 2008[58‡]	248	+	+	+	+	+	+	+	-	NR	NR	NR	NR	-
Kusters, 2015[59]	138	+	+	+	+	+	+	-	NR	+	+	+	NR	NR

Abbreviations: FH=familial hypercholesterolemia, BSAs=bile sequestering agents, GI=gastrointestinal, ENT=ear, nose and throat, Derm=dermatologic, NOS=not otherwise specified, Misc=miscellaneous

*Study assessed pravastatin + colestipol vs. colestipol only
†N=205 participants included in tolerability analysis. N=188 participants included in adherence analysis
‡Study assessed ezetimibe + simvastatin vs. placebo + simvastatin
§Sinzinger, 2004 study included 22 participants age 13-35. In this table, we report data from a pediatric subgroup of this population (n=6, age range 13-20)

Table 10. Overall summary of evidence by key question

Key Question	Studies (k) Participants (n)	Overall quality	Consistency	Applicability	Summary of findings
SCREENING					
KQ1 Health outcomes in adulthood KQ2. Intermediate outcomes	0	-	-	-	No evidence on the impact of either selective or universal screening for FH on adult health outcomes or intermediate outcomes in childhood and adolescence.
KQ3. Diagnostic yield of screening for FH	k=2 n=83,241	Fair	N/A (different screening tests, different populations: U.S. and Denmark)	School-based setting is relevant to primary care. Limited applicability of findings from non-US population.	Using two different tests, the diagnostic yield of screening for FH ranged 0.13% to 0.48%.
KQ4. Adverse effects of screening	0	-	-	-	No evidence on harms of screening.
TREATMENT					
KQ5. Treatment and adult health outcomes	0	-	-	-	No evidence on effect of treatment in childhood or adolescence on adult health outcomes.
KQ6. Effect of treatment on intermediate outcomes	Statins: k=8 n=1,071 Non-statins: k=5 n=718	Good/fair: Three studies had <80% retention.	Consistent treatment effects on LDL-C and TC across five different statins. Non-statins (three bile sequestering agents and an inhibitor of cholesterol absorption) had more modest effects.	Studies applicable to youth with FH cared for in U.S. primary care settings. Participants were recruited from tertiary clinics and were not screen-identified.	Statins: All trials reported statistically significant LDL-C decreases, with most effect sizes ranging from 20 to 40%, compared to negligible changes with placebo. Dose response was seen in two studies. All eight studies that evaluated effect on TC found decreases that were smaller than for LDL-C and consistent across studies. One trial reported decrease in CIMT. Non-statins: All five trials (including bile sequestering agents and ezetimibe) reported decreases in LDL-C ranging from 10% to 27%.
KQ7. Harms of treatment	k=18 n=2,210*	Fair: Most studies were less than 2 years duration.	Consistent findings of harms within class: statins, and bile sequestering agents	Good. Most studies were applicable to U.S. primary care setting.	Statins were generally well-tolerated; adverse effects were transient. There was no reported impact on growth or maturation. One trial showed lower DHEAS in children with FH treated with pravastatin compared to unaffected siblings. Bile sequestering agents were commonly associated with gastrointestinal symptoms and poor palatability.

Key Question	Studies (k) Participants (n)	Overall quality	Consistency	Applicability	Summary of findings
OUTCOMES					
KQ8. Association of intermediate outcomes and adult health outcomes	0	-	-	-	No evidence on the association between intermediate outcomes ins childhood or adolescence and adult health outcomes in persons with FH.

Abbreviations: KQ=key question, FH=familial hypercholesterolemia, N/A=not applicable, TC=total cholesterol, LDL-C=low density lipoprotein cholesterol, CIMT=carotid intima media thickness, DHEAS=dehydroepiandrosterone sulfate

*Studies included for KQ7 involved 2,210 patients, 2,197 of whom had FH

Appendix A. Detailed Methods

Search Strategy

Sources searched:
Cochrane Central Register of Controlled Clinical Trials, via Wiley
Medline, via Ovid
PubMed, publisher-supplied

Key:
/ = MeSH subject heading
$ = truncation
ti = word in title
ab = word in abstract
adj# = adjacent within x number of words
pt = publication type
* = truncation
ae = adverse effects
ci = chemically induced
de=drug effects
mo=mortality
nm = name of substance

Cochrane Central Register of Controlled Clinical Trials Issue 1 of 12, January 2014
#1 (hyperlipid*emia*:ti,ab,kw or dyslipid*emia*:ti,ab,kw or hypercholesterol*emia*:ti,ab,kw or hyperlipoprotein*emia*:ti,ab,kw or hypertriglycerid*emia*:ti,ab,kw or dysbetalipoprotein*emia*:ti,ab,kw)
#2 (familial next hypercholesterol*emi*):ti,ab,kw or (familial next hyperlipid*emi*):ti,ab,kw or (essential next hypercholesterol*emi*):ti,ab,kw or (familial near/3 apolipoprotein):ti,ab,kw
#3 "heterozygous fh":ti,ab,kw or "homozygous fh":ti,ab,kw
#4 (lipid next disorder*):ti,ab,kw or (lipid near/3 dysfunction*):ti,ab,kw
#5 (high or elevated or abnormal or aberr*):ti,ab,kw near/3 (cholesterol or lipid* or LDL*):ti,ab,kw #6 (low or decrease* or deficien* or abnormal or aberr*):ti,ab,kw near/3 HDL*:ti,ab,kw
#7 (cholesterol or lipid* or lipoprotein* or LDL* or HDL*):ti,ab,kw near/3 (detect* or measure* or check* or assess* or analyz* or analys* or test* or panel* or profile*):ti,ab,kw
#8 (fasting or nonfasting or non-fasting):ti,ab,kw next (lipid* or lipoprotein* or cholesterol):ti,ab,kw #9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 (child*:ti,ab,kw or adolesc*:ti,ab,kw or teen:ti,ab,kw or teens:ti,ab,kw or teenage*:ti,ab,kw or youth:ti,ab,kw or youths:ti,ab,kw or p*ediatric*:ti,ab,kw)
#11 #9 and #10 from 2007 to 2014, in Trials

MEDLINE
Dyslipidemia screening, screening harms

Database: Ovid MEDLINE(R) without Revisions <1996 to January Week 5 2014>, Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations <February 11, 2014>, Ovid MEDLINE(R) Daily Update <February 11, 2014>
Search Strategy:
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1 Hyperlipidemias/
2 Dyslipidemias/
3 Hypercholesterolemia/
4 Lipid Metabolism Disorders/
5 Hyperlipoproteinemias/
6 Hypertriglyceridemia/
7 Hyperlipoproteinemia Type II/
8 Hyperlipidemia, Familial Combined/
9 Hypobetalipoproteinemias/
10 Abetalipoproteinemia/
11 hyperlipid?emia$.ti,ab.
12 dyslipid?emia$.ti,ab.
13 hypercholesterol?emia$.ti,ab.
14 hyperlipoprotein?emia$.ti,ab.
15 hypertriglycerid?emia$.ti,ab.
16 dysbetalipoprotein?emia$.ti,ab.
17 familial hypercholesterol$emi*.ti,ab.
18 familial hyperlipid?emi*.ti,ab.
19 essential hypercholesterol?emi*.ti,ab.
20 (familial adj3 apolipoprotein).ti,ab.
21 heterozygous fh.ti,ab.
22 homozygous fh.ti,ab.
23 lipid disorder$.ti,ab.
24 or/1-23
25 Cholesterol/bl
26 Triglycerides/bl
27 Lipoproteins/bl
28 Cholesterol, HDL/
29 Cholesterol, LDL/
30 Apolipoprotein B-100/
31 Apolipoprotein B 100.ti,ab.
32 apob 100.ti,ab.
33 apo b 100.ti,ab.
34 ((high or elevated or abnormal or aberr$) adj3 (cholesterol or lipid$ or LDL$)).ti,ab.
35 ((low or decrease$ or deficien$ or abnormal or aberr$) adj3 HDL$).ti,ab.
36 or/25-35
37 Mass screening/
38 screen$.ti,ab.

39 ((cholesterol or lipid$ or lipoprotein$ or LDL$ or HDL$) adj3 (detect$ or measur$ or check$ or assess$ or analyz$ or analys$ or test$ or panel$ or profile$)).ti,ab.
40 (fasting adj (lipid$ or lipoprotein$ or cholesterol)).ti,ab.
41 (non-fasting adj (lipid$ or lipoprotein$ or cholesterol)).ti,ab.
42 37 or 38 or 39 or 40 or 41
43 (24 or 36) and 42
44 adolescent/ or child/ or young adult/
45 43 and 44
46 (child$ or teen or teens or teenage$ or adolescen$ or youth or youths or young people or pediatric$ or paediatric$).ti,ab.
47 43 and 46
48 limit 47 to ("in data review" or in process or "pubmed not medline")
49 45 or 48
50 limit 49 to english language
51 limit 50 to yr="2007 -Current"
52 remove duplicates from 51

Dx yield/accuracy

Database: Ovid MEDLINE(R) without Revisions <1996 to January Week 5 2014>, Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations <February 11, 2014>, Ovid MEDLINE(R) Daily Update <February 11, 2014>
Search Strategy:
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3 Hypercholesterolemia/
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6 Hypertriglyceridemia/
7 Hyperlipoproteinemia Type II/
8 Hyperlipidemia, Familial Combined/
9 Hypobetalipoproteinemias/
10 Abetalipoproteinemia/
11 hyperlipid?emia$.ti,ab.
12 dyslipid?emia$.ti,ab.
13 hypercholesterol?emia$.ti,ab.
14 hyperlipoprotein?emia$.ti,ab.
15 hypertriglycerid?emia$.ti,ab.
16 dysbetalipoprotein?emia$.ti,ab.
17 familial hypercholesterol$emi*.ti,ab.
18 familial hyperlipid?emi*.ti,ab.
19 essential hypercholesterol?emi*.ti,ab.
20 (familial adj3 apolipoprotein).ti,ab.
21 heterozygous fh.ti,ab.
22 homozygous fh.ti,ab.

23 lipid disorder$.ti,ab.
24 or/1-23
25 Cholesterol/bl
26 Triglycerides/bl
27 Lipoproteins/bl
28 Cholesterol, HDL/
29 Cholesterol, LDL/
30 Apolipoprotein B-100/
31 Apolipoprotein B 100.ti,ab.
32 apob 100.ti,ab.
33 apo b 100.ti,ab.
34 ((high or elevated or abnormal or aberr$) adj3 (cholesterol or lipid$ or LDL$)).ti,ab.
35 ((low or decrease$ or deficien$ or abnormal or aberr$) adj3 HDL$).ti,ab.
36 ((cholesterol or lipid$ or lipoprotein$ or LDL$ or HDL$) adj3 (detect$ or measur$ or check$ or assess$ or analyz$ or analys$ or test$ or panel$ or profile$)).ti,ab.
37 (fasting adj (lipid$ or lipoprotein$ or cholesterol)).ti,ab.
38 (non-fasting adj (lipid$ or lipoprotein$ or cholesterol)).ti,ab.
39 or/25-38
40 "Sensitivity and Specificity"/
41 "Predictive Value of Tests"/
42 ROC Curve/
43 False Negative Reactions/
44 False Positive Reactions/
45 Diagnostic Errors/
46 "Reproducibility of Results"/
47 Reference Values/
48 Reference Standards/
49 Observer Variation/
50 Receiver operat$.ti,ab.
51 ROC curve$.ti,ab.
52 sensitivit$.ti,ab.
53 specificit$.ti,ab.
54 predictive value.ti,ab.
55 accuracy.ti,ab.
56 false positive$.ti,ab.
57 false negative$.ti,ab.
58 miss rate$.ti,ab.
59 error rate$.ti,ab.
60 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59
61 (24 or 39) and 60
62 adolescent/ or child/ or young adult/
63 61 and 62
64 (child$ or teen or teens or teenage$ or adolescen$ or youth or youths or young people or pediatric$ or paediatric$).ti,ab.
65 61 and 64

66 limit 65 to ("in data review" or in process or "pubmed not medline")
67 63 or 66
68 limit 67 to (english language and yr="2007 -Current")
69 remove duplicates from 68

Drug Tx Harms

Database: Ovid MEDLINE(R) without Revisions <1996 to January Week 5 2014>, Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations <February 11, 2014>, Ovid MEDLINE(R) Daily Update <February 11, 2014>
Search Strategy:
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7 Hyperlipoproteinemia Type II/
8 Hyperlipidemia, Familial Combined/
9 Hypobetalipoproteinemias/
10 Abetalipoproteinemia/
11 hyperlipid?emia$.ti,ab.
12 dyslipid?emia$.ti,ab.
13 hypercholesterol?emia$.ti,ab.
14 hyperlipoprotein?emia$.ti,ab.
15 hypertriglycerid?emia$.ti,ab.
16 dysbetalipoprotein?emia$.ti,ab.
17 familial hypercholesterol$emi*.ti,ab.
18 familial hyperlipid?emi*.ti,ab.
19 essential hypercholesterol?emi*.ti,ab.
20 (familial adj3 apolipoprotein).ti,ab.
21 heterozygous fh.ti,ab.
22 homozygous fh.ti,ab.
23 lipid disorder$.ti,ab.
24 ((high or elevated or abnormal or aberr$) adj3 (cholesterol or lipid$ or LDL$)).ti,ab.
25 ((low or decrease$ or deficien$ or abnormal or aberr$) adj3 HDL$).ti,ab.
26 or/1-25
27 hypolipidemic agents/ or bezafibrate/ or butoxamine/ or clofenapate/ or clofibrate/ or clofibric acid/ or colestipol/ or fenofibrate/ or gemfibrozil/ or halofenate/ or meglutol/ or nafenopin/ or niacin/ or niceritrol/ or pyridinolcarbamate/ or simvastatin/ or triparanol/
28 anticholesteremic agents/ or azacosterol/ or chitosan/ or cholestyramine resin/ or clofibrate/ or clofibric acid/ or lovastatin/ or meglutol/ or pravastatin/ or probucol/ or simvastatin/ or "trans-1,4-bis(2-chlorobenzaminomethyl)cyclohexane dihydrochloride"/
29 hydroxymethylglutaryl-coa reductase inhibitors/ or lovastatin/
30 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor$.ti,ab.

31 hydroxymethylglutaryl coa reductase inhibitor$.ti,ab.
32 hydroxymethylglutaryl coa inhibitor$.ti,ab.
33 hydroxymethylglutaryl coenzyme a reductase.ti,ab.
34 hydroxymethylglutaryl coenzyme a inhibitor$.ti,ab.
35 hmg coa reductase inhibitor$.ti,ab.
36 hmg coa inhibitor$.ti,ab.
37 atorvastatin.ti,ab.
38 fluvastatin.ti,ab.
39 lovastatin.ti,ab.
40 pitavastatin.ti,ab.
41 pravastatin.ti,ab.
42 rosuvastatin.ti,ab.
43 simvastatin.ti,ab.
44 hypolipidemic$.ti,ab.
45 anticholesteremic$.ti,ab.
46 antilipidemic.ti,ab.
47 statin$.ti,ab.
48 lipid lower$.ti,ab.
49 (treat$ or therap$ or medicat$).ti.
50 or/27-49
51 ae.fs.
52 "Drug-Related Side Effects and Adverse Reactions"/
53 Mortality/
54 Morbidity/
55 Death/
56 mo.fs.
57 (harm or harms or harmful or harmed).ti,ab.
58 (adverse adj (effect$ or event$ or outcome$)).ti,ab.
59 safety.ti,ab.
60 overtreat$.ti,ab.
61 (death or deaths).ti,ab.
62 drug-induced liver injury/
63 drug-induced liver injury, chronic/
64 Liver Neoplasms/ci
65 Liver/de
66 Liver failure/ci
67 Liver failure, acute/ci
68 (liver adj3 (injur$ or dysfunction$ or failure$)).ti,ab.
69 (Hepatic adj3 (injur$ or dysfunction$ or failure$)).ti,ab.
70 (transaminase adj3 (elevat$ or abnormal$ or dysfunction$)).ti,ab.
71 Liver enzyme$.ti,ab.
72 alanine transaminase.ti,ab.
73 alanine aminotransferase.ti,ab.
74 aspartate transaminase.ti,ab.
75 aspartate aminotransferase.ti,ab.
76 (AST or ALT).ti,ab.

77 Muscular Diseases/ci
78 Myositis/
79 Myositis.ti,ab.
80 Dermatomyositis/
81 Dermatomyositis.ti,ab.
82 myositis ossificans.ti,ab.
83 Rhabdomyolysis/
84 rhabdomyolysis.ti,ab.
85 myotoxicity.ti,ab.
86 myopathy.ti,ab.
87 muscle enzyme$.ti,ab.
88 (creatine adj3 (high or elevat$ or abnormal$)).ti,ab.
89 Myalgia/
90 myalgia.ti,ab.
91 or/51-90
92 26 and 50 and 91
93 adolescent/ or child/ or young adult/
94 92 and 93
95 (child$ or teen or teens or teenage$ or adolescen$ or youth or youths or young people or pediatric$ or paediatric$).ti,ab.
96 92 and 95
97 limit 96 to ("in data review" or in process or "pubmed not medline")
98 94 or 97
99 limit 98 to english language
100 limit 99 to yr="2007 -Current"

Drug and lifestyle treatment efficacy

Database: Ovid MEDLINE(R) without Revisions <1996 to June Week 1 2014>, Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations <June 12, 2014>, Ovid MEDLINE(R) Daily Update <June 12, 2014>
Search Strategy:
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1 Hyperlipidemias/
2 Dyslipidemias/
3 Hypercholesterolemia/
4 Lipid Metabolism Disorders/
5 Hyperlipoproteinemias/
6 Hypertriglyceridemia/
7 Hyperlipoproteinemia Type II/
8 Hyperlipidemia, Familial Combined/
9 Hypobetalipoproteinemias/
10 Abetalipoproteinemia/
11 hyperlipid?emia$.ti,ab.
12 dyslipid?emia$.ti,ab.
13 hypercholesterol?emia$.ti,ab.

14 hyperlipoprotein?emia$.ti,ab.
15 hypertriglycerid?emia$.ti,ab.
16 dysbetalipoprotein?emia$.ti,ab.
17 familial hypercholesterol$emi*.ti,ab.
18 familial hyperlipid?emi*.ti,ab.
19 essential hypercholesterol?emi*.ti,ab.
20 (familial adj3 apolipoprotein).ti,ab.
21 heterozygous fh.ti,ab.
22 homozygous fh.ti,ab.
23 lipid disorder$.ti,ab.
24 ((high or elevated or abnormal or aberr$) adj3 (cholesterol or lipid$ or LDL$)).ti,ab.
25 ((low or decrease$ or deficien$ or abnormal or aberr$) adj3 HDL$).ti,ab.
26 or/1-25
27 hypolipidemic agents/ or bezafibrate/ or butoxamine/ or clofenapate/ or clofibrate/ or clofibric acid/ or colestipol/ or fenofibrate/ or gemfibrozil/ or halofenate/ or meglutol/ or nafenopin/ or niacin/ or niceritrol/ or pyridinolcarbamate/ or simvastatin/ or triparanol/
28 anticholesteremic agents/ or azacosterol/ or chitosan/ or cholestyramine resin/ or clofibrate/ or clofibric acid/ or lovastatin/ or meglutol/ or pravastatin/ or probucol/ or simvastatin/ or "trans-1,4-bis(2-chlorobenzaminomethyl)cyclohexane dihydrochloride"/
29 hydroxymethylglutaryl-coa reductase inhibitors/ or lovastatin/
30 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor$.ti,ab.
31 hydroxymethylglutaryl coa reductase inhibitor$.ti,ab.
32 hydroxymethylglutaryl coa inhibitor$.ti,ab.
33 hydroxymethylglutaryl coenzyme a reductase.ti,ab.
34 hydroxymethylglutaryl coenzyme a inhibitor$.ti,ab.
35 hmg coa reductase inhibitor$.ti,ab.
36 hmg coa inhibitor$.ti,ab.
37 atorvastatin.ti,ab.
38 fluvastatin.ti,ab.
39 lovastatin.ti,ab.
40 pitavastatin.ti,ab.
41 pravastatin.ti,ab.
42 rosuvastatin.ti,ab.
43 simvastatin.ti,ab.
44 hypolipidemic$.ti,ab.
45 anticholesteremic$.ti,ab.
46 antilipidemic.ti,ab.
47 statin$.ti,ab.
48 lipid lower$.ti,ab.
49 (treat$ or therap$ or medicat$).ti.
50 or/27-49
51 diet/
52 diet, carbohydrate-restricted/
53 diet, fat-restricted/
54 diet, mediterranean/
55 diet, protein-restricted/

56 diet, reducing/
57 diet, vegetarian/
58 caloric restriction/
59 portion size/
60 Food habits/
61 Diet Therapy/
62 Soybean Proteins/
63 Fatty Acids, Omega-3/
64 Phytosterols/
65 Dietary Fiber/
66 Dietary Protein/
67 Dietary Carbohydrates/
68 Dietary Fats/
69 diet$.ti,ab.
70 ((reduce$ or reduction$ or manipulat$ or restrict$) adj3 (fat$ or carbohydrate$ or cholesterol)).ti,ab.
71 low fat.ti,ab.
72 lowfat.ti,ab.
73 fiber.ti,ab.
74 omega 3 fatty acid$.ti,ab.
75 n 3 polyunsaturated fatty acid$.ti,ab.
76 n 3 fatty acid$.ti,ab.
77 n 3 pufa.ti,ab.
78 soy$ protein$.ti,ab.
79 plant stanol$.ti,ab.
80 esters.ti,ab.
81 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80
82 Exercise/
83 Exercise therapy/
84 Motor activity/
85 Physical fitness/
86 Plyometric Exercise/
87 Physical Conditioning, Human/
88 Running/
89 Jogging/
90 Swimming/
91 Walking/
92 Resistance training/
93 (exercise or exercising or exercises).ti,ab.
94 physical fitness.ti,ab.
95 physical conditioning.ti,ab.
96 (running or jog$ or swim$ or walk$).ti,ab.
97 (lifestyle$ or life style$).ti,ab.
98 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97
99 26 and (50 or 81 or 98)

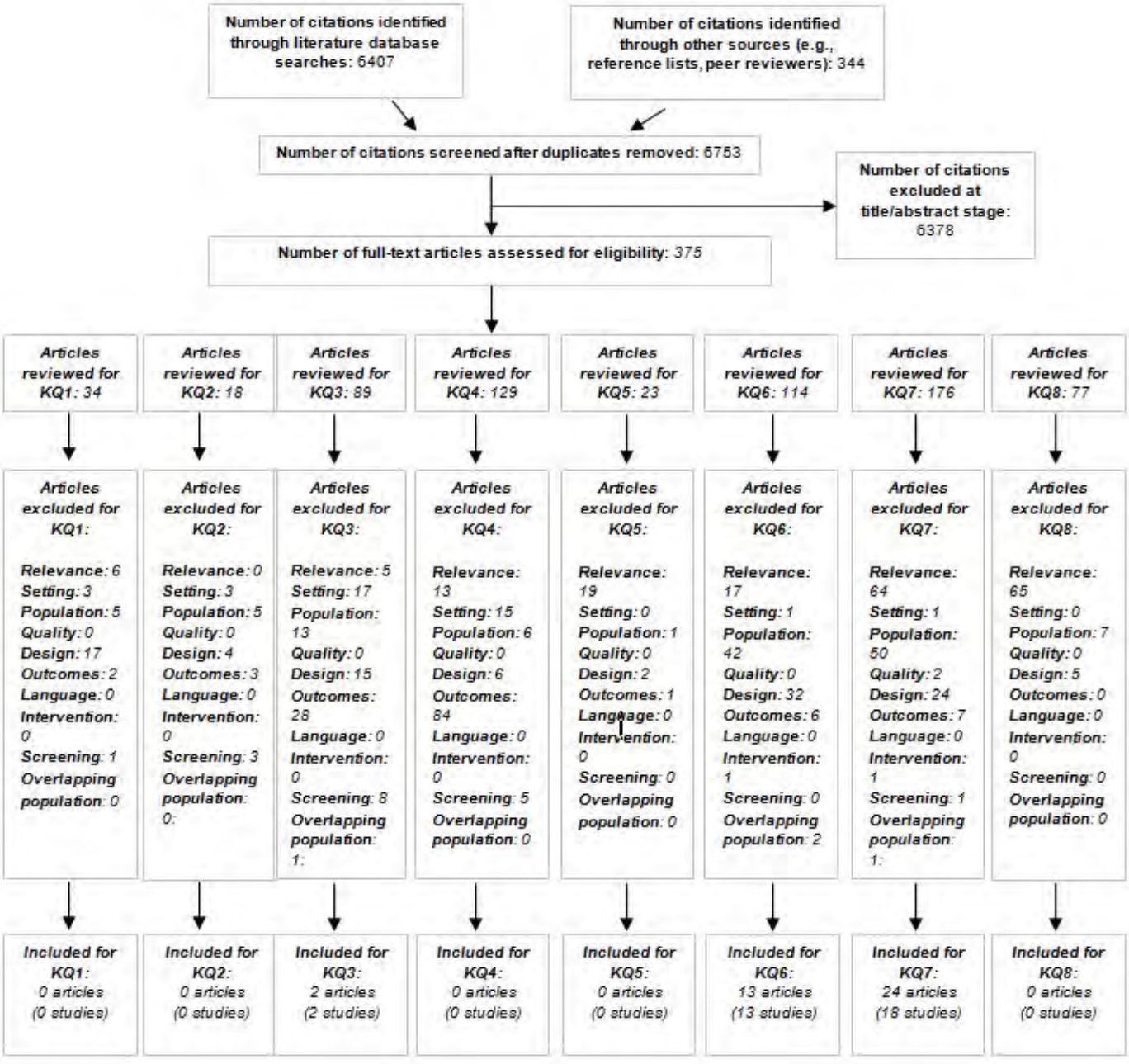
100 Hyperlipidemias/dh, dt, pc, th [Diet Therapy, Drug Therapy, Prevention and Control, Therapy]
101 Dyslipidemias/dh, dt, pc, th
102 Hypercholesterolemia/dh, dt, pc, th
103 Lipid Metabolism Disorders/dh, dt, pc, th
104 Hyperlipoproteinemias/dh, dt, pc, th
105 Hypertriglyceridemia/dh, dt, pc, th
106 Hyperlipoproteinemia Type II/dh, dt, pc, th
107 Hyperlipidemia, Familial Combined/dh, dt, pc, th
108 Hypobetalipoproteinemias/dh, dt, pc, th
109 Abetalipoproteinemia/dh, dt, pc, th
110 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109
111 adolescent/ or child/ or young adult/
112 110 and 111
113 (child$ or teen or teens or teenage$ or adolescen$ or youth or youths or young people or pediatric$ or paediatric$).ti,ab.
114 110 and 113
115 limit 114 to ("in data review" or in process or "pubmed not medline")
116 112 or 115
117 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or meta-analysis as topic/
118 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt.
119 Random$.ti,ab.
120 control groups/ or double-blind method/ or single-blind method/
121 clinical trial$.ti,ab.
122 controlled trial$.ti,ab.
123 meta analy$.ti,ab.
124 117 or 118 or 119 or 120 or 121 or 122 or 123
125 116 and 124
126 limit 125 to (english language and yr="2007 -Current")
127 remove duplicates from 126

PubMed search strategy [publisher-supplied references only], searched 2.12.2014

Search	Query
#11	Search #10 AND publisher[sb] Filters: Publication date from 2007/01/01 to 2014/12/31; English
#10	Search #8 AND #9
#9	Search child*[tiab] OR teen[tiab] OR teens[tiab] OR teenage*[tiab] OR adolescen*[tiab] OR youth[tiab] OR youths[tiab] OR "young people"[tiab] OR pediatric*[tiab] OR paediatric*[tiab]
#8	Search #1 or #2 or #3 or #4 or #5 or #6 or #7
#7	Search (fasting[tiab] or non fasting[tiab] OR nonfasting[tiab]) AND

Search	Query
	(lipid*[tiab] OR lipoprotein*[tiab] OR cholesterol[tiab])
#6	Search (lipid[tiab] OR lipids[tiab] OR lipoprotein*[tiab] OR cholesterol[tiab] OR LDL*[tiab] OR HDL*[tiab]) AND (detect*[tiab] OR measur*[tiab] OR check*[tiab] OR assess*[tiab] OR analyz*[tiab] OR analys*[tiab] OR test*[tiab] OR panel*[tiab] OR profile*[tiab])
#5	Search (lipid[tiab] OR lipids[tiab] OR lipoprotein*[tiab] OR cholesterol[tiab] OR LDL*[tiab] OR HDL*[tiab]) AND (low[tiab] OR high[tiab] OR elevated[tiab] OR abnormal[tiab] OR aberr*[tiab])
#4	Search lipid disorder*[tiab] OR lipid dysfunction*[tiab]
#3	Search familial[tiab] AND apolipoprotein[tiab]
#2	Search familial hypercholesterolemia*[tiab] OR familial hypercholesterolaemia*[tiab] OR familial hyperlipidemi*[tiab] OR familial hyperlipidaemi*[tiab] OR essential hypercholesterolemi*[tiab] OR essential hypercholesterolaemi*[tiab] OR heterozygous fh[tiab] OR homozygous fh[tiab]
#1	Search (hyperlipidemia*[tiab] OR hyperlipidaemia*[tiab] OR dyslipidemia*[tiab] OR dyslipidaemia*[tiab] OR hypercholesterolemia*[tiab] OR hypercholesterolaemia*[tiab] OR hyperlipoproteinemia*[tiab] OR hyperlipoproteinaemia*[tiab] OR hypertriglyceridemia*[tiab] OR hypertriglyceridaemia*[tiab] OR dysbetalipoproteinemia*[tiab] OR dysbetalipoproteinaemia*[tiab])

Figure 1. Literature flow diagram



Abbreviations: KQ=key question

Table 1. Inclusion and exclusion criteria

	Included	Excluded
Population	**KQs 1–4:** Asymptomatic children and adolescents ages 0 to 20 years at time of screening **KQs 5–7:** Children and adolescents ages 0 to 20 years at time of treatment initiation with a diagnosis of familial hypercholesterolemia **KQ 8:** Children and adolescents ages 0 to 20 years at beginning of study period with a diagnosis of familial hypercholesterolemia	**KQs 1–4:** Children and adolescents with any of the following: • Known dyslipidemia • Diagnosis associated with secondary dyslipidemia* • Established family history of familial hypercholesterolemia **KQs 5–7:** Children and adolescents with dyslipidemia not due to familial hypercholesterolemia
Diseases	**KQs 5–7:** Familial hypercholesterolemia	**KQs 5–7:** • Monogenic dyslipidemia other than familial hypercholesterolemia • Secondary dyslipidemia* • Multifactorial dyslipidemia
Screening interventions	**KQs 1–4:** • Lipid panel (fasting or nonfasting lipid measurement, total or LDL cholesterol alone or in combination with HDL cholesterol) • Comparison with no screening or usual care • Universal or selective screening strategy	**KQs 1–4:** • Genetic screening alone • Cascade screening
Treatments	**KQs 5–7:** • Lipid-lowering medications • Lifestyle modifications, including diet or exercise	**KQs 5–7:** • Apheresis • Revascularization
Outcomes	**KQs 1, 5, 8:** • MI • Ischemic stroke **KQs 2, 6:** • Lipid concentrations (total and LDL cholesterol) • Atherosclerosis markers (carotid intima–media thickness, calcium score, pathological findings) **KQ 3:** • Diagnostic yield (true positives/number screened) • Positive predictive value (true positives/true positives + false positives) **KQ 4:** All harms (e.g., false-positive or false-negative results, psychosocial effects, overdiagnosis) **KQ 7:** All harms from lipid-lowering medications (e.g., AEs, long-term safety, overtreatment)	**KQs 1, 5, 8:** • Diabetes • Metabolic syndrome • Hypothyroidism • Renal failure • Obstructive liver disease • Nephrotic syndrome • Lipodystrophy
Study design	**KQs 1–3**: RCTs, CCTs, cohort studies, systematic reviews **KQs 4, 7:** RCTs, CCTs, cohort studies, systematic reviews, observational studies, systematically selected case series **KQs 5, 6:** RCTs, systematic reviews **KQ 8:** RCTs, CCTs, cohort studies, systematic reviews, registry studies, long-term trial followup, high-quality case-control studies	**All KQs:** Studies rated as poor quality **KQs 1–3, 5, 6, 8:** Qualitative studies, case reports, cost-effectiveness studies **KQs 4, 7:** None **KQs 5, 6**: Cohort studies, plus all study designs excluded for KQ 1 **KQ 8:** All study designs excluded for KQ 1

Settings	• Publication date of 2007 to present • Conducted in countries with a Human Development Index score of ≥0.9, as defined by the United Nations	Settings not generalizable to primary care

Abbreviations: KQ=key question, LDL=low density lipoprotein, HDL=high density lipoprotein, MI=myocardial infarction, AE=adverse effects, RCT=randomized controlled trial, CCT=controlled clinical trial

Additional definitions: Secondary dyslipidemias: Renal (chronic renal disease, hemolytic uremic syndrome, nephrotic syndrome); Infectious (acute viral or bacterial infections, HIV, hepatitis); hepatic (obstructive liver disease, cholestasis, biliary cirrhosis, Alagille syndrome); inflammatory (systemic lupus erythematosus, juvenile rheumatoid arthritis); storage (glycogen storage disease, Gaucher's disease, cystine storage disease, Tay-Sachs, Niemann-Pick); other (Kawasaki disease, anorexia nervosa, cancer, previous solid organ transplantation, progeria, idiopathic hypercalcemia, Klinefelter, Werner's syndrome

Table 2. Quality assessment criteria

Study Design	Adapted Quality Criteria
Randomized controlled trials, adapted from the USPSTF methods[1]	• Valid random assignment? • Was allocation concealed? • Was eligibility criteria specified? • Were groups similar at baseline? • Were measurements equal, valid and reliable? • Was there intervention fidelity? • Was there adequate adherence to the intervention? • Were outcome assessors blinded? • Was there acceptable followup? • Were the statistical methods acceptable? • Was the handling of missing data appropriate? • Was there evidence of selective reporting of outcomes? • Was the device calibration and/or maintenance reported?

Abbreviations: USPSTF = U.S. Preventive Services Task Force

References

1. U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Procedure Manual. Rockville, MD: U.S. Preventive Services Task Force; 2008.

Appendix B. Ongoing Studies

We identified one potentially relevant ongoing or recently completed RCT through four registries: ClinicalTrials.gov (http://clinicaltrials.gov), Current Controlled Trials (http://www.controlled-trials.com), Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au) and the World Health Organization's International Clinical Trials Registry Platform (http://www.who.int/ictrp). We restricted our searches to (heterozygous) familial hypercholesterolemia in children.

One RCT studied rapeseed oil and sunflower oil as treatments for FH in children. This study, "Effect of a Diet With Rapeseed Oil /Sunflower Oil on Lipoprotein in Children and Adolescents With Familial Hypercholesterolemia," was last updated on clinicaltrials.gov in June of 2009 (NCT00924274).[1] It is a randomized double-blind trial for the purpose of treatment. One group received rapeseed oil as a dietary supplement, and the active comparator group received sunflower oil. The current recruitment status of the study is unknown.

We identified one patient registry study currently recruiting participants as of February 27, 2015. This study is based in Montreal and is establishing an FH patient registry of children, adults, and seniors with FH. The primary outcome measure is the number of patients with FH. The secondary outcome measure is the prevalence of FH. The study began in November 2013. The estimated study completion date is November 2020.[2]

We identified a Russian cohort and registry of FH begun in January 2014 that has an estimated completion date of December 2026, and a primary outcome measure completion date of December 2016.[3]

One randomized double crossover study of a Mediterranean diet in children with FH or familial combined hyperlipidemia has completed. Results are not yet available.[4]

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2. Familial Hypercholesterolemia Canada / Hypercholesterolemie Familiale Canada. Bethesda (MD): National Library of Medicine (US) [2015 March 3]. https://clinicaltrials.gov/ct2/show/NCT02009345.
3. Prospective Russian Study Evaluating the Extent of Underdiagnosed and Undertreated of Familial Hypercholesterolaemia in the Population. National Library of Medicine (US) [2015 March 3]. https://clinicaltrials.gov/ct2/show/NCT02208869.
4. Endothelial Assessment of Risk From Lipids in Youth: Mediterranean Diet. Bethesda (MD): National Library of Medicine (US) [2015 March 3]. https://clinicaltrials.gov/ct2/show/NCT01308710.

Appendix C. Excluded Studies

Table 1. Exclusion codes

Code*	Reason for Exclusion
E1	Not English
E2	Not original research in a peer-reviewed journal
E4	Ineligible SETTING (a) non-generalizable to primary care; (b) low HDI country
E5	Ineligible POPULATION
E6	Ineligible OUTCOMES
E7	Ineligible screening strategy
E8	Ineligible treatment
E9	Ineligible study design
E10	Study rated as poor quality
E11	Overlapping study population
E12	N/A

Abbreviations: HDI = Human Development Index, N/A = not applicable

*The exclusion code E3 was not used

1. Two controversial recommendations: screening (and treating) children for cholesterol. Child Health Alert. 2008;26:1-2. PMID: 18953695. **KQ1E2.**
2. American Academy of Pediatrics. National Cholesterol Education Program: Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Pediatrics. 1992;89(3 Pt 2):525-84. PMID: 1538956. **KQ4E6.**
3. American Academy of Pediatrics Committee on Nutrition American Academy of Pediatrics. Committee on Nutrition. Cholesterol in childhood. Pediatrics. 1998;101(1 Pt 1):141-7. PMID: 11345978. **KQ4E6.**
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6. Andersen GE, Nielsen HG. Neonatal screening for hyperlipoproteinemia. Methods for direct estimation of cord serum VLDL + LDL. Clin Chim Acta. 1976;66(1): 29-41. PMID: 177231. **KQ4E6.**
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Appendix D. Diagnostic Criteria for Familial Hypercholesterolemia

Table 1. MEDPED Criteria (U.S.)*[1]

	Total Cholesterol (LDL-C) concentrations in mg/dL			
Age	1st degree relative	2nd degree relative	3rd degree relative	General population
<18	220 (155)	230 (165)	240 (170)	270 (200)
20	240 (170)	250 (180)	260 (185)	290 (220)
30	270 (190)	280 (200)	290 (210)	340 (240)
40 +	290 (205)	300 (215)	310 (225)	360 (260)

Abbreviations: LDL-C=low density lipoprotein cholesterol, mg/dL=milligrams per deciliter

*Cutoffs for 98% specificity and 54% to 88% sensitivity

Table 2. Simon Broome Criteria (U.K.)[2]

Total Cholesterol (LDL-C) in mg/dL 290 (190) in adults, or 260 (155) in pediatrics (under 16) AND:	
1) DNA mutation	Definite FH
2) Tendon xanthomas in the patient or in a 1st or 2nd degree relative	Probable FH
3) Family history of MI at age <50 in 2nd degree relative or at age <60 in 1st degree relative OR Family history of total cholesterol >290 mg/dL in 1st or 2nd degree relative	Possible FH

Abbreviations: LDL-C=low density lipoprotein cholesterol, mg/dL=milligrams per deciliter, MI=myocardial infarction, FH=familial hypercholesterolemia

Table 3. Dutch Criteria (The Netherlands)[3]

1 point	1st degree relative with premature cardiovascular disease or LDL-C >95th percentile, or Personal history of premature peripheral or cerebrovascular disease, or LDL-C between 155 and 189 mg/dL
2 points	1st degree relative with tendinous xanthoma or corneal arcus, or 1st degree relative child (<18 yrs) with LDL-C > 95th percentile, or personal history of coronary artery disease
3 points	LDL-C between 190 and 249 mg/dL
4 points	Presence of corneal arcus in patient less than 45 yrs old
5 points	LDL-C between 250 and 329 mg/dL
6 points	Presence of a tendon xanthoma
8 points	LDL-C above 330 mg/dL, or Functional mutation in the LDLR gene

Abbreviations: LDL-C=low density lipoprotein cholesterol, mg/dL=milligrams per deciliter, LDLR=low density lipoprotein receptor, FH=familial hypercholesterolemia

Definite FH (≥8 points); Probable FH (6-7 points); Possible FH (3-5 points)

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Appendix E. Cohort Studies

National Health and Nutritional Examination Survey (NHANES)
Bogalusa Heart Study
Pathobiological Determinants of Atherosclerosis in Youth (PDAY)
Muscatine Study
Princeton Lipid Research Clinics Follow-up Study
Cardiovascular Risk in Young Finns Study (Young Finns)
National Heart, Lung, and Blood Institute Growth and Health Study (NGHS)
Special Turku Coronary Risk Factor Intervention Project (STRIP)
Coronary Artery Risk Development in Young Adults Study (CARDIA)
Minnesota Children's Blood Pressure Study
Beaver County Lipid Study
Fels Longitudinal Study
National Children's Study (NIH)
Four Provinces study (4P)