Supplementary Online Content


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This supplementary material has been provided by the authors to give readers additional information about their work.
eMethods. Literature Search Strategies

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
#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 2015, in Trials

MEDLINE
Dyslipidemia screening, screening harms

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Search Strategy:

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?emia*.ti,ab.
18 familial hyperlipid?emia*.ti,ab.
19 essential hypercholesterol?emia*.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 deficient$ 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.

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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 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 June 2, 2015>, Ovid
MEDLINE(R) In-Process and Other Non-Indexed Citations <June 2, 2015>, Ovid
MEDLINE(R) Daily Update <June 2, 2015>
Search Strategy:
--------------------------------------------------------------------------------
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 apo b 100.ti,ab.
33 ((high or elevated or abnormal or aberr$) adj3 (cholesterol or lipid$ or LDL$)).ti,ab.
34 ((low or decrease$ or deficien$ or abnormal or aberr$) adj3 HDL$).ti,ab.
35 ((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$)).ti,ab.
36 (fasting adj (lipid$ or lipoprotein$ or cholesterol)).ti,ab.
37 (non-fasting adj (lipid$ or lipoprotein$ or cholesterol)).ti,ab.
38 or/25-38
39 "Sensitivity and Specificity"/
40 "Predictive Value of Tests"/
41 ROC Curve/
42 False Negative Reactions/
43 False Positive Reactions/
44 Diagnostic Errors/
45 Reproducibility of Results/
46 Reference Values/
47 Reference Standards/
48 Observer Variation/
49 Receiver operat$.ti,ab.
50 ROC curve$.ti,ab.
51 sensitivit$.ti,ab.
52 specificit$.ti,ab.
53 predictive value.ti,ab.
54 accuracy.ti,ab.
55 false positive$.ti,ab.
56 false negative$.ti,ab.
57 miss rate$.ti,ab.
58 error rate$.ti,ab.
59 or/24 or 39 and 60
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 teenager$ or adolescent$ 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

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Drug Tx Harms

Database: Ovid MEDLINE(R) without Revisions <1996 to June Week 1 2015>, Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations <June 2, 2015>, Ovid MEDLINE(R) Daily Update <June 2, 2015>

Search Strategy:
--------------------------------------------------------------------------------
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 haloefenate/ 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$.ti,ab.
hydroxymethylglutaryl coenzyme a reductase.
hydroxymethylglutaryl coenzyme a inhibitor.
hmg coa reductase inhibitor.
hmg coa inhibitor.
atorvastatin.
fluvastatin.
lovastatin.
pitavastatin.
pravastatin.
rosuvastatin.
simvastatin.
hypolipidemic.
anticholesteremic.
antilipidemic.
statin.
lipid lower.
(treat or therap or medicat).
or/27-49
"Drug-Related Side Effects and Adverse Reactions"/
Mortality/
Morbidity/
Death/
mo.fs.
(harm or harms or harmful or harmed).
(adverse adj (effect or event or outcome)).
safety.
overtreat.
(death or deaths).
drug-induced liver injury/
drug-induced liver injury, chronic/
Liver Neoplasms/ci
Liver/de
Liver failure/ci
Liver failure, acute/ci
(liver adj3 (injur$ or dysfunction$ or failure$)).
(Hepatic adj3 (injur$ or dysfunction$ or failure$)).
(transaminase adj3 (elevat$ or abnormal$ or dysfunction$)).
Liver enzyme.
alanine transaminase.
alanine aminotransferase.
aspartate transaminase.
aspartate aminotransferase.
(AST or ALT).
Muscular Diseases/ci
Myositis/
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Drug and lifestyle treatment efficacy

Database: Ovid MEDLINE(R) without Revisions <1996 to June Week 1 2015>, Ovid MEDLINE(R) In-Process and Other Non-Indexed Citations <June 2, 2015>, Ovid MEDLINE(R) Daily Update <June 2, 2015>

Search Strategy:

1 Hyperlipidemias/
2 Dyslipidemias/
3 Hypercholesterolemia/
4 Lipid Metabolism Disorders/
5 Hyperlipoproteinemias/
6 Hypertriglycerideridemia/
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 hypertriglyceriderid?emia$.ti,ab.

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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
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<th>Search</th>
<th>Query</th>
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</tr>
<tr>
<td>#10</td>
<td>Search #8 AND #9</td>
</tr>
<tr>
<td>#8</td>
<td>Search #1 or #2 or #3 or #4 or #5 or #6 or #7</td>
</tr>
<tr>
<td>#7</td>
<td>Search (fasting*[tiab] or non fasting*[tiab] OR nonfasting*[tiab]) AND (lipid*[tiab] OR lipoprotein*[tiab] OR cholesterol*[tiab])</td>
</tr>
<tr>
<td>#4</td>
<td>Search lipid disorder*[tiab] OR lipid dysfunction*[tiab]</td>
</tr>
<tr>
<td>#3</td>
<td>Search familial*[tiab] AND apolipoprotein*[tiab]</td>
</tr>
</tbody>
</table>
eTable 1. Diagnostic Criteria for FH: MEDPED Criteria (U.S.)<sup>a</sup>

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

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

<sup>a</sup>Cutoffs for 98% specificity and 54% to 88% sensitivity
## eTable 2. Diagnostic Criteria for FH: Simon Broome Criteria (U.K.)²

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

Abbreviations: LDL-C=low density lipoprotein cholesterol, mg/dL=milligrams per deciliter, MI=myocardial infarction, FH=familial hypercholesterolemia
Table 3. Diagnostic Criteria for FH: Dutch Criteria (The Netherlands)\(^3\)

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

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)
**eTable 4. Quality Assessment Criteria**

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Adapted Quality Criteria</th>
</tr>
</thead>
</table>
| Randomized controlled trials, adapted from the USPSTF methods\(^4\) | • 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? |
| Observational studies (e.g., prospective cohort studies), adapted from the Newcastle-Ottawa Scale (NOS)\(^5\) | • Was the cohort systematically selected to avoid bias?  
• Was eligibility criteria specified?  
• Were groups similar at baseline?  
• Was the outcome of interest not present at baseline?  
• Were measurements equal, valid, and reliable?  
• Were outcome assessors blinded?  
• Was there acceptable followup?  
• Were the statistical methods acceptable?  
• Was the handling of missing data appropriate? |

Abbreviations: USPSTF = U.S. Preventive Services Task Force  
Good quality studies generally meet all quality criteria. Fair quality studies do not meet all the criteria but do not have critical limitations that could invalidate study findings. Poor quality studies have a single fatal flaw or multiple important limitations that could invalidate study findings. Critical appraisal of studies using a priori quality criteria are conducted independently by at least two reviewers. Disagreements in final quality assessment are resolved by consensus, and, if needed, consultation with a third independent reviewer.
KQ indicates Key Question.

Details about reasons for exclusion are as follows. Relevance: study aim not relevant. Setting: study was not conducted in a setting or country relevant to US primary care. Population: study not conducted in a population of children and adolescents aged 0 to 20 years. For KQs 1-4, studies were excluded if they involved children and adolescents with known dyslipidemia, and for KQs 5-7, studies were excluded if they involved children and adolescents with dyslipidemia not due to familial hypercholesterolemia. Quality: study did not meet criteria for fair or good quality (ie, it was poor quality). Design: study did not use an included design. Outcomes: study did not have relevant outcomes or had incomplete outcomes. Language: study published in a non-English language. Intervention: study used an excluded intervention approach. Screening: study used an excluded screening approach. Overlapping population: study population overlapped with 1 or more studies included for this KQ.

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**Table 5. Adverse Effects Reported in Studies of Pravastatin (Key Question 7)**

<table>
<thead>
<tr>
<th>Source</th>
<th>Quality</th>
<th>Study Design</th>
<th>Location</th>
<th>Drug</th>
<th>No. With FH</th>
<th>Age Range, y</th>
<th>Study Duration</th>
<th>Harms Assessed</th>
<th>Effects</th>
<th>Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knipscheer et al, 1996</td>
<td>Good</td>
<td>RCT</td>
<td>Netherlands</td>
<td>Pravastatin vs placebo</td>
<td>72 (IG = 54; CG = 18)</td>
<td>8-16</td>
<td>12 wk</td>
<td>Hematology, ALT, AST, CK, alkaline phosphatase, urinalysis, TSH, cortisol, ACTH</td>
<td>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)</td>
<td>No significant difference between treatment and placebo groups for laboratory AEs. CK level abnormal in placebo (n = 8) and in 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 in pravastatin 5 mg/d (n = 2), 10 mg/d (n = 5), and 20 mg/d (n = 3) groups. For other laboratory effects, &lt;5 participants had abnormal values in placebo group, as well as in all pravastatin groups combined.</td>
</tr>
<tr>
<td>McCrindle et al, 2002</td>
<td>Good</td>
<td>RCT (crossover)</td>
<td>Canada</td>
<td>Pravastatin +</td>
<td>36 (IG = 20; CG = 18)</td>
<td>9-18</td>
<td>18 wk</td>
<td>Height, weight, blood</td>
<td>Clinical AEs more prevalent in CO group.</td>
<td>No effects on CK, AST, other blood</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Country</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Duration</td>
<td>Outcome Measures</td>
<td>Results</td>
<td></td>
<td></td>
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<tr>
<td>Hedman et al, 2003</td>
<td>Fair Prospective Observational</td>
<td>Finland</td>
<td>Pravastatin</td>
<td>20 (no CG)</td>
<td>4-15 wk</td>
<td>GI symptoms, headache, skin reactions, sleep disturbance, muscle/tendon tenderness, pain, creatinine, CK, ALT</td>
<td>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.</td>
<td></td>
<td></td>
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<tr>
<td>Wiegman et al, 2004</td>
<td>Good RCT</td>
<td>Netherlands</td>
<td>Pravastatin vs placebo</td>
<td>214 (IG = 106; CG = 108)</td>
<td>8-18 wk</td>
<td>Sex steroids, gonadotropins, pituitary adrenal axis markers,</td>
<td>No effects on growth, sexual development, or academic progress. No effects on muscle or liver enzyme levels (AST, ALT, CK) or on endocrine function.</td>
<td></td>
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</tr>
<tr>
<td>Rodenburg et al,\textsuperscript{10} 2007 (Dutch Pravastatin Trial)</td>
<td>Fair</td>
<td>Prospective observational\textsuperscript{b}</td>
<td>Netherland\textsuperscript{s}</td>
<td>Pravastatin</td>
<td>186 (no CG in follow-up period)</td>
<td>Mean age, 13.7</td>
<td>4.5 y (follow-up after initial trial of 104 wk)\textsuperscript{b}</td>
<td>Sex steroids, gonadotropins, pituitary adrenal axis markers, muscle and liver enzymes, growth, sexual development</td>
<td>Myalgia without CK elevation (n = 4); no effects on growth or sexual development</td>
<td>No serious laboratory AEs reported; no participants discontinued treatment due to laboratory AEs. Laboratory 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)</td>
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<tr>
<td>Kusters et al,\textsuperscript{11} 2014 (Dutch Pravastatin Trial)</td>
<td>Good</td>
<td>Prospective observational\textsuperscript{b}</td>
<td>Netherland\textsuperscript{s}</td>
<td>Pravastatin</td>
<td>194 (no CG)\textsuperscript{c}</td>
<td>Mean age, 24.0</td>
<td>10 y (follow-up after initial trial of 104 wk)\textsuperscript{b}</td>
<td>Growth, sexual development, AST, ALT, CK, glomerular filtration rate, C-reactive protein, level of education, reported AEs</td>
<td>No effects on growth, sexual development, or education level; no reports of rhabdomyolysis or other serious major AEs; 3 participants discontinued treatment due to unspecified AEs.</td>
<td>No effects on AST, ALT, CK, glomerular filtration rate, C-reactive protein. No differences between patients with FH and non-FH siblings for laboratory AEs.</td>
</tr>
<tr>
<td>Study Authors, Year</td>
<td>Design</td>
<td>Country</td>
<td>Pravastatin</td>
<td>Follow-up</td>
<td>Adverse Events and Reasons for Discontinuation</td>
<td>Follow-up</td>
<td>FSH, LH, DHEAS</td>
<td>Testosterone, Estradiol, LH, FSH, and DHEAS</td>
<td>Growth, Sexual Development, CK, AST, ALT AEs Assessed by Review of Medical Files</td>
<td>Public Health Impact</td>
</tr>
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</tr>
<tr>
<td>Braamskamp et al, 2015A (Dutch Pravastatin Trial)</td>
<td>Good Prospective Observational</td>
<td>Netherlands</td>
<td>Pravastatin</td>
<td>205 (no CG)</td>
<td>8-18 (start of RCT) 18-30 (end of follow-up)</td>
<td>10 y (follow-up after initial trial of 104 wk)</td>
<td>3 participants discontinued treatment due to AEs (GI, muscle/joint pain, headache). Over 10 y, 55 AEs reported by 40 participants (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.</td>
<td>Compared with unaffected siblings, DHEAS was significantly lower in participants with FH (although still within normal range). No effects on testosterone, estradiol, LH, or FSH concentrations.</td>
<td></td>
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</tr>
<tr>
<td>Braamskamp et al, 2015B (Dutch Pravastatin Trial)</td>
<td>Good Prospective Observational</td>
<td>Netherlands</td>
<td>Pravastatin</td>
<td>88 (no CG)</td>
<td>8-18e</td>
<td>10 y (follow-up after initial trial of 104 wk)</td>
<td>Testosterone, estradiol, LH, FSH, and DHEAS</td>
<td>No reports of irregular menstrual cycle, hyperandrogenism, or involuntary childlessness.</td>
<td></td>
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</tr>
<tr>
<td>Carreau et al, 2011</td>
<td>Fair Prospective Observational</td>
<td>France</td>
<td>Pravastatin</td>
<td>185 (no CG)</td>
<td>4-17</td>
<td>2 y +2 mo (mean duration)</td>
<td>Growth, sexual development, CK, AST, ALT AEs assessed by review of medical files</td>
<td>24 participants (13%) reported AEs, including muscle pain that resolved after changing statins (n = 4), muscle pain not</td>
<td>Asymptomatic CK elevation (n = 8), pain with moderate CK elevation that resolved without changing treatment.</td>
<td></td>
</tr>
</tbody>
</table>
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. (n = 2). No effects on AST or ALT.

| Abbreviations: ACTH, adrenocorticotropic hormone; AE, adverse effect; ALT, alanine transaminase; AST, aspartate transaminase; CG, control group; CK, creatine kinase; CO, colestimol only group; DHEAS, dehydroepiandrosterone sulfate; FH, familial hypercholesterolemia; FSH, follicle-stimulating hormone; GI, gastrointestinal; IG, intervention group; LH, luteinizing hormone; PC, pravastatin + colestimol group; RCT, randomized clinical trial; TSH, thyroid-stimulating hormone. |
| Quality assessed using criteria developed by the US Preventive Services Task Force.15 |
| Wiegman 2004, Rodenburg 2007, Kusters 2014, Braamskamp 2015a, and Braamskamp 2015b are part of the Dutch Pravastatin Trial, which included an initial RCT followed by an open-label period. |
| Kusters, 2014 article compared 194 participants with FH (with statin treatment) with 83 unaffected siblings (without statin treatment). Braamskamp 2015B article compared 88 participants with FH (with statin treatment) with 62 unaffected siblings (without statin treatment). |
| 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. |
| Other indicates frequent urination (×2), weight reduction, hair loss, forgetfulness. |
**eTable 6. Adverse Effects Reported in Studies of Other Statins (Key Question 7)**

<table>
<thead>
<tr>
<th>Source</th>
<th>Quality</th>
<th>Study Design</th>
<th>Location</th>
<th>Drug</th>
<th>No. With FH</th>
<th>Age range, y</th>
<th>Study Duration</th>
<th>Harms Assessed</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stein et al,(^{16}) 1999</td>
<td>Good</td>
<td>RCT</td>
<td>United States, Finland</td>
<td>Lovastatin vs placebo</td>
<td>132 (IG = 67; CG = 65)</td>
<td>10-17</td>
<td>48 wk</td>
<td>Growth, sexual development, ALT, AST, CK, urinalysis, routine hematology, blood coagulation, thyroid function, blood nutrients, cortisol, DHEAS, FSH, LH, testosterone</td>
<td>No effect on growth or sexual development. AEs reported by 70.1% of participants 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.</td>
</tr>
<tr>
<td>Clauss et al,(^{17}) 2005</td>
<td>Good</td>
<td>RCT</td>
<td>United States</td>
<td>Lovastatin vs placebo</td>
<td>54 girls (IG = 35; CG = 19)</td>
<td>11-18</td>
<td>24 wk</td>
<td>ALT, AST, CK, creatinine, glucose, β-human chorionic gonadotrophin</td>
<td>No patients discontinued treatment due to AEs. No clinically meaningful differences between groups.</td>
</tr>
</tbody>
</table>

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<p>| de Jongh et al.(^{18}) 2002A | Good | RCT | International multicenter | Simvastatin vs placebo | 173 (IG = 106; CG = 67) | 10-17 | RCT: 24 wk Extention: 24 wk | Growth, sexual development, ALT, AST, CK, cortisol, DHEAS, estradiol, testosterone, LH, FSH, human chorionic gonadotropin | 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), | No statistically significant differences between placebo and simvastatin groups in period 1 or period 2. Laboratory AEs in simvastatin group included increased ALT (n = 3), AST (n = 3), and CK (n = 1) levels. No serious laboratory AEs reported; no | n, hematology, urinalysis, sexual development, DHEAS, FSH, LH | 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 &lt; 0.05). No effects on growth or menstrual cycle length. No reports of myopathy or rhabdomyolysis. |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Countries</th>
<th>Patients</th>
<th>Follow-up</th>
<th>Outcomes</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Jongh et al, 2002B</td>
<td>Fair</td>
<td>Netherlands</td>
<td>50 (IG = 28; CG = 22)</td>
<td>9-18</td>
<td>Growth, blood pressure, ALT, AST, CK</td>
<td>Sleep disorder (n = 1), weight gain (n = 1), and pruritus (n = 1). No effect on growth or cortisol levels. No serious clinical AEs reported.</td>
</tr>
<tr>
<td>McCrindle et al, 2003</td>
<td>Good</td>
<td>United States, Canada, Europe, South Africa</td>
<td>187 (IG = 140; CG = 47)</td>
<td>10-17</td>
<td>RCT: 26 wk Open-label: 26 wk Blood pressure, physical examination, hemoglobin, hematocrit, red blood cell count, white blood cell count, platelet count, AST, ALT, CK, alkaline phosphatase, blood urea</td>
<td>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.</td>
</tr>
</tbody>
</table>
Gandelman et al,\textsuperscript{21} 2011

<table>
<thead>
<tr>
<th>Study</th>
<th>Quality</th>
<th>Design</th>
<th>Countries</th>
<th>Treatment</th>
<th>Age Range</th>
<th>Follow-Up</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good Open label trial</td>
<td>Fair</td>
<td>Greece, Norway, and Canada</td>
<td>Atorvastatin 39 (no CG)</td>
<td>Growth, sexual development, hematology, biochemical tests, AST, ALT, CK, urinalysis, ECG, blood pressure and pulse</td>
<td>6 to 17</td>
<td>8 wk</td>
<td>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.\textsuperscript{b}</td>
</tr>
<tr>
<td>Avis et al,\textsuperscript{22} 2010 (PLUTO)</td>
<td>Good</td>
<td>RCT with follow-up open label\textsuperscript{c}</td>
<td>Europe and North America Rosuvastatin vs placebo 176 (IG = 130; CG = 46)</td>
<td>Growth, sexual development, AE reports, blood count,</td>
<td>10-17</td>
<td>RCT: 12 wk Open-label: 40 wk</td>
<td>No effect on growth or sexual development. During RCT period, clinical AEs in rosvastatin groups included transaminase</td>
</tr>
</tbody>
</table>

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<p>| Avis et al,23 2011 (PLUTO) | Good | RCT with follow-up open label | Netherlands | Rosuvastatin | 29 (no CG) | RCT: 12 wk Open-label: 40 wk | PBMC CoQ10, plasma CoQ10, ATP synthesis | Not reported | Participants taking rosuvastatin experienced a significant decrease in both PBMC CoQ10 concentrations in plasma CoQ10 concentrations; however, the | elevation (n = 3) and CK elevation (n = 4). Changes in ALT, AST, and CK were similar among groups. During open-label period, laboratory 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. |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Quality</th>
<th>Study Design</th>
<th>Country</th>
<th>Drug(s)</th>
<th>N (no CG)</th>
<th>Duration</th>
<th>AE Reports</th>
<th>Clinical Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braamskamp et al, 2015C</td>
<td>Good</td>
<td>Open-label trial</td>
<td>Netherlands, Canada, Belgium, Norway, United States</td>
<td>Rosuvastatin</td>
<td>198 (no CG)</td>
<td>6-17</td>
<td>Growth, sexual development, AE reports, AST, ALT, urine protein: creatine ratio, CK, ECG</td>
<td>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. Laboratory 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.</td>
</tr>
<tr>
<td>Sinzinger et al, 2004</td>
<td>Fair</td>
<td>Prospective observational</td>
<td>Austria</td>
<td>Various statins</td>
<td>6 (no CG)</td>
<td>13-20h</td>
<td>Blood samples for CK and liver enzymes (GGT, AST, ALT) drawn at On average, participants reported muscle pain in 80% of periods of statin therapy (mean time</td>
<td>Elevated CK level in 2 participants; no increase in liver enzyme levels.</td>
</tr>
</tbody>
</table>

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Abbreviations: AE, adverse effect; ALT, alanine transaminase; AST, aspartate transaminase; ATP, adenosine triphosphate; CG, control group; CHARON, Hyperc holesterolaemia in Children and Adolescents Taking Rosuvastatin Open Label; CK, creatine kinase; CoQ10, coenzyme Q10; DHEAS, dehydroepiandrosterone sulfate; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ENT, ear, nose, and throat; FH, familial hypercholesterolemia; FSH, follicle-stimulating hormone; GGT, gamma-glutamyl transpeptidase; GI, gastrointestinal; IG, intervention group; LH, luteinizing hormone; PLUTO, Pediatric Lipid-Reduction Trial of Rosuvastatin; RCT, randomized clinical trial; TSH, thyroid-stimulating hormone.

| Monitoring intervals | of onset, 6.2 d. | b |

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<table>
<thead>
<tr>
<th>Source</th>
<th>Quality ^a</th>
<th>Study Design</th>
<th>Location</th>
<th>Drug</th>
<th>No. With FH</th>
<th>Age Range, y</th>
<th>Study Duration</th>
<th>Harms Assessed</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonstad et al,^26 1996B</td>
<td>Good</td>
<td>RCT with follow-up open label</td>
<td>Norway</td>
<td>Colestipol vs placebo</td>
<td>66 (IG = 33; CG = 33)</td>
<td>10-16</td>
<td>RCT: 8 wk Open-label: 52 wk</td>
<td>Physical examination, growth, sexual development, nutrient levels</td>
<td>No effects on growth or sexual development; in colestipol group, participants reported GI AEs (n = 8), including constipation, nausea, dyspepsia, flatulence, decreased appetite, and abdominal pain. After 8 wk, colestipol group experienced reduced serum folate, serum vitamin E, and carotenoid levels (significant compared with placebo). After 1 y, vitamin D levels decreased more in participants who took ≥80% of dose compared with participants taking &lt;80% of dose.</td>
</tr>
<tr>
<td>Tonstad et al,^27 1996A</td>
<td>Fair</td>
<td>RCT</td>
<td>Norway</td>
<td>Cholestyramine vs placebo</td>
<td>72 (IG = 36; CG = 36)</td>
<td>6-11</td>
<td>52 wk</td>
<td>Physical examination, growth, sexual development, nutrient levels, hemoglobin, AST, ALT, TSH, free thyroxine, ferritin, erythrocyte</td>
<td>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 participants not taking multivitamin) and significant increase in total homocysteine (which was negatively correlated with serum folate at baseline and 1 y).</td>
</tr>
<tr>
<td>Stein et al,^28 2010</td>
<td>Good</td>
<td>RCT international</td>
<td>Internaional</td>
<td>Colesevelam vs</td>
<td>194 (IG = 129; CG)</td>
<td>10-17</td>
<td>RCT: 8 wk</td>
<td>Vital signs, physical</td>
<td>No effects on growth or sexual</td>
</tr>
<tr>
<td>van der Graaf et al, 2008</td>
<td>Good</td>
<td>RCT with follow-up open-label</td>
<td>Netherlands, United States, Canada</td>
<td>Ezetimibe + simvastatin vs placebo + simvastatin</td>
<td>248 (IG = 126; CG = 122)</td>
<td>10-17</td>
<td>RCT: 33 wk</td>
<td>Open-label: 18 wk</td>
<td>examination, laboratory safety, chemistry, and hematologic studies, urinalysis, LH, TSH, FSH, testosterone, estradiol, fatsoluble vitamins, clotting factors, hsCRP 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).</td>
</tr>
</tbody>
</table>
discontinuation were myalgia (n = 2), nausea (n = 1) and muscle spasms (n = 1).

| Kusters et al, 2015 | Good | RCT | 9 countries | Ezetimibe vs placebo | 138 (IG = 93; CG = 45) | 6-10 | 12 wk | Physical examination, 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. Laboratory AEs in ezetimibe group included elevated ALT >3× the upper limit of normal (n = 1). |

Abbreviations: AE, adverse effect; ALT, alanine transaminase; AST, aspartate transaminase; CG, control group; CK, creatine kinase; ECG, electrocardiogram; FH, familial hypercholesterolemia; FSH, follicle-stimulating hormone; GI, gastrointestinal; hsCRP, high-sensitivity C-reactive protein; LH, luteinizing hormone; RCT, randomized clinical trial; TSH, thyroid-stimulating hormone.  

aQuality assessed using criteria developed by the US Preventive Services Task Force.  
bThirteen participants without FH (9 in treatment group, 4 in placebo group) were not analyzed separately.
eReferences

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