Appendix C
Clinical data extractions and excluded studies

Included studies

Please note, all extractions and gradings will be checked for the final version.

Question 1: In adults and children, what is the effectiveness of the following tests to diagnose FH: biochemical assays, clinical signs and symptoms, DNA testing or a combination of methods?

Study descriptions

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
Results from a family and DNA based active identification programme for familial hypercholesterolaemia.	Asbroek AH; de Mheen PJ; Defesche JC; Kastelein JJ; Gunning-Schepers LJ;	2001	COH	2+	1005 subjects	All subjects had DNA test results as well as cholesterol measurements and were age 20-60	These are Dutch subjects who were screened as a result of a family based active identification programme for FH. There were 478 men and 527 women. No other demographic data was supplied	Between 1994 and 1998 2814 adults were screened. A non selective sample of those who met the inclusion criteria was chosen.	Academic Medical Centre; University of Amsterdam	The prevalence of hypercholesterolaemia among screenees with a proven LDL receptor gene mutation	Cholesterol levels in FH+ and FH- patients were compared. FH status was determined by DNA testing. The screenees were not yet treated with statins.	This is a cross-sectional study	TC levels and DNA result
Familial hypercholesterolemia: molecular, biochemical, and clinical characterization of a French-Canadian pediatric population.	Assouline L; Levy E; Feoli-Fonseca JC; Godbout C; Lambert M;	1995	COH	2+	88 unrelated French Canadian children with high cholesterol and 41 controls age and sex matched with children of group 1(see below).	These children persistently presented LDL cholesterol levels >130 mg/dl (3.36 mmol/l) with a parental history of hyperlipidemia.	The three study groups were similar with respect to age, weight, height, body mass index, Z score for body mass index, pubertal state and family history of premature atherosclerosis.	Pubertal stage and family history of premature atherosclerosis. The make to female ratio was different in groups 1 and 2 compared with group 3.	Lipid clinic of Hopital Sainte-Justine Canada	Diagnosis of FH in French Canadian children with elevated cholesterol	Use of biochemical, clinical and genetic techniques to diagnose FH	This is cross-sectional research	LDL levels; genetic testing and clinical signs and symptoms
Molecular genetic analysis of 1053 Danish individuals with clinical signs of familial hypercholesterolemia.	Brusgaard K; Jordan P; Hansen H; Hansen AB; Horder M;	2006	COH	2+	1053	Patients with FH recruited from lipids clinics in southern Denmark	671 FH probands and 382 relatives	Attendance at lipid clinic	Southern Denmark	This primary aim of this study was to identify mutations in this population. The study is of interest because a table is provided of average lipid values for those with and without	Comparisons are made between those with and without mutations and those with different types of	This is a cross sectional study	Primary outcome: mutation type. Secondary outcome: lipid levels compared to mutation type

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
										mutations	mutations		
The relationship of molecular genetic to clinical diagnosis of familial hypercholesterolemia in a Danish population	Damgaard D; Larsen ML; Nissen PH; Jensen JM; Jensen HK; Soerensen VR; Jensen LG; Faergeman O;	2005	DIAG	2+	08 index patients and 385 relatives were included. Index patients had to met two of three criteria: elevated cholesterol; tendon xanthomata; history of coronary artery disease before age 60 in patient or first degree relative. Relatives of index patients, in whom a mutation was identified, were included. Secondary hypercholesterolaemia was ruled out clinically and by a small array of biochemical analyses to exclude renal failure, nephrotic syndrome, liver disease, hypothyroidism and diabetes.		FH diagnosis by clinical signs and symptoms or biochemical testing compared to DNA testing			Estimation of sensitivities and specificities of different clinical diagnostic criteria for FH to predict results of molecular genetic analysis of index patients. Three sets of clinical criteria developed in the UK, USA and the Netherlands were evaluated	Screening for the 3 mutations in the LDL receptor gene with subsequent sequencing if necessary		
Mutation screening and genotype:phenotype correlation in familial hypercholesterolaemia.	Graham CA; McClean E; Ward AJ; Beattie ED; Martin S; O'Kane M; Young IS; Nicholls DP;	1999	COH	2+	38 with a diagnosis of definite FH; 120 with a diagnosis of possible FH	Definite FH: tendon xanthomata in a member of the family. Possible FH: a family history of premature myocardial infarction (at age <60) or of significant hypercholesterolaemia (LDL-c > 4.9mmo.l)	Demographics (except age - see below) not provided. These were family groups from the Lipid clinics in Belfast and Londonderry	Unknown	Northern Ireland Lipid Clinics	Use of mutation identification in relation to lipid profile and presentation of tendon xanthomata.	Presence of specific gene mutations in relation to lipid levels and presence of tendon xanthomata	Cross sectional data	Gene mutation and lipid levels and presence of tendon xanthomata
Genetic screening protocol for familial hypercholesterolemia which includes splicing defects gives an improved mutation detection rate.	Graham CA; McIlhatton BP; Kirk CW; Beattie ED; Lyttle K; Hart P; Neely RD; Young IS; Nicholls DP;	2005	COH	2+	198 families with FH of which 68 were classified as definite FH because of the presence of tendon xanthomata in the proband or a relative	68 families with definite FH by Simon Broome criteria and 130 families with possible FH (TC >7.5 mmol/l and family history of MI below age 50 in second degree relative or below 60 in first degree relative.	No demographics were provided	Patients attended Lipid Clinics in Northern Ireland and North East of England.	Northern Ireland; north east England	Detection rate of LDLR mutations when using primer sets which would enable the detection of splice site mutations in the LDLR gene.	Comparison is made between two different detection methods	This is a cross-sectional study	Rate of detection of mutation positive patients is the outcome measure.
The use of Achilles tendon sonography to distinguish familial hypercholesterolemia from other genetic dyslipidemias.	Junyent M; Gilabert R; Zambon D; Nunez I; Vela M; Civeira F; Pocovi M; Ros E;	2005	COH	2+	290; 127 FH subjects 88 controls - also FCH and polygenic hypercholesterolemic patients.	These were consecutive adults with a diagnosis of primary hypercholesterolemia attending the Lipid Clinic of Hospital Clinic, Barcelona. Depending on family history, physical signs and lipid levels, subjects were given a clinical diagnosis.	None of the subjects had been on cholesterol lowering medication or had a history of AT tears or tendonitis. There were 45 men and 36 women with DNA + FH and a mean age of 45 years; 24 men and 22 women with DNA -FH and a mean age of 46 years.	Subjects were referred for diagnosis or because of refractoriness to treatment.	Barcelona, Spain	Use of AT sonography to distinguish genetically ascertained FH from clinical FH without a molecular diagnosis.	Concordance between physical examination and sonography in the diagnosis of AT xanthomas	Cross-sectional study	Sonographic findings and molecularly defined FH vs no identified mutation
Rising cholesterol	Kessling AM;	1990	COH	2+	571 children without	Children between 4-19	149 boys; 422 girls. 15	Unknown	Metabolic	Change in cholesterol	Mean	One to	Mean

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
levels in children with familial hypercholesterolaemia.	Seed M; Taylor R; Wynn V; Humphries SE;				known medical or familial predisposition to hypercholesterolaemia. 85 children had a first degree relative with FH and 18 of these were followed for 1-7 years along with 55 children from the control group.	attending the Metabolic Unit at St. Mary's Hospital London from 1966-1984.	children less than or equal to 12 years old. No known medical of familial predisposition to hypercholesterolaemia.		Unit at St. Mary's Hospital London	with age	cholesterol levels over time in controls and in 18 children with a first degree relative with FH and a cholesterol level below the childhood 95th percentile.	seven years	cholesterol levels are the primary outcome. Retrospective DNA testing was done 3 children.
Diagnosis of Heterozygous Familial Hypercholesterolemia - DNA Analysis Complements Clinical Examination and Analysis of Serum-Lipid Levels	Koivisto PVI; Koivisto UM; Miettinen TA; Kontula K;	1992	COH	2+	Ten propositi with large deletions of the LD receptor gene and their first degree relatives were investigated. A total of 65 of the 69 invited individuals participated.	See above. Children less than 7 years of age and relatives living outside the Helsinki University Central Hospital district were not invited.	54 were adults (including the 10 propositi) and 11 were children (<18 years).	Subjects were invited by letter	Helsinki University Central Hospital	Presence of FH by DNA testing	Comparison to FH by clinical and biochemical methods	Cross-sectional study	DNA results; LDL and HDL; clinical signs and symptoms including xanthoma and corneal arcus
Sonography of the Achilles tendon in hypercholesterolaemia.	Koivunen-Niemela T; Alanen A; Viikari J;	1993	COH	2+	130 patients with hypercholesterolaemia were examined by ultrasound (US). Patients with obvious secondary hypercholesterolaemias were excluded. 40 patients had clinically evident FH. 51 patients had clinically evident non FH hypercholesterolaemia. In	Patients with primary hypercholesterolaemia were included. 41normolipidemic controls were also included.	In the three groups (FH, non FH and normal) ages ranged from 43-53; in total 67 women and 65 men participated. The patients were Finnish.	Patients were volunteers.	University of Turku, Finland	Achilles tendon xanthoma and thickness	Comparison is made between tendon thickness and echogenicity in FH, non-FH and control patients	This is a cross sectional study	Tendon thickness (mm) and presence or absence of echogenicity
Sonography in the detection of Achilles tendon xanthomata in children with familial hypercholesterolaemia.	Koivunen-Niemela T; Viikari J; Niinikoski H; Simell O; Alanen A;	1994	COH	3	21	Children with FH identified in relation to FH family studies. Eleven children had positive LDL-r tests; three had a first degree relative with a positive LDL-r test; and seven had one first degree relative with xanthomatous hypercholesterolaemia.	21 FH children (10 boys and 11 girls)aged 3-18 years old. 68 healthy controls,34 boys; 34 girls, 16 of whom were normocholesterolemic siblings of subjects	Unknown	University of Turku, Finland	Presence of Achilles tendon xanthomata	Presence or absence of Achilles tendon xanthomata in children with FH compared to controls	Cross sectional study. In seven children a second study was done at 1-2 year interval	Presence of Achilles tendon xanthomata
Familial hypercholesterolemia: potential diagnostic value of mutation screening in a pediatric population of South Africa.	Kotze MJ; Peeters AV; Loubser O; Theart L; du P; Hayes VM; De J; de V; Lombard CJ; Hansen PS; Raal FJ;	1998	COH	2+	221 children were tested. 60 boys and 56 girls were identified as heterozygotes. The presence of mutations were excluded in 50 boys and 55 girls.	The children were identified by follow-up studies performed in 85 South African FH families in whom the disease was caused by one of three founder related LDLR gene mutations	The children were South African ranging in age from 2-18	Recruitment occurred through follow up of known FH families	A South African 'region'	Plasma lipid levels in children with a range of LDLR gene mutations and children with no identified mutation	Lipid levels are compared	This is a cross sectional study	TC, LDL, HDL and TG
Neonatal diagnosis of	Kwiterovich	1973	COH	2+	29 infants who were	All infants had one	Newborn babies in US	Unknown	National	Total cholesterol,	Controls are	Up to 2	TC, HDL,

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
familial type-II hyperlipoproteinaemia.	PO; Levy RI; Fredrickson DS;	Jan 20			subject; 36 babies who were controls	parent with FH	from one of 18 kindreds		Heart and Lung Institute, Bethesda, Md.	HDL, LDL and VLDL and TG from cord blood. 19 babies were followed at 1-2 1/4 years.	compared with at risk infants considered 'positive' due to LDL greater than 41 mg/ml (1.05 mmol/l) and at risk infants considered 'negative' due to LDL less than 41 mg/ml (1.05mmol/l).	1/4 years	LDL
Familial hypercholesterolemia (one form of familial type II hyperlipoproteinemia). A study of its biochemical, genetic and clinical presentation in childhood.	Kwiterovich POJ; Fredrickson DS; Levy RI;	1974	COH	2+	236 children	Age 1-19; both parents has LDL determined; one parent had FH and the other parent had normal LDL	117 males and 119 females; 103 children in first decade and 133 in second decade	Recruited from a registry at National Heart and Lung Institute, Bethesda Md.	Metropolitan Washington DC	LDL levels in children of an FH parent	LDL levels in affected and non affected children	This is a cross sectional study	LDL and TC
Diagnosing Familial Hypercholesterolemia in Childhood by Measuring Serum-Cholesterol.	Leonard JV; Whitelaw AGL; Wolff OH; Lloyd JK; Slack J;	1977	COH	2-	134 children; numbers of affected and unaffected children not reported.	Aged 1-16 years from 57 kinships with at least one first degree relative who was considered to have FH	Additional demographic data not supplied. Study took place at Great Ormond St. Hospital	All had been referred to Great Ormond Street Hospital for evaluation of cholesterol due to family history	Study took place at Great Ormond St. Hospital	Total serum cholesterol	TC in affected vs unaffected children	Cross-sectional	TC levels
Cutoff point separating affected and unaffected familial hypercholesterolemic patients validated by LDL-receptor gene mutants	Mabuchi H; Higashikata T; Nohara A; Lu H; Yu WX; Nozue T; Noji Y; Katsuda S; Kawashiri MA; Inazu A; Kobayashi J; Koizumi J;	2005	COH	2+	181 FH patients and 100 unaffected first and second degree relatives.	All FH patients were heterozygous and were diagnosed by abnormalities of the LDL receptor gene while unaffected family members showed no LDL receptor gene mutations.	90 male FH patients; 91 female FH patients. 49 non FH patients; 51 non FH female patients. No subjects were taking lipid lowering drugs and none had a disease affecting serum lipid concentrations.	Unknown	Ishikawa, Japan	Cutoff point separating affected and unaffected FH patients	Different levels of TC and LDL-c	Cross-sectional study	TC and LDL-c were primary outcomes. HDL and log TG were secondary outcomes.
Heterozygous familial hypercholesterolemia in children: low-density lipoprotein receptor mutational analysis and variation in the expression of plasma lipoprotein-lipid concentrations.	Torres AL; Moorjani S; Vohl MC; Gagne C; Lamarche B; Brun LD; Lupien PJ; Despres JP;	1996	COH	2+	266 FH children with whole lipoprotein lipid profile and bearing the >15 kb (n=188), W66G missense mutation in exon 3 (n=57) and C646Y missense mutation in exon 14 (n=21) were used for this study. 120 controls were healthy sibs and unrelated children.	Most children studied were first degree relatives of patients with FH followed at the Lipid Research Clinic in Quebec City. All were DNA positive for FH.	Mean ages ranged between 7.06-9.05 years. BMI ranged 16.55 - 17.94. No other demographic data was provided.	The sample came from a cohort of 343 children suspected for FH by clinical criteria.	Quebec City	Lipoprotein and lipids among mutation and age groups	Mutation type and lipid levels in various paediatric age groups	Cross sectional study	Gene mutation; TC; LDL; HDL; TG and TC/HDL
Review of first 5 years of screening for familial	Umans-Eckenhausen	2001	COH	2+									

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
hypercholesterolaemia in the Netherlands.	MA; Defesche JC; Sijbrands EJ; Scheerder RL; Kastelein JJ;												
Diagnosing familial hypercholesterolaemia: The relevance of genetic testing.	van Aalst Cohen ES; Jansen ACM; Tanck MWT; Defesche JC; Trip MD; Lansberg PJ; Stalenhoef AFH; Kastelein JJP;	2006	COH	2++	2400 patients; 1255 LDR-r plus, 464 with xanthomas present and 658 with xanthomas absent; 1145 LDL-r minus (further sequencing in progress), 444 with xanthomas present and 648 with xanthomas absent.	Inclusion: adults age 18 years or older with documented LDL-receptor mutation or LDL-c above 95th percentile for age and sex, in combination with at least one of the following: the presence of xanthoma in the patient or first degree relative; an LDL-c ab	52.3% of cohort was LDL-r plus and 47.8% were LDL-r minus. There were significantly different clinical and laboratory profiles between groups with regard to demographic factors, risk factors, physical examination and laboratory parameters. (see results	The patients were individuals whose DNA samples were held at a central laboratory at the Academic Medical Centre of the University of Amsterdam.	This is a Dutch study.	This study aims to determine whether patients with a DNA diagnosis differed significantly from those diagnosed clinically.	The comparison is between patients with LDL-r plus and LDL-r minus status. In the latter case, probable FH has been diagnosed clinically	NA	LDL-r status and presence of tendon xanthoma are the primary and secondary outcome measures
Clinical versus molecular diagnosis of heterozygous familial hypercholesterolaemia in the diverse South African population.	Vergotine J; Thiart R; Kotze MJ;	2001	DIAG	2+	443 at risk family members above the age of 18 . 150/443 (34%) of those screened had disease.		Biochemical versus DNA diagnosis in family members of Afrikaner index patients			TC levels v DNA testing	DNA testing		
Neonatal diagnosis of familial hypercholesterolemia in newborns born to a parent with a molecularly defined heterozygous familial hypercholesterolemia.	Vuorio AF; Turtola H; Kontula K;	1997	COH	2+	25 newborn babies; 30 randomly collected cord blood samples of full term newborns; follow - up samples from 17 of 25 original newborns and from another cohort of 17 children	The babies were children whose mother or father had FH by DNA .	These were Finnish children. There were 9 boys and 14 girls in the original sample.	Unknown	Joensuu, Finland	Discriminative power of serum lipid levels in early diagnosis of FH and to obtain information on changes in serum lips levels in FH patients during the first year of life.	Cord blood DNA samples compared to cord blood lipid levels at birth. A one year follow up of mean serum TC and LDL in original group and a newly recruited group of 1-2 year old affected patients and non-affected siblings.	One year	DNA result; LDL and TC
Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics.	Williams RR; Hunt SC; Schumacher MC; Hegele RA; Leppert MF; Ludwig EH; Hopkins PN;	1993	DIAG	2+	Statistics for FH adults were based on 4 studies (total number of patients not provided). The statistics for HF children were based upon two studies (number of patients not given). For non FH patients, the general population data were taken from the Lipid Research Clinic's		This report presents the statistical rationale and genetic validation for greatly improved criteria for making the diagnosis of heterozygous FH among close relatives of confirmed FH index cases and another set of criteria for diagnosing FH from general population			Statistical cholesterol criteria	DNA testing		

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
					population study of 48,482 persons. The probability of having FH is 50% in those with a first degree relative and 25% in those with a second degree relative.		screening and examinations of normal patients.						

Study results

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
Results from a family and DNA based active identification programme for familial hypercholesterolaemia.	Asbroek AH; de Mheen PJ; Defesche JC; Kastelein JJ; Gunning-Schepers LJ;	2001	Results of total cholesterol using conventional cut off values (6.5 and 8.0 mmol/l) compared with FH status by DNA testing: All Men +FH -FH Untreated 405 (100) 99 (24.4) 306 (75.6) TC 6.1(1.3) 7.3 (1.3) 5.7(1.1) TC<6.5% 272(67.2) 27 (27.3) 245 (80.1) 6.5<TC<8.0 94(23.2) 42 (42.4) 52 (17.0) TC>8.0 39(9.6) 30 (30.3) 9 (2.9) %>C95 27.9 67.7 15.0 All Women +FH -FH Untreated 448 (100) 101 (22.5) 347 (77.5) TC 5.9(1.4) 7.4 (1.4) 5.5(1.1) TC<6.5% 309(69.0) 28 (27.7) 281 (81.0) 6.5<TC<8.0 104(23.2) 44 (43.6) 60 (17.3) TC>8.0 35(7.3) 29 (28.7) 6(1.7) %>C95 26.3 71.3 13.3"	Health Research and Development Council	None	ConclKQQ3-9 This study shows that if in a high risk population of yet untreated, mainly asymptomatic mutation carriers, a single TC level would be used for the diagnosis of FH rather than the current gold standard - that is the presence of an LDL receptor gene mutation - the diagnosis would be missed in more than a quarter of the FH patients. The importance of these findings depends upon whether patients with an LDL receptor gene mutation but without hypercholesterolaemia, experience an increased risk of coronary heart disease and whether they need the same rigorous treatment as other FH patients.	This is a review of over 1000 patients and is thus adequately powered for this comparison.	Yes		
Familial hypercholesterolemia: molecular, biochemical, and clinical characterization of a French-Canadian pediatric population.	Assouline L; Levy E; Feoli-Fonseca JC; Godbout C; Lambert M;	1995	The first objective was to define the molecular basis for hypercholesterolaemia in the 88 paediatric subjects. Heterozygosity for the common French-Canadian LDL receptor gene mutation (>10-kb deletion) was found in 50 subjects (57% - group 1). The presence of one of the other four LDL receptor gene mutation previously identified in this population was noted in 12 patients	Fondation de l'hopital Sainte-Justine	NA	This data suggests that in children, a persistent primary increase in LDL cholesterol associated with a parental history of hyperlipidemia is a good predictor of an underlying monogenic disorder as opposed to a polygenic disorder, at least in French-Canada	The tables and actual values must be evaluated. Assuming the global statements in the report are accurate it would seem that the conclusions of the study are	Yes	Yes	Study is missing essential tables for complete assessment of study results

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			(14% - group 2). None of these five mutations was detected in 26 children (29% - group 3). Clinically, only one patient in group 1 displayed arcus corneae and none had xanthomas. Group 1 Group 2 Group 3 Control P-value TC mmol/l 7.6 (0.1) 6.8 (0.9) 7.3 (1.5) 3.8 (0.6) .0001 LDL mmol/l 6.2 (1.3) 5.3 (1.1) 5.6 (1.5) 2.3 (0.03) .0001 HDL mmol/l 1.03(0.3) 1.05(0.2) 1.2 (0.3) 1.2 (0.4) .0030 There were wide interindividual variations in TC, LDL and apo B among subjects with proven HF in both groups 1 and 3 which was not explained by any of the possible confounders (sex, age, pubertal status, BMI, alcohol , smoking or OCP use)."				valid			
Molecular genetic analysis of 1053 Danish individuals with clinical signs of familial hypercholesterolemia.	Brusgaard K; Jordan P; Hansen H; Hansen AB; Horder M;	2006	The following results are a secondary outcome which is the outcome of interest for this review. All results are in mmol/l: Proband (mutation) Proband (no mutation) Relatives (mutation) Relatives (no mutation) TC 9.82 +/-2.15 8.97 +/-1.55 8.02 +/-2.18 6.23 +/-1.87 HDL 1.53 +/-1.57 1.56 +/-0.53 1.53 +/-0.66 1.51 +/-0.39 TG 2.05 +/-3.25 2.01 +/-1.13 1.43 +/-0.70 1.48 +/-0.96 LDL 7.12 +/-1.96 6.22 +/-1.51 5.73 +/-1.98 4.00 +/-1.64"	Unknown	None	This study demonstrates that levels of LDL and TC are higher in patients with clinical FH and their relatives when they are mutation positive.	This is a large study with a robust methodology and the results are likely to be due to the mutations identified.	Yes	Yes	
The relationship of molecular genetic to clinical diagnosis of familial hypercholesterolemia in a Danish population	Damgaard D; Larsen ML; Nissen PH; Jensen JM; Jensen HK; Soerensen VR; Jensen LG;	2005	Simon Broome definite FH: 61.3 % (49.4-72.4) mutation detection rate. If only these patients were offered molecular genetic analysis the sensitivity would be 34.1% (26.1-42.7)and specificity would be 89.4% (85.1-92.8). The false positive rate							The index patients tested were those at high risk for FH who met two of three criteria: elevated cholesterol; tendon xanthomata; history of coronary artery disease

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
	Faergeman O;		would be 10.6% (7.2-14.9). Dutch Lipid Clinic Network criteria definite FH: 62.9 % (52.0-72.9) mutation detection rate. If only these patients were offered molecular genetic analysis the sensitivity would be 41.5% (33.1-50.3)and specificity would be 89.4% (83.4-91.5). The false positive rate would be 12.1%(8.5-16.6). If patients with a diagnosis of possible FH are included in molecular genetic analysis, both set of criteria result in high sensitivities (90.4 and 99.3% respectively) with correspondingly lower mutation detection rates (38.3 and 34.3% respectively). Patients with LDL-c >95th percentile(%) Mutation carriers(Index); Non carriers(Index); 94.7% 70.5% Mutation carriers (relative);Non carrier (relative) 67.0% 6.5% Patients with LDL-c >90th percentile(%) Mutation carriers(Index); Non carriers(Index); 99.2% 91.2% Mutation carriers (relative);Non carrier (relative) 76.5% 14.7% The authors conclude that either inadequacy of the molecular genetic analysis or a more complex, polygenic background for the FH phenotype, must be invoked to explain that almost 40% of patients with definite FH by clinical criteria did not have an identifiable mutation in either LDL receptor gene or the apoB gene."						before age 60 in patient or first degree relative.
Mutation screening and genotype:phenotype correlation in familial hypercholesterolaemia.	Graham CA; McClean E; Ward AJ; Beattie ED; Martin S; O'Kane M; Young IS; Nicholls DP;	1999	Mutation n Age TC LDL TX Frameshift 12 38.5 +/-12.9 11.4 +/- 1.8 9.3 +/-1.7 83% Nonsense 8 39.4 +/-14.2 10.3 +/- 1.7 8.5 +/-2.0 50% Mis-sense 21 41.0 +/-17.3 10.1	Northern Ireland Chest, Heart and Stroke Association	None	The following findings were of interest: The presentation of tendon xanthomata occurred in only 57% of families with a defined mutation. Cholesterol levels observed in the FS group were highest Eight clinically definite FH families	The methodology was sound and results are plausible	Yes		

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			+/- 1.7 7.8 +/-1.9 62% FDB-R3500Q 8 44.3 +/-12.2 8.8 +/- 1.3 6.4 +/-1.4 25% No mutation 8 47.8 +/-9.2 10.2 +/- 1.5 8.3 +/-1.8 100%"			had no identified mutation"				
Genetic screening protocol for familial hypercholesterolemia which includes splicing defects gives an improved mutation detection rate.	Graham CA; McIlhatton BP; Kirk CW; Beattie ED; Lyttle K; Hart P; Neely RD; Young IS; Nicholls DP;	2005	In this study the non-coding intron splice regions of the LDLR gene were included. In families with definite FH (n-68) the improved genetic screening protocol increased the detection rate of mutations was 87% compared to 80% in a previous study by the same researchers. The use of a limited screen (limitations not described) in patients with possible FH resulted in a detection rate of 26%. The overall total of 93 definite FH families had a total of 44 distinct LDLR mutations.	British Heart Foundation	None reported	This study proposes the expansion of the basic DNA screen to include two additional exons (12 and 15) to increase detection rates.	Yes	Yes	Yes	
The use of Achilles tendon sonography to distinguish familial hypercholesterolemia from other genetic dyslipidemias.	Junyent M; Gilabert R; Zambon D; Nunez I; Vela M; Civeira F; Pocovi M; Ros E;	2005	OutcomesQ3-7 "Concordance between physical examination and sono in the diagnosis of xanthoma Physical examination Normal sono Xanthoma + Total DNA + FH Normal 23 23 46(57%) Xanthoma 3 32 35(43%) Total 26(32%) 55 (68%) 81 DNA - FH Normal 23 13 36(22%) Xanthoma 2 8 10(22%) Total 25(354%) 21 (46%) 46"	Fondo de Investigaciones Sanitarias, Spanish Ministry of Health and RT and Fundacio Privada Catalana de Nutricio I Lipids.	None	Application of AT thickness thresholds to individuals with clinical FH and no DNA diagnosis classified 41% of them as FH. Future refinements of molecular testing should clarify diagnoses in this ill defined group of clinically severe hypercholesterolemia				
Rising cholesterol levels in children with familial hypercholesterolaemia.	Kessling AM; Seed M; Taylor R; Wynn V; Humphries SE;	1990	Mean cholesterol feral boys was higher than for all girls but not significantly different. Of the 85 children with first degree FH relatives 39 (46%) had a cholesterol level above the appropriate 95th percentiles for age and gender. Eighteen of the remaining 46 children with cholesterol levels below the childhood 95th percentile were followed with serial cholesterol measurements. Eleven of these children showed a small	Heart Disease and Diabetes Research Trust, the British Heart Foundation and the Charing Cross Sunley Research Trust.	None	Children whose cholesterol levels are below the 95th percentile for age and gender may not be detected using this marker alone. Levels appear to rise over time and may not be evident in early childhood. The authors suggest that genetic testing should be	This is a small study but the results are plausible.	Yes	Yes	This is a cross sectional study on children with no FH or medical pre-disposition to hypercholesterolaemia and a longitudinal study on cholesterol levels in a subgroup of these child and in a group of first degree relatives of individuals with FH who are

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			elevation with a mean year to year increase of 0.096mmol/l, sem 0.080 (ns difference to control). Seven of the children showed marked increases in serum cholesterol levels over an interval of 1-7 years, reaching above 95th percentile (about 5.6mmol/l per graph presented in the paper), which was significantly different to control with mean year to year change of 0.34 mmol/l, sem 0.062 ($p<0.01$). Thus children who would not have been diagnosed as having FH on initial cholesterol level, developed hypercholesterolaemia consistent with a diagnosis of FH. The diagnosis of FH was confirmed retrospectively in three of these children. It is important to note that 6 of the 7 children were under the age of thirteen when first tested.							
Diagnosis of Heterozygous Familial Hypercholesterolemia - DNA Analysis Complements Clinical Examination and Analysis of Serum-Lipid Levels	Koivisto PVI; Koivisto UM; Miettinen TA; Kontula K;	1992	OutcomesQ3-7 "The enrichment of a specific LDL receptor gene mutation in the Finnish population facilitates an unequivocal discrimination between FH and non-FH members of families. All patients in the study had a family history of FH. Using DNA testing as the 'gold standard' A correct clinical diagnosis occurred in 55 (85%) of 65 subjects. In the age group <18 years only two of the five FH children were correctly diagnosed clinically because the serum LDL levels in the remaining three patients were lower than diagnostic limits. When age and sex specific LDL cholesterol concentration curves were used permitted correct diagnosis in 95% of subjects with a family history. Two of the four undiagnosed patients were children. The other two patients had co-morbidities. Xanthomatosis was demonstrated in 17 of the 25 adult DNA verified FH patients (68%) but in none of the non FH patients. Xanthomatosis was also suspected in one young and six adult FH patients. Thus, only two (8%) of the 25 adult FH patients were totally free of signs of xanthomatosis."	Unknown	None	The authors conclude that in individuals belonging to FH families may be correctly classified using age, population and sex specific 95th percentile values for serum LDL . In doubtful cases and in particular in the evaluation of children, detection of an	This study of 65 subjects, 10 with confirmed FH and 55 first degree relatives from 10 families with FH provides an interesting population for comparison of methods of diagnosis and the results are plausible.	Yes	Yes	
Sonography of the Achilles tendon in hypercholesterolaemia.	Koivunen-Niemela T; Alanen A; Viikari J;	1993	OutcomesQ3-7 " FH patients Non FH Controls n=40 n=51	Berner Co., Helsinki provided the equipment for the study	None	US offered a sensitive, rapid and safe method for detecting xanthomas however the presence of xanthoma is not absolutely specific.	The accuracy of the study results is not questioned.	Yes	Yes	

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			n=41 Achilles tendon thickness (mm) 11.0+/-0.5 7.3 +/-0.2 7.1 +/-0.2 Thickened tendons 25/40 2/51 0/41 Low or mixed echogenicity of tendons 36/40 3/51 0/41 FH could not be confirmed by DNA testing in the three non-FH patients with tendon xanthoma"							
Sonography in the detection of Achilles tendon xanthomata in children with familial hypercholesterolaemia.	Koivunen-Niemela T; Viikari J; Niinikoski H; Simell O; Alanen A;	1994	OutcomesQ3-7 There were no structural abnormalities found in the control population. The tendons of the FH children were significantly thicker (mean +/- SD 7.1 +/- 1.5 (range 5-10) mm) than controls (5.8 +/- 1.0 (3-7)mm) (p=0.0001). Achilles tendon US were abnormal in 33% (3/9) of children aged <10 years and in 42% (5/12) of children aged 10-18 years. Interestingly, only four of the eleven LDL-r positive children had evidence of xanthomata. One was age 3, one age 8 and one age 15. One boy aged 9 years who was LDL-r positive developed hypoechoic areas on US when he was re-studied after two years. Five of seven children with a family history had xanthomata and the three children with a first degree relative with positive LDL-r had no evidence of xanthomata.	Unknown	None	This study indicates that while Achilles tendon xanthomata may be detected by US before they are clinically palpable, they are not necessarily present in children with confirmed disease.	This is a small study but the results are plausible.	Yes	Yes	Normocholesterolaemic siblings formed part of the control group. These are also 'at risk' children and it is possible that rises in cholesterol above normal limits have not yet been observed due to young age.
Familial hypercholesterolemia: potential diagnostic value of mutation screening in a pediatric population of South Africa.	Kotze MJ; Peeters AV; Loubser O; Theart L; du P; Hayes VM; De J; de V; Lombard CJ; Hansen PS; Raal FJ;	1998	Mean plasma lipid levels FH Non-FH Male/female 60/56 50/54 Age (years) 11(4) 12(4) TC (mmol/l) 7.7 (1.3) 4.70(0.7) LDL (mmol/l) 6.0 (1.3) 2.8 (0.6) HDL (mmol/l) 1.2 (0.3) 1.3(0.3) TG (mmol/l) 1.0(0.6) 1.1(0.7) Among these children a TC level of 6mmol/l was the best at discriminating	South African Medical Research Council and the Universities of Stellenbosch and Witwatersrand.	None	It is possible to use cholesterol levels for diagnosis in those with a family history of FH but in the general population the specificity would not be adequate.	The study accuracy is not questioned.	Yes	Yes	

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			between FH and non FH. Using this value 4.5% of the total group of 220 children would have been misdiagnosed compared with 11.4% using the 80th percentile and 7.7 using the 95th percentile for age and sex. In total, 8/116 (6.9%) of the children with an FH mutation were falsely classified as normal (negative predictive value of 93%) whilst 2/104 (1.9%) without the mutation were falsely classified as FH (positive predictive value of 98%). The sensitivity and specificity of FH diagnosis according to TC values were 93 and 98% when testing children from FH families where the prevalence is expected to be 50%. The sensitivity, specificity and predictive values would be considerably lower in the general population."							
Neonatal diagnosis of familial type-II hyperlipoproteinaemia.	Kwiterovich PO; Levy RI; Fredrickson DS;	1973 Jan 20	OutcomesQ3-7 " TC mmol/l HDL mmol/l LDL mmol/l Controls 1.9+/-.28 .42+/.09 0.79+/.15 Positive 2.56+/.38 .34+/.79 1.59+/.41 p-value(v. control) <0.001 <0.005 Not done Negative 1.87+/.33 .82+/.10 0.85+/.13 p-value(v. control) NS NS NS Among 19 children from whom later samples were obtained at age 1-2 1/4 years seven had been considered to have normal LDL levels at birth and at follow up all seven had LDL cholesterols <4.36 mmol/l which was the upper limit for age 1-19. Only one of the 12 children considered to have hyperbetalipoproteinaemia at birth had a normal LDL at follow up. This infant had been on a strict low cholesterol diet since birth. The correlation between TC and LDL improved at follow up."	Unknown	None	These results indicate that the concentration of LDL in cord blood may permit the ascertainment of an affect child of a parent with FH.	The sample size in small and this study should be repeated.	Early study with no precedant	Yes	
Familial hypercholesterolemia (one form of familial type II hyperlipoproteinemia). A study of its biochemical, genetic and clinical presentation in childhood.	Kwiterovich POJ; Fredrickson DS; Levy RI;	1974	The natural logarithm of the LDL from 217 was plotted and the observed distribution was bimodal and two populations were derived by the maximum likelihood method. The 'antimod' was 4.2mmol/l and 55% of the observations were in the left	Unknown	None	The data provide a statistical confirmation of a bimodal distribution of LDL levels among affected and non affected children which may be helpful in setting diagnostic criteria in high risk individuals	Yes the effect appears to be related to the laboratory values under investigation	Yes	Yes	

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			distribution. 7.2%							
Diagnosing Familial Hypercholesterolemia in Childhood by Measuring Serum-Cholesterol.	Leonard JV; Whitelaw AGL; Wolff OH; Lloyd JK; Slack J;	1977	The natural logarithm of the LDL from 217 was plotted and the observed distribution was bimodal and two populations were derived by the maximum likelihood method. The 'antimod' was 4.2mmol/l and 55% of the observations were in the left distribution. 7.2% of the children in the normal (left) population were above the cut point (false positives) and 9.7% of those in the affected (right) population were below the cut point (false negatives). When TC was plotted in 236 children the degree of overlap was sufficiently great so that the sum of the two population was not bimodal but bitangential. The antimode for TC was 6.03 mmol/l. 8.5% of children in the normal (left) population were above the cut point (false positives) and 18.9% of the children in the affected (right) population were below the cut point (false negatives). The analysis of the data collected for this study also support the hypothesis (at the time of this study) that FH is inherited as a monogenic train with early expression in children."	Unknown	None	This study identifies potential misdiagnosis of FH in children using serum total cholesterol levels.	This small study does not clarify diagnostic criteria and notes that in some cases TC was not obtained at the hospital. There were also cases in which non-fasting samples were used. Further studies are required.	Yes	Yes	The defining characteristics of FH which differentiated the two groups have not been clearly described.
Cutoff point separating affected and unaffected familial hypercholesterolemic patients validated by LDL-receptor gene mutants	Mabuchi H; Higashikata T; Nohara A; Lu H; Yu WX; Nozue T; Noji Y; Katsuda S; Kawashiri MA; Inazu A; Kobayashi J; Koizumi J;	2005	Distributions of serum total cholesterol and LDL cholesterol showed distinct bimodality when graphed, while HDL and log TG levels did not. A TC of 225 mg/dl (5.77 mmol/l) and an LDL cholesterol of 160 mg/dl (4.10 mmol/l) were seen to be the cutoff points between normal subjects and FH patients. Sensitivity and specificity of these criteria were tested by ROC analysis of a sample of 281 sequentially sampled first and second degree relatives in which the diagnosis of FH was established using genetic markers. The proposed total cholesterol criteria of 224mg/dl (5.74 mmol/l) and 225 mg/dl (5.77 mmol/dl) were in agreement with DNA marker, resulting in an observed specificity of 98.5% and sensitivity of 99.4%. LDL-c cutoffs of 161 mg/dl (4.13mmo/l) to 163 mg/dl (4.18mmol/dl) produced an observed specificity of 98.5% and a sensitivity of 98.3%. Three of the 181 FH patients showed LDL-0c levels less than 160 mg/dl (4.10 mmol/l) and none of the non-FH patients showed	Unknown	None	As a result of this study an LDL-c concentration of 160 mg/dl (4.10 mmol/l) and a total cholesterol of 225 mg/dl (5.77 mmol/l) had the best ability to discriminate between subjects with and without FH.	Limited sample size (181 patients) and Japanese population but results appear to be robust.	Yes	Yes	

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			LDL -c levels higher than 160 mg/dl.							
Heterozygous familial hypercholesterolemia in children: low-density lipoprotein receptor mutational analysis and variation in the expression of plasma lipoprotein-lipid concentrations.	Torres AL; Moorjani S; Vohl MC; Gagne C; Lamarche B; Brun LD; Lupien PJ; Despres JP;	1996	Controls FH >15 kb FH C646Y FH W66G N= 120 188 21 57 Age (years) 9.05 + 4.63 8.21+4.14 7.06+ 4.09 8.00 + 4.12 TC (mmol/l) 4.32 + 0.60 8.17+1.45 8.18+ 1.53 7.19 + 1.23 LDL (mmol/l) 2.60 + 0.56 6.58+1.42 6.65+ 1.50 5.62 + 1.16 HDL (mmol/l) 1.26 + 0.29 1.11+0.23 1.08+ 0.28 1.14 + 0.20 TG (mmol/l) 1.04 + 0.40 1.09 +0.49 1.24+ 0.76 1.01 + 0.43 TC/HDL ratio 3.56 + 0.82 7.70+2.15 8.25+ 3.35 6.48 + 1.57 Plasma TC and LDL levels were significantly lower in mutation W66G which is a defective mutation compared to >15 kb and C646Y ($p<0.05$). In the latter groups TC and LDL were essentially similar. The significant differences between mutation groups remained when results were analyzed by gender. Effects of gender and age were also studied."	Fonds de la rechereche en sante du Quebec; Hydro-Quebec.	None	This study demonstrated that the LDLR gene type mutations found in heterozygous FH children modulate the magnitude of elevation in plasma TC and LDL-C and hence may have important implications for the progression of disease and for the onset of manifestation	The results of this study are likely to be accurate.	Yes	Yes	
Review of first 5 years of screening for familial hypercholesterolaemia in the Netherlands.	Umans-Eckenhausen MA; Defesche JC; Sijbrands EJ; Scheerder RL; Kastelein JJ;	2001								
Diagnosing familial hypercholesterolaemia: The relevance of genetic testing.	van Aalst Cohen ES; Jansen ACM; Tanck MWT; Defesche JC; Trip MD; Lansberg PJ; Stalenhoef AFH; Kastelein JJP;	2006	"Significant difference in clinical and laboratory profiles between LDL-r plus and LDL-r minus patients: LDL-r plus, n=1255 LDL-r minus, n=1145 p-value Male gender 45.8 % (575/680) 52.8% (605/540) <0.001 Age at first visit 42.1 (+/-12.6) 47.6 (=/-12.2) <0.001 Smoking,ever 68.7%(787/359) 79.5 (811/209) <0.001 Hypertension 7.8 (97/1146) 11.7 (133/1000) 0.001 First degree family hx 56.4 (596/460) 65.5 (664/350) <0.001	Netherlands Heart Foundation	None	The phenotypic heterogeneity detected in this cohort challenges the value of the current clinical criteria including use of LDL-c at less than 95th percentile and the presence of tendon xanthomas. Corneal arcus and positive family history for premature C	This is an excellent cohort study and the sample size supports the validity of the findings.	Yes	Yes	Well conducted multicentre cohort study

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			BMI 24.7 (+/-3.4) 25.6 (+/-3.6) <0.001 Systolic BP 133 (+/-19) 137 (+/-20) <0.001 Diastolic BP 81 (+/-10) 83 (+/-10) <0.001 Xanthoma 41.8 (489/682) 40.2(419/624) 0.462 TC (mmol/l) 10.25(+/-2.13) 8.80(+/-1.54) <0.001 LDL 8.18(+/-2.05) 6.61(+/-1.47) <0.001 HDL 1.19 (+/-0.35) 1.23(+/-0.36) 0.003 TG 1.39 (0.98-2.03) 1.71(1.24-2.35) <0.001 Glucose 4.9 (4.5-5.3) 5.0 (4.6-5.5) <0.001"							
Clinical versus molecular diagnosis of heterozygous familial hypercholesterolaemia in the diverse South African population.	Vergotine J; Thiart R; Kotze MJ;	2001	OutcomesQ3-7 "The sensitivity and specificity of FH diagnosis according to TC values (80th percentile) were 89.3% and 81.9% respectively. Evaluation of biochemical versus DNA diagnosis revealed that 15.6% of cases may be misdiagnosed when the 80th percentile is used as a biochemical cut-off point for a diagnosis of FH compared with 12.4% using the 95th percentile for age and gender. In total, 16/150 relatives (10.7%) with an FH mutation were falsely classified as normal (negative predictive value of 89.3%), while 53/293 (18.1%) without the mutation were falsely classified as FH heterozygotes (positive predictive value of 81.9%)."	University of Stellenbosch, Tygerberg Hospital, the South African Medical Research Council, the Technology and Human Resources for Industry Programme and a grant from Merck & Co.		DNA testing may provide a definitive tool for family tracing in asymptomatic individuals. Although lipid levels did not result accurate diagnosis of FH in all cases, likewise the specificity of DNA testing may also result in cases missed.			Yes	Yes
Neonatal diagnosis of familial hypercholesterolemia in newborns born to a parent with a molecularly defined heterozygous familial hypercholesterolemia.	Vuorio AF; Turtola H; Kontula K;	1997	OutcomesQ3-7 "Of 25 babies born to an FH parent, 14 were DNA positive and 11 were non affected. Mean TC and LDL cholesterol levels in cord serum were significantly elevated (p<.001) in the affected newborns compared to non-affected or controls. Group (n) TC mmol/l LDL mmol/l HDL mmol/l TG mmol/l Controls(30) 1.84 +/-0.46 1.03 +/-0.30 0.75 +/-0.24 0.13+/-0.08 DNA neg (10) 1.54 +/-0.23 0.78 +/-0.15 0.63 +/-0.14 0.28+/-0.23	Finnish Academy of Sciences, the Sigrid Juselius Foundation, the University of Helsinki, the Paulo Foundation, the Finnish Heart Foundation, the Orion Corporation Research Foundation, Finnish Cultural Foundation and the Finnish Medical Society Duodecim.	None	This study, using DNA diagnosis, indicates that serum LDL levels are an unreliable diagnostic method in newborns but are more discriminatory at age 1 year.	This is a small study but the results are interesting and should be discussed in deciding screening and diagnostic methods in children.	Yes	Yes	

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			DNA pos (14) 2.60 +/-0.70 1.77 +/-0.56 0.69 +/-0.23 0.29+/-0.24 DNA neg, age 1(16) 4.40 +/-0.66 2.89 +/-0.68 1.16 +/-0.15 0.78+/-0.39 DNA pos, age 1 (18) 8.38 +/-1.18 7.02 +/-1.07 0.95 +/-0.14 0.93+/-0.40 Mean TC and LDL levels in cord serum were significantly elevated in the affected newborns compared to the non-affected or controls. There was however, a considerable overlap between the ranges of individual lipid levels in these three groups . The mean serum TC and LDL in the combined two non-affected groups would yield 95th percentile values of 2.60 and 1.44mmol/l. If these levels were used as diagnostic criteria then only 5 or 6 of the 14 DNA pos newborns would have been correctly."						
Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics.	Williams RR; Hunt SC; Schumacher MC; Hegele RA; Leppert MF; Ludwig EH; Hopkins PN;	1993	OutcomesQ3-7 The statistical concept of a priori probabilities was applied to derive 2 sets of practical screening criteria: one for persons participating in general population screening studies and another for close relatives of confirmed FH cases, showing dramatic differences. At a cholesterol level of 310 mg/dl (7.95 mmol/l) only 4% of persons in the general population would have FH but 95% of persons who were first degree relatives of known cases would have FH. In population screening the calculated FH criteria required a TC >360 mg/dl (9.23 mmol/l) for age 40+ or 270 mg/dl (6.92 mmol/l) in youth under 18 years. Among first degree relatives of confirmed cases in families with FH the new TC is much lower - 290 mg/dl (7.44 mmol/l) for age 40+ and >220 mg/dl (5.64 mmol/l) in youth under 18. These criteria were validated among 207 persons in 5 large FH pedigrees in whom genetic testing established (n=75) or ruled out (n=132) the diagnosis of FH revealing 98% specificity and 87% sensitivity. Using the proposed LDL cholesterol criteria the sensitivity was 91% while specificity was again 98%.	Unknown		These new cut off points potentially provide substantial improvement in the sensitivity of diagnosing FH in relatives of known cases and better specificity for diagnosing FH in population screening.			Yes	Yes

Question 2: What is the cardiovascular risk of people with suspected FH: (i) who have a confirmed DNA mutation or (ii) who do not have a confirmed DNA mutation?

Study descriptions

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
Impact of genetic defects on atherosclerosis in patients suspected of familial hypercholesterolaemia	Descamps OS; Gilbeau JP; Leysen X; Van L; Heller FR;	2001	COH	2+	273 patients were evaluated; 122 were identified as FH patients	Patients had severe hypercholesterolaemia and a family history of early cardiovascular disease. Patients with a previous history of CV disease and patients with hyperlipoproteinaemia type III were excluded.	There were 150 men and 123 women in the study; mean age of non FH men was 46.6 (9.3) and FH men was 44.8 (10.8); NS. The mean age of FH women was 46.0 (11.9) and 51.5 (11.0); p=0.01. 3% of FH men were diabetic and 15% of non FH men had this diagnosis; p=	Patients were in part, recruited by GPs in local practices.	Centre Hospitalier Jolimont-Lobbs, Belgium	Atherosclerosis	FH and non FH patients are compared by evaluating IMT in carotid and femoral arteries	This is a cross sectional study	Measurements of carotid and femoral IMT
Impact of genetic defects on coronary atherosclerosis in patients suspected of having familial hypercholesterolaemia	Descamps OS; Gilbeau JP; Luwaert R; Heller FR;	2003	COH	2+	235 patients; 95 patients were classified as FH patients and 140 as non-FH patients.	All patients had severe hypercholesterolaemia (above 95th percentile for age and sex and a family history for early cardiovascular disease). Patients with a known history of CHD or abnormal resting ECG and women below 35 years of age were excluded.	There were 141 men and 94 women in the study; mean age of non FH men was 46.7 (9.2) and FH men was 45.0 (10.8); NS. The mean age of FH women was 48.9 (8.5) and 53.8 (9.0); p<0.01. 4% of FH men were diabetic and 15% of non FH men had this diagnosis; p=0.0	Patients were recruited in lipid clinics involved in the study.	Centre Hospitalier Jolimont-Lobbs, Belgium	Coronary calcification and exercise stress testing	FH and non FH patients are compared by evaluating coronary calcification and exercise stress testing	This is a cross sectional study	Presence or absence of coronary calcification and positive or negative exercise stress test
Relationships of abdominal obesity and hyperinsulinaemia to angiographically assessed coronary artery disease in men with known mutations in the LDL receptor gene	Gaudet D; Vohl MC; Perron P; Tremblay G; Gagne C; Lesiege D; Bergeron J; Moorjani S; Despres JP;	1998	COH	2+	120 FH patients and 280non FH patients	Unrelated patients aged <60 who underwent coronary angiography . All patients were DNA tested.	All patients were men who had undergone coronary angiography for investigation of ischemic heart disease (typical angina or a positive exercise tolerance test or both). Mean age of FH patients was 46.7 +/- 0.7 and of non-FH was 46.9 +/- 0.4.	Unknown	Chicoutimi Hospital Clinic, Quebec	The primary purpose of the study was to assess the relationships of abdominal adiposity to CAD among men with and without DNA verified FH	FH and non-FH patients are compared with regard to CAD, BMI, abdominal obesity and lipid levels	This is a cross sectional study	The primary outcome measure is abdominal obesity. However, for the purposes of this review the comparison of CAD in FH and non FH men is of interest and is the outcome reported.
Genetic causes of familial hypercholesterolaemia in patients in the UK: relation to plasma lipid levels and coronary heart disease risk	Humphries SE; Whittall RA; Hubbart CS; Maplebeck S; Cooper JA; Soutar AK; Naoumova R;	2006	CC	2+	409 total patients. 251 controls and 158 cases.	Inclusion in the Simon Broome Register (further information not reported)	Caucasian patients who form part of the Simon Broome Register aged 18 years or above with treated heterozygous familial hypercholesterolemia,	409	UK study.	Presence of LDLR, ApoB, PCSK9 mutations.	CHD status compared to presence of DNA mutations in genes LDLR, ApoB and PCSK9.	Cross-sectional study not applicable.	Primary outcome: risk (defined as the odds ratio of having CHD) compared with the presence of

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
	Thompson GR; Seed M; Durrington PN; Miller JP; Betteridge DJ; Neil HA; Simon B;						with or without clinically documented CHD.						LDLR, ApoB, PCSK9 mutations. Secondary outcome post-statin lipid profiles compared with the presence of LDLR, ApoB, PCKS9 mutations.
Carotid intima-media thickness and plaque in patients with familial hypercholesterolaemia mutations and control subjects	Tonstad,S.; Joakimsen,O.; Stensland-Bugge,E.; Ose,L.; Bonaa,K.H.; Leren,T.P.	1998	COH	2+	79 subjects and 79 controls	Subjects: non smoking men and women between ages of 26 and 46 with a DNA based diagnosis of FH and no known cardiovascular disease. Controls: non smoking individuals from Tomso who were matched to each case by age (+/- 3 years) and sex and BMI.	Mean age 38 years; female to male 38/41 in each group; BMI 26.1	Subjects registered at lipid clinic, National Hospital, Oslo	Oslo, Norway	Carotid intima media thickness in patients with FH and in controls	Presence or absence of thickening and or plaque	This is a cross sectional study	Carotid IMT & presence of plaque are primary outcomes. Lipid levels are secondary outcomes
Low-density lipoprotein receptor gene mutations and cardiovascular risk in a large genetic cascade screening population	Umans-Eckenhausen MA; Sijbrands EJ; Kastelein JJ; Defesche JC;	2002	COH	2+	1695 relatives of 66 index patients were screened for the LDL receptor gene mutation	Only relatives of index cases were included. Participation rate was 90%. Index cases were excluded.	The mean age differed significantly between treated and untreated carriers: 47 +/- 0.9 years versus 31 +/- 1.1 years, respectively ($p<0.001$). The proportion of men was similar in the two groups: 47% +/- 3% and 49% +/- respectively ($p=0.7$).	Patients were recruited through the nation genetic testing program for FH in the Netherlands	University of Amsterdam, The Netherlands	Lipoprotein levels and risk of CVD	FH and non FH patients as well as patients with different LDL receptor gene mutations	This is a cross sectional study	RR of CVD in patients with and without +DNA test for FH
Low-density lipoprotein receptor gene mutation analysis and clinical correlation in Belgian hypercholesterolaemics	Van Gaal LF; Peeters AV; De B; de L; Thiart R; Kotze MJ;	2001	COH	2+	98 patients	The patients were unrelated hyperlipidaemic individuals with TC >6.5 mmol/l and LDL >4.7 mmol/l and a minimum of two additional first degree relatives with hypercholesterolaemia. Subjects with secondary causes of hyperlipidaemia, triglyceride levels > 4.	There were 44 males and 54 females; 24 were DNA + and 61 were DNA -. The average age of DNA + patients was 46 (9-72) and the DNA - patients was 52 (20-72).	The patients attended the lipid clinic of the University Hospital of Antwerp.	University Hospital, Antwerp	Cardiovascular status among FH and non FH patients	The objectives of the study were to define the spectrum of LDLR gene mutations and to determine possible differences in lipid profile and clinical cardiovascular status between DNA + and DNA - patients.	This is a cross sectional study	Biochemical and cardiovascular data in patients with and without LDLR mutation

Study results

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
Impact of genetic defects on atherosclerosis in patients suspected of familial hypercholesterolaemia	Descamps OS; Gilbeau JP; Leysen X; Van L; Heller FR;	2001	OutcomesQ3-7 " FH patients Non FH patients P-value Unadjusted Men Carotid artery IMT (mm) 1.27 +/- 0.47 1.00+/-0.40 <0.001 Femoral artery IMT (mm) 1.30 +/- 0.53 1.08 +/-0.46 0.01 Women Carotid artery IMT (mm) 1.04 +/- 0.45 0.93+/-0.33 0.15 Femoral artery IMT (mm) 1.05 +/- 0.49 0.84 +/-0.32 0.01"	Hospital of Jolimont	None	Patients with genetically ascertained FH had a higher degree of atherosclerosis than non FH patients in the carotid and femoral arteries. The study reinforces the idea that the precise identification of FH by DNA testing may be useful in proper cardiovascular risk assessment and especially in primary prevention.	The results of this study are plausible.	Yes	Yes	
Impact of genetic defects on coronary atherosclerosis in patients suspected of having familial hypercholesterolaemia	Descamps OS; Gilbeau JP; Luwaert R; Heller FR;	2003	OutcomesQ3-7 "Coronary calcification was present in 75% of FH men compared with 44% of non FH men (OR 3.90, [95% CI 1.85-8.18]; p<0.001) and in 53% of the FH women compared with 31% in the non-FH women (OR 2.65 [95% CI 1.14-6.15]p<0.01). Forty two FH men, 66 non FH men, 32 FH women and 36 non-FH women had an interpretable exercise stress test. Positive EST was present in 38% of the FH men compared with 9% of the non FH men (OR 6.15 [95% CI 2.16-17.49]; p<0.01) and in 22% of FH women compared with 6% of the non FH women (OR 4.76 [95% CI 0.91-24.85]; p=0.06. The ESTs were positive only on the basis of ECG criteria and none of the patients complained of angina-like chest pain during the test."	Unknown	None	The study demonstrates that among patients with severe hypercholesterolaemia and a family history of early CVD, those with FH are more likely to have a positive exercise stress test and coronary calcifications on CT scan than those without FH.	The results of this study are plausible given sample size and methodology.	Yes	Yes	
Relationships of abdominal obesity and hyperinsulinaemia to angiographically assessed coronary artery disease in men with known mutations in the LDL receptor gene	Gaudet D; Vohl MC; Perron P; Tremblay G; Gagne C; Lesiege D; Bergeron J; Moorjani S; Despres JP;	1998	OutcomesQ3-7 "Outcome of interest: FH Non FH P-value n=120 n=280 Number of diseased vessels (% of patients)	Fonds de la Recherche en Sante du Quebec and by Hydro-Quebec.	None	The study shows a significant difference in sever heart disease among FH patients compared to non FH patients in their mid forties. It also shows that abdominal obesity and hyperinsulinaemia appear to be important risk factors for CAD even among well char	The results of this study are plausible based on sample size and method.	Yes	Yes	

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			0 vessels with >50% stenosis 6(5.0%) 31(11%) .0001 1 vessel with >50% stenosis 27(22.5%) 98(35.0%) .005 2 vessels with >50% stenosis 30(25%) 72(25.7%) .96 3 vessels with >50% stenosis 28(23.3%) 58(20.7%) .65 4 vessels with >50% stenosis 29(24.1%) 21(7.5%) .0001 Other outcomes of interest: BMI 26.0+/-0.3 27.9+/-0.3 .0001 Waist circumference 92.3 +/- 0.8 97.6 +/-0.7 .0001 Waist-to-hip ratio 0.92+/-0.01 0.96+/-0.01 .0001 Fasting insulin, mU/L 16.2+/-0.8 19.0+/-0.7 .02"							
Genetic causes of familial hypercholesterolaemia in patients in the UK: relation to plasma lipid levels and coronary heart disease risk	Humphries SE; Whittall RA; Hubbart CS; Maplebeck S; Cooper JA; Soutar AK; Naoumova R; Thompson GR; Seed M; Durrington PN; Miller JP; Betteridge DJ; Neil HA; Simon B;	2006	After adjusting for age, sex smoking and systolic blood pressure, compared to those with no detectable mutation, the odds ratio of having CHD in those with an LDLR mutation was 1.84 (95% CI 1.10 to 3.06), for ApoB 3.40 (0.71 to 16.36), and for PCSK9 19.96 (1.88 to 211.5; p=0.001 overall). The post-statin treatment lipid profile in PCSK9p.Y374 carriers was worse than in patients with no identified mutation (LDL-C, 6.77 (1.82) mmol/l v 4.19 (1.26) mmol/l, p=0.001, HDL-C 1.09 (0.27) mmol/l v 1.36 (0.36) mmol/l, p=0.03). Overall, there was an 84% higher risk of CHD in those with an identified LDLR mutation compared with those with no detected mutation. There was also a relatively high frequency and extremely high risk of CHD in carriers of the PCSK9 p.D374Y."	British Heart Foundation.	Not applicable.	Yes, the main conclusions were that mutations in genes LDLR, ApoB and PCSK9 increased the risk of heart disease with patients with heterozygous FH compared to patients with unidentified mutations. This directly answer the KCQ question above.	The sample size for this population size was reasonable, and the data definitely indicates that the overall effect on heart disease is due to the identified mutations, they have adjusted for most all other risk factors. Long-term follow up of patients would	Unknown	Direct comparison (although is does not include homozygous FH patients)	
Carotid intima-media thickness and plaque in patients with familial hypercholesterolaemia mutations and control subjects	Tonstad,S.; Joakimsen,O.; Stensland-Bugge,E.; Ose,L.; Bonaa,K.H.; Leren,T.P.	1998	FH (male) Controls (male) FH (female) Controls (female) n 41 41 38 38 Carotid IMT Mean, far wall (mm) 0.61(0.13) 0.55(0.14)* 0.52(0.09) 0.53 (0.07) Max, far wall (mm) 0.74(0.15) 0.68(0.16) 0.65(0.11) 0.65(0.09) Carotid bifurcation IMT Mean, far wall (mm) 0.81(0.15) 0.74(0.19)** 0.74(0.17) 0.66							

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			(0.15)** Max, far wall (mm) 1.08(0.27) 0.97(0.35)** 0.99(0.31) 0.85(0.23)** Carotid plaque yes/no 22/19 8/35*** 21/17 3/35*** *p=0.03 **p=0.01 ***p=0.0001 compared with FH"							
Low-density lipoprotein receptor gene mutations and cardiovascular risk in a large genetic cascade screening population	Umans-Eckenhausen MA; Sijbrands EJ; Kastelein JJ; Defesche JC;	2002	Unadjusted risk for CVD Adjusted risk for CVD All mutations (n=608 carriers/1087 non-carriers) RR=4.00 (95%CI 2.83-5.65) RR=8.54 (95%CI 5.29-13.80) Patients with FH had onset of CVD symptoms at a younger age."	Dutch Ministry of Public Health, Welfare and Sport, the Health Care Insurance Council and the Netherlands Hert Foundation.	None	A clear geno-type/ pheno-type relationship exists between specific LDL receptor mutations, plasma lipids and CVD burden. However, independent of lipoprotein profiles additional familial risk factors contributed to the CVD burden of FH.	Yes, the results of this study are plausible.	Yes	Yes	
Low-density lipoprotein receptor gene mutation analysis and clinical correlation in Belgian hypercholesterolaemics	Van Gaal LF; Peeters AV; De B; de L; Thiart R; Kotze MJ;	2001	Mutation + Mutation - P-value Total 24 61 Coronary heart 7 (29.2%) 19 (31.1%) NS disease * *CHD included 1. a medical history of coronary ischaemic heart disease documented by electrocardiography and/or cycloergometry 2. a history of acute MI3. having undergone a CABG or PTCA. TC, LDL and HDL were significantly different between the two groups - p=0.0025,0.002, and 0.03 respectively."	South African Medical Research Council and Universities of Antwerp and Stellenbosch.	None	Statistical analysis indicated that the CV status of LDLR mutation positive patients is not significantly worse than of mutation negative hyperlipidaemics, despite higher lipid levels.	This is a small study and should be repeated in a larger population	The findings are in accord with recent data indicating that FH is a heterogeneous disease caused by several different genetic defects in lipoprotein metabolism. It may also reflect the importance of gene-gene and gene-environment interactions.	Yes	

Question 3: What is effectiveness of the following strategies for identifying people with FH: cascade screening; GP note searching; secondary care registers; pathology registers or family history?

Study descriptions

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
Outcome of case finding among relatives of patients with known heterozygous familial hypercholesterolaemia.	Bhatnagar D; Morgan J; Siddiq S; Mackness MI; Miller JP; Durrington PN;	2000	COH	2+	259 probands and 285 first degree relatives	Probands aged 18 years or over attending two adjacent lipid clinics in the UK for the first time between 1987 and 1998 and their first degree relatives	137 male and 122 female probands with mean age of 45 and 48.9 years respectively. There were 83 male relatives and 117 female relatives with mean age of 34.5 in affected men and 26.7 in unaffected men, 38.2 in affected women and 36.7 in unaffected women.	Through lipid clinic registers	Central and south Manchester	The feasibility of detecting new cases of heterozygous FH by using a nurse led genetic register	This study is designed to assess case finding among relatives of patients with FH based on use of a genetic register and cascading to first degree relatives of an identified proband	This study does not involve follow-up but rather, patient identification	Numbers of positive FH (by Simon Broome criteria) detected.
Cascade screening for familial hypercholesterolaemia: implications of a pilot study for national screening programmes	Marks D; Thorogood M; Neil SM; Humphries SE; Neil HA;	2006	COH	2+	227 adult index cases had 1075 first degree relatives. Ultimately 52 adult relatives were tested and 113 children were tested.	Index cases were patients at the Oxford lipid clinic and met the Simon Broome diagnostic criteria	Excluded were 516 adult residents outside Oxfordshire &171 unaffected adults previously screened. 46 wee excluded for other reasons. 29 planned to consult their GP, 12 refused and 132 did not respond. Parents of 4 children refused.	Multiple sources of ascertainment were used to identify cases consisting of a research register (Simon Broome Register of FH), the Oxford lipid clinic computerized diagnostic register and general practice records.	Oxford	Assessment of a clinic based cascade screening programme. Index patients were given letters to deliver to family members.	Prevalence levels are compared	This is not a longitudinal study	Number of cases identified
Review of first 5 years of screening for familial hypercholesterolaemia in the Netherlands.[see comment]	Umans-Eckenhausen MA; Defesche JC; Sijbrands EJ; Scheerder RL; Kastelein JJ;	2001	COH	2+	In an active screening program of index cases with a confirmed mutation, 5442 relatives of 237 people with FH were tested; 2039 individuals were identified as heterozygous by LDL receptor gene mutation analysis.	First or second degree relative of an 'index' case (that is, an individual who met Dutch FH criteria and had a positive DNA test).	Mean age of FH cohort was 37.6 years compared to 42.9 years in the non-carrier group. No other significant differences were reported between groups with regard to smoking, incidence of diabetes, hypertension or family history for CVD.	Participants were identified as a result of the Dutch screening program started in 1994	University of Amsterdam	Diagnostic methods for FH and resultant impact on treatment	A comparison of diagnosis by DNA versus cholesterol measurement alone. The investigators also assessed whether or not active identification of FH patients would lead to more cholesterol lowering treatment.	1 year	

Study results

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
Outcome of case finding among relatives of patients with known heterozygous familial hypercholesterolaemia.	Bhatnagar D; Morgan J; Siddiq S; Mackness MI; Miller JP; Durrington PN;	2000	200 first degree relatives were tested and 121 (60%)were found to have inherited FH. To detect a similar number by population screening over 60,000 tests would be required and only a few of these patients would have been detected had cholesterol testing been restricted to those with other risk factors for coronary heart disease. The newly diagnosed patients were younger than the probands and were generally detected before they had clinically overt atherosclerosis. Concentrations of serum cholesterol were, respectively 8.4 (1.7 SD) mmol/l and 81. (1.9 SD) mmol/l in affected men and women and 5.6 (1.0 D) mmol/l and 5.6 (1.1 SD) mmol/l in unaffected men and women. Screening for risk factors would have failed to identify most of the affected relatives in whom hypertension, diabetes mellitus, cigarette smoking and obesity were uncommon.	NHS Research and Development grant	None	Yes, this study demonstrates the effectiveness of cascade screening and makes a case for organising a genetic register which would link lipid clinics nationally	Yes	Yes	Yes	
Cascade screening for familial hypercholesterolaemia: implications of a pilot study for national screening programmes	Marks D; Thorogood M; Neil SM; Humphries SE; Neil HA;	2006	The positive diagnostic rate was 29% (15/52) in adults and 32% (36/113) in children. DNA testing was not done. Screening increased prevalence by 14.4% from 0.58/1000 (95% CI 0.52-0.65) to 0.67/1000 (95% CI 0.60-0.73), representing 33.5% of predicted cases.	HEART UK and Pfizer	None	The authors conclude that cascade screening conducted by a specialist hospital clinic within its population catchment area did not substantially increase the prevalence of diagnosed FH. For cascade screening to identify most individuals with FH a comprehensive national screening programme would be needed.	It was hypothesized by the authors that the poor response in this study was due to approaching relatives indirectly via the index case. Also, LDL-C levels which are age specific and which take account of the higher pre-test probability of a positive diagnosis in first degree relatives have not been agreed in the UK. DNA testing remains expensive and has limited sensitivity.	Yes	Yes	
Review of first 5 years of screening for familial hypercholesterolaemia in the Netherlands.[see comment]	Umans-Eckenhausen MA; Defesche JC; Sijbrands EJ; Scheerder RL; Kastelein JJ;	2001	"Lipoproteins (mmol/l) Carriers n=2039 Non carriers n=3403 Mean (SD) Mean (SD) TC 7.43 (1.65) 5.49 (1.34) LDL 5.62 (1.59) 3.56 (1.11) HDL 1.09 (o.35) 1.20 (0.37) TG 1.47 (1.08) 1.66 (1.10) Treatment with statins 667 (39%) 160 (5%)"	Lipoproteins (mmol/l) Carriers n=2039 Non carriers n=3403 Mean (SD) Mean (SD) TC	Dutch Ministry of Public Health, Welfare and Sport, the Health Care Insurance Council and the Netherlands heart Foundation	None	The figure used to diagnose FH in relatives by total cholesterol concentration was the age-specific and sex-specific 90th percentile. A total cholesterol concentration below these percentiles was reported in 18% of patients (false negatives; 95% CI 13-22%	The fact that 39% of carriers were on statins may have affected the comparison of lipid levels and DNA testing. It would be interesting to see the data with these subjects excluded.	Yes	Yes

Question 4: What is the effectiveness of DNA testing in all people (adults and children) who are suspected to have FH?

See Question 1.

Question 5: What is effectiveness of DNA testing for FH mutations among relatives of people with identified mutations for FH?

See also Question 1.

Study description

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
Development of sensitive and specific age- and gender-specific Low Density Lipoprotein cholesterol cut-offs for diagnosis of 1st degree relatives with Familial Hypercholesterolaemia in cascade testing.	Starr B; Hadfield SG; Hutten BA; Landsberg PJ; Leren TP; Damgaard D; Neil HAW; Humphries SE;	2008	COH	2+	Netherlands (mutation carriers/non carriers n=825/2469); Denmark (n=160/161) and Norway (n=374/742)	Genetically tested 1st degree relatives of FH probands were included. Individuals on lipid lowering therapy and where non fasting samples were analysed, those with triglycerides >2 mmol/l were excluded.	In the total sample 45.5% were male. The ages ranged across the entire age spectrum with an average from 27.3 (+/- 17.2) years in mutation positive Norwegians to 42.8 (+/-19.3) years in mutation negative Dutch individuals.	This was a retrospective review of plasma biochemistry results	The Netherlands, Denmark and Norway	LDL-C cut offs to identify "affected" first degree relatives	The cut offs were compared against two molecularly characterised cohorts from Denmark and Norway and with the MedPed cut offs	Not applicable - this is a cross sectional study	LDL-C levels

Study results

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
Development of sensitive and specific age- and gender-specific Low Density Lipoprotein cholesterol cut-offs for diagnosis of 1st degree relatives with Familial Hypercholesterolaemia in cascade testing.	Starr B; Hadfield SG; Hutten BA; Landsberg PJ; Leren TP; Damgaard D; Neil HAW; Humphries SE;	2008	OutcomesQ3-7 In the Netherlands the cut offs performed best for the youngest cohort (<15 years) where sensitivity was 85% and specificity 93%. Sensitivity decreased with age from 85% in the youngest cohort to 38% in over 55 year olds. This means that specificity dropped rapidly after 14 years of age (93% to 85%) and then remained fairly constant at between 83-86%. The accuracy (as assessed by Youden's index) was 0.53, but the cut offs performed significantly better amongst younger 1st degree relatives (<45 years) compared to older ages (Youden's Index, 0.59 vs. 0.33 p<0.001). The Norwegian and Danish values were adjusted to take into account the higher levels seen in these countries. The pattern seen in the Dutch cohort of greater accuracy in younger age groups was mirrored in the Norwegian data whilst for the Danish cohort the pattern was reversed and sensitivity increased with age.	UK FH Cascade Audit Project supported by the DOH and additional support from the British Heart Foundation	Not applicable	The plasma LDL-C levels that are used as diagnostic criteria for FH probands in the general population are too stringent for use in 1st degree relatives given a 50% probability of being FH. This study indicates that the Bayesian model of LDL-C cut offs for 1st degree relatives has a higher sensitivity than MedPed for identification of potential FH individuals.	Yes	No other studies	Yes	This study is a comparison of age and gender specific LDL-C diagnostic cutoffs for 1st degree relatives in the Netherlands, Denmark and Norway using a Bayesian model versus the MedPed model

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			Overall the Youden's index in the Norwegian data was 0.68 and in the Danish data was 0.64, 84% and 81% accuracy respectively. Overall the LDL-C cut offs gave a significantly better performance (p<0.001) than the MedPed cut offs when tested on the Dutch sample and at least as well for the Norwegian and Danish data sets. The sensitivity was higher for all datasets when using the LDL-C cut offs and specificity consistently lower.							

Question 6: What information and support is required for individuals (adults and children) being considered for diagnosis of FH ?

No studies were identified.

Question 7: What is the effectiveness of aggressive (maximal) cholesterol lowering in people with FH using pharmacological therapy?

Study descriptions

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
Treatment of heterozygous familial hypercholesterolemia: atorvastatin vs simvastatin	Bo M; Nicolello MT; Fiandra U; Mercadante G; Piliego T; Fabris F;	2001	RCT	1-	26 patients	These patients all had a validated diagnosis of HFH and blood TC <4.5 mmol/L; age 18-75. Exclusion criteria were evidence of hepatic, renal, neurological or endocrine disease; alcohol abuse; childbearing potential; neoplasms; use of other lipid-lowering drug	16 men; 10 women; mean age 55.1+/- 11.3 years; mean BMI 23.2 +/- 2.9; 30.8% in group 1 and 23.1% group 2 had CAD.	Unknown	Lipid Clinic, University of Turin, Italy	Atorvastatin vs simvastatin	Comparison between treatments starting at 10 mg/day. At weeks 6, 12 and 18, this dose was progressively raised to 20, 40 and 80 mg/day.	2 month washout; 24 week trial	TC, LDL, TG, HDL, TC/HDL ratio, Apo AI, Apo B, Apo B/Apo AI ratio
Comparative effects of simvastatin and pravastatin on cholesterol synthesis in patients with primary hypercholesterolemia	Feillet C; Farnier M; Monnier LH; Percheron C; Colette C; Descomps B; Crastes D;	1995	RCT	1-	26 patients	Primary hypercholesterolemia from two centers were included.	12 males and 14 females aged 17-71 years. Patients were excluded if they had a BMI> 30 kg/m sq, secondary hypercholesterolemia, diabetes mellitus, hepatic disease, unstable or vasospastic angina, had suffered an MI or CABG. Premenopausal women using oral contraceptives or with child bearing potential were excluded.	Unknown	2 centers (Dijion and Montpellier France)	Simvastatin versus pravastatin	A comparison between treatments is made	The trial had 4 six week periods - a 6 week washout period; a six week therapeutic period, a six week washout; a six week new therapeutic sequence period.	TC, LDL, TG, HDL Apo AI and Apo B.
Comparative hypolipidaemic effects of lovastatin and simvastatin in patients with heterozygous familial hypercholesterolemia	Illingworth DR; Bacon S; Pappu AS; Sexton GJ;	1992	RCT	1-	23 patients	All are adults with heterozygous familial hypercholesterolemia. None of the patients had diabetes or were above 30% ideal body weight and all had normal thyroid renal and hepatic function.	6 males and 17 females; age range 24-55 years with mean 38.4 +/- years; 5 had CAD; 3 had PVD; body weight mean was 69.5 kg +/- 3.2. Several patients were on drugs known to influence lipid metabolism (eg estrogens) but therapy remained constant during the period of diet and drug treatment.	Unknown	Clinical Research Center at Oregon Health Sciences	Lovastatin vs simvastatin at increasing doses over 8 months time	Comparisons are between treatments and dose response	56 weeks	Total Cholesterol, LDL-C, HDL-C, Apo B, Apo AI, Apo AII, Trig

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
Efficacy and safety of high dose fluvastatin in patients with familial hypercholesterolaemia	Leitersdorf E; Eisenberg S; Eliav O; Berkman N; Dann EJ; Landsberger D; Sehayek E; Meiner V; Peters TK; Muratti EN; et a;	1993	RCT	1+	52 patients	FH patients who had participated in previous research with LDL levels greater than 160 mg/dl and at least 5% lower than the baseline value when 20 mg fluvastatin per day was prescribed. Patients with the Sephardic mutation were excluded.	SCQ3-2 Mean age of group A 41.3 (24-62) and Group B 47.8 (21-74) [p<0.05]. There were no significant differences in gender (% males 58.3 and 53.6) or BMI (25.4 and 26.2). The most prevalent risk factors were CHD (70.8% in Group A and 75% in Group B) and cigarette smoking (62.5% in A and 53.6% in B).	Patients were recruited from participants in previous research.	The English Hospital, Nazareth, Israel	After 6 weeks of a single blind dosage stabilization period, in which patients received fluva 40 mg qpm patients were randomly allocated to either group A receiving fluva 20 mg bid for 12 weeks and then fluva 20 mg qam and 40 mg qpm for a further 12 weeks	Efficacy, safety and tolerability were compared	36 weeks	TC, TG, HDL, LDL, Apo A1, Apo B and Lp (a)
Effects of synvinolin (MK-733) on plasma lipids in familial hypercholesterolaemia	Mol MJ; Erkelens DW; Leuven JA; Schouten JA; Stalenhoef AF;	1986	RCT	1+	43 patients total divided into 10 treatment groups - placebo (8 patients) and 8 groups of 4 patients and 1 group of 3 patients receiving different doses of simva. Simva was given either twice daily (1.25 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg) or in one d	All had heterozygous FH.	There were 28 men and 15 women from four centres in the Netherlands. The mean age was 44 years and mean relative body weight 106%. 11 had CHD. Treatment groups were comparable with regard to age, sex, body weight and plasma lipid levels.	Unknown	Four Dutch centres	Treatment of lipid levels with simva	Simva versus placebo and versus differing doses and dosing regimes	4 weeks	TC, LDL, HDL, TG
Expanded-dose simvastatin is effective in homozygous familial hypercholesterolaemia	Raal FJ; Pilcher GJ; Illingworth DR; Pappu AS; Stein EA; Laskarzewski P; Mitchel YB; Melino MR;	1997	RCT	1+	12 patients: group 1 n=8; group 2 n=4	Patients with homozygous FH were included. Atients were excluded if they had previously undergone portacaval shunting or ileal bypass surgery, had hepatic or renal dysfunction or had known hypersensitivity to statins. None were receiving LDL apheresis.	SCQ3-2 Nine patients were homozygotes or compound heterozygotes for FH Afrikaner -1, -2 -3. One subject also had an exon nine mutation. The remaining two subjects were true homozygotes for an exon 16 mutation and a promoter mutation respectively. The mean age was 26 years (15-39) and BMI was 23.1 (17.2-30.7). Five	Patients with HFH attending the Lipid clinic at Johannesburg Hospital were asked to participate in the study.	Lipid clinic at Johannesburg Hospital	This study evaluates the efficacy and safety of simvastatin at doses beyond 40 mg/day. After a 4 week placebo diet run-in period, 12 patients were randomised to simva 80 mg/day in three divided doses (n=8 group 1) or 40 mg daily (n=4,	Comparisons are made between treatments.	18 weeks	TC, TG, HDL, LDL, VLDL, Apo B Lp(a) and Apo E.

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
							females and 7 males participated.			group 2) . After 9			
Treatment of Primary Hypercholesterolemia with Pravastatin - Efficacy and Safety Over 3 Years	Simons LA; Nestel PJ; Clifton P; Janus ED; Simons J; Parfitt A;	1992	RCT	1+	60 patients completed the short term study	Patients with primary hypercholesterolaemia. Exclusion criteria not described.	37 men and 23 women with a mean age of 52.3 years. No other information provided.	Unknown	3 centres in Australia	This study aimed to assess the efficacy, safety and tolerability of pravastatin 20 mg and 40mg doses.	In the short term study pravastatin 20 mg was compared to pravastatin 40 mg and to use of resins 16g/day representing 'standard therapy.'	12 weeks	TC, LDL, HDL and TG
Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial.[see comment]	Smilde TJ; van W; Wollersheim H; Trip MD; Kastelein JJ; Stalenhoef AF;	2001	RCT	1+	325 subjects - 162 assigned atorvastatin and 168 assigned simvastatin	Men and women aged 30-70 years with familial hypercholesterolaemia who had LDL-C levels above 4.5 mmol/l and were either treated or untreated	29% in both groups were previously untreated; mean age was 48 years (SD10); mean body mass index was 26 (3) kg/m2; CVD (31%), smoking(32%) and use of concomitant medication (52%) was equally distributed between groups.	Multi-centre trial. Recruitment methods not described.	The Netherlands	The aim of the study was to determine whether aggressive lipid lowering therapy with 80 mg atorvastatin versus 40 mg simvastatin would slow atherosclerosis progression as measured by carotid IMT. Lipid levels were a secondary outcome measure.	The comparison is between treatment with simva 40mg versus atorva 80 mg for 2 years.	After an 8 week placebo run in period subjects were randomly allocated 40 mg atorva or 20 mg simva for 4 weeks. The dose was then increased to 80 mg atorva and 20 mg simva for two years. A resin was added if TC remained greater than 8 mmol/l	Carotid intima thickness was the primary outcome. Lipid levels were secondary outcomes.
Comparison of rosuvastatin versus atorvastatin in patients with heterozygous familial hypercholesterolemia	Stein EA; Strutt K; Southworth H; Diggle PJ; Miller E; HeFH S;	2003	RCT	1+	623 total; 436 rosuvastatin and 187 atorvastatin	Heterozygous FH patients were included; exclusion criteria included hepatic impairment, active arterial disease within 3 months, uncontrolled hypertension, uncontrolled hypothyroidism, use of cyclic hormonal therapy or other lipid affecting	There were no significant differences in patients participating in two arms of the study: In the rosuvastatin arm mean age 48; 54% men and 46% women; 96% Caucasian, <1% black, 4% other; body weight 77 kg.	Unknown	58 clinical centres world wide	Atorvastatin versus rosuvastatin in patients with heterozygous FH	Comparison of drugs and dosages	18 weeks	LDL, TC, HDL, TG, Apo B, Apo A-1

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
						drugs							
Comparison of therapy with simvastatin 80 mg and atorvastatin 80 mg in patients with familial hypercholesterolaemia.	Wierzbicki AS; Lumb PJ; Chik G; Crook MA;	1999	RCT	1-	26 patients	Patients had severe familial hypercholesterolaemia; Patients unable to tolerate previous statin therapy were excluded.	Patients were aged 55 +/- 12.7 years; 65% were male.	Those who did not achieve an LDL target of 2.5 mmol/l on previous therapy were recruited.	Unknown	This study compared the safety and efficacy of simvastatin 80 mg with atorvastatin 80 mg in the treatment of patients with FH	This study compares treatments.	12 weeks for each arm of the study	TC, TG, HDL, LDL, Apo A1, Apo A2, ApoB, Lp(a)

Study results

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
Treatment of heterozygous familial hypercholesterolemia: atorvastatin vs simvastatin	Bo M; Nicolello MT; Fiandra U; Mercadante G; Piliego T; Fabris F;	2001	Significant reductions of TC (p<0.001), LDL (p<0.001), TC/ HDL (p<0.005). TG (p<0.005), apo B (p<0.001) were observed in both groups. At the end of the study, all these lipid values were lower in the atorvastatin group, and atorvastatin also induced significantly greater reductions of total cholesterol (atorva 6.3 +/- 0.9 mmol/l and simva 7.7 +/- 1 mmol/l ; p<0.001;) and LDL (atorva 4.3 +/- 1.1 mmol/l and simva 5.4 +/- 1.2 mmol/l ; p<0.01)	Unknown	No serious adverse events. The incidence of side effect (mainly asthenia and myalgia) was 5% in the simvastatin and 3% in the atorvastatin group.	The results indicate that atorvastatin may be more effective than simvastatin in reducing total cholesterol and LDL-C in patients with FH.	This study is methodologically flawed and has high potential for bias.	Unknown	Yes	This is a head to head study and there is no placebo or control group.
Comparative effects of simvastatin and pravastatin on cholesterol synthesis in patients with primary hypercholesterolemia	Feillet C; Farnier M; Monnier LH; Percheron C; Colette C; Descomps B; Crastes D;	1995	Both simvastatin and pravastatin resulted in a significant reduction (p<0.001) in serum concentrations of TC, LDL and apo B. The diminuations of serum TC and LDL were significantly greater with simva than with pravastatin (p<0.005 [6.32 +/- 0.20and 7.24 +/- 0.24] and p<0.02 [4.45 +/- 0.22 and 5.32 +/- 0.25] respectively). Apo B also showed a significant difference of p<0.05 [simva 136 +/- 6 and prava 157 +/-]. The	University of Montpellier	None reported in this study.	This study indicates that simvastatin has better efficacy on serum cholesterol and LDL than pravastatin and this may be due to greater inhibitory action of simva on cholesterol synthesis.	This is a small study and allocation concealment is not described. There is no placebo group and the study population is not stratified into FH and polygenic groups.	Unknown	This study does apply to the FH population.	This is a head to head trial and there is no placebo control. This is also a cross over trial in which the treatment periods lasted 6 weeks.

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			difference in the relative changes of TC and LDL from baseline between simva and prava were also statistically significant (p<0.001). Lathosterol changes were also reported but are not an outcome measure for this guideline."							
Comparative hypolipidaemic effects of lovastatin and simvastatin in patients with heterozygous familial hypercholesterolemia	Illingworth DR; Bacon S; Pappu AS; Sexton GJ;	1992	Concentrations of total cholesterol decreased significantly in response to treatment with lovastatin or simvastatin and fell from a baseline value of 343 +/- 9 mg/dl (8.9 mmol/dl +/- .2) to 285 +/- 8 (7.3 mmol/dl +/- .2), 267 +/- 8 mg/dl (6.8 mmol/dl +/- .2) and 250 +/- 8 mg/dl (6.4 mmol/dl +/- .2) on lovastatin at doses of 20, 40, 80 mg/day, respectively. Treatment with simvastatin resulted in a decrease in the total cholesterol concentrations to 266 +/- 8 mg/dl 6.8 mmol/dl +/-.2), 242 +/- 7 6.2 mmol/dl +/- .18) and 225 +/- 6 mg/dl (5.8 mmol/dl +/- .15) on doses of 20, 40 and 80 mg/ day , respectively. Concentrations of LDL fell in parallel with reductions in TC and decreased from a baseline value of 274 +/- 9 mg/dl (6.3 +/- .23) to values of 211 +/-8 (5.4 mmol/l +/-.2), 192 +/- 8 (4.9 mmol/ld +/- .2) and 178 +/- 7 mg/dl (4.6 mmol/l +/- .18), respectively, on lovastatin at doses of 20, 40 and 80 mg/day, respectively. Treatment with simvastatin reduced LDL cholesterol concentrations to 194 +/- 8(4.97 mmol/l +/- .2), 168 +/- 6 (4.3 mmol/l +/- .2) and 156 +/- 6 mg/dl (4 mmol/l +/- .15) on doses of 20, 40 and 80 mg/day, respectively. The decrease in concentrations of LDL was significant for both drugs at all doses (p<0.01). Statistically significant decreases in TC and LDL occurred as the dose of each drug was increased from 20 to 40 to 80 mg/day. (p<0.01-0.05). Treatment with simvastatin at 20 and 40 mg/day reduced total and LDL	NIH and General Clinical Research Center's Program	Side effects were mild and none resulted in discontinuation of therapy or withdrawal from the study. There were no reports of myalgia or myopathy. Liver enzymes did not show significant differences.	This study further documents the dose-dependent hypocholesterolaemic effects of lovastatin and simvastatin in adult patients with heterozygous familial hypercholesterolemia.	As blinding and allocation concealment were not described there is potential for bias in the design of this study.	There does appear to be a dose response effect when statins are administered to patients with high cholesterol.	This study is applicable to FH patients.	This trial is a head to head comparison and is not placebo controlled. It is designed as a cross over study in which patients are randomised to lova or simva for 6 months and then, after a 4 week washout period, the patients were crossed over to the other

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			cholesterol concentrations significantly more (p<0.001) than was seen in response to lovastatin at the same dose. However, the reduction in LDL achieved with lovastatin at 40 and 80 mg/day was virtually identical to simva at 20and 40 mg, respectively. These are the maximally recommended doses of these two drugs. A modest further decrease in the concentration of LDL cholesterol was achieved during treatment with simva at a dose of 80 mg/day (-43%) as compared to the 38.7% decrease noted during treatment with 40 mg/day of simva. Statistically significant decreases in TG and occurred in response to all doses of simva and with lova at 40 and 80 mg/day. Apo B was significantly reduced with both lova and simva at all doses."							
Efficacy and safety of high dose fluvastatin in patients with familial hypercholesterolaemia	Leitersdorf E; Eisenberg S; Eliav O; Berkman N; Dann EJ; Landsberger D; Sehayek E; Meiner V; Peters TK; Muratti EN; et a;	1993	"TC: Group A 363 mg/dl (56.9) (1.6 mmol/dl +/- 1.46) to -25.8% (9.8) in week 30; Group B 361 mg/dl (73.5) (9.26 mmol/l +/- 1.88) to -20.2% (7.9) in week 30. TG: Group A 147 mg/dl (61.3) (1.65 mmol/dl +/-.69) to 2.3% (35.4) in week 30; Group B 143 mg/dl (63) (1.61 mmol/l +/- .71) to -3.7% (24.8) in week 30. HDL: Group A 37.2 mg/dl (10.0) (.95 mmol/l +/- .26) to 16.2% (17.2) in week 30; Group B 36.6 mg/dl (7.3) (.93 mmol/l +/- .19) to 9.6 %(13.4) in week 30. LDL: Group A 296 mg/dl (55.0) (7.6 mmol/l +/- 1.4) to -34.3% (11.9) in week 30; Group B 295 mg/dl (70.0)(7.6 mmol/l +/- 1.8) to -25.4% (9.4) in week 30. Apo A1: Group A 118 mg/dl (23.5) to 0.8% (22.9) in week 30; Group B 116 mg/dl (18.0) to 0.0% (5.7) in week 30.Apo B: Group A 210 mg/dl (59.5) to -14.6% (13.1) in week 30; Group B 221 mg/dl (45.0) to -14.4% (13.9) in week 30. No significant differences were noted at week 18 in the response to fluva as a result of the mode of administration. In Group A LDL was further	Sandoz	There were no statistically significant differences between treatment groups in the primary biochemical safety parameters. No patient discontinued the study because of a clinical adverse event.	This study showed a statistically significant decrease in LDL when the fluva dose was increased from 40 mg to 60 mg and addresses the high dose question.	The overall effect in this study appears to be likely due to the intervention.	Unknown	Yes, this study applies to the population of interest.	

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			reduced on a dose of 60 mg fluva (7.1% p<0.05) compared to 40 mg a day. In comparison with Group B on 40 mg qd, Group A on 60 mg LDL differed by -8.9% (p<0.01)."							
Effects of synvinolin (MK-733) on plasma lipids in familial hypercholesterolaemia	Mol MJ; Erkelens DW; Leuven JA; Schouten JA; Stalenhoef AF;	1986	Results reported in mmol/l. All doses of simva except for treatment with 2.5 mg once a day produced significantly (p<0.05) greater reductions in total and LDL cholesterol than placebo. One dose appeared to have the same effect as the twice daily regime. The 80 mg dose was no more effective than 40 mg or 20 mg in these small groups. TC: placebo 11.32 +/- 1.12; 2.5 mg 10.06 +/- 2.20; 5mg 7.93 +/- 1.36; 10 mg 9.19 +/-1.92; 20 mg 9.02 +/-2.67; 40 mg 7.09 +/- 1.19; 80 mg 6.54 +/- 0.48. LDL: placebo 9.55 +/- 1.12; 2.5 mg 8.17 +/- 2.15; 5mg 6.46 +/- 1.42; 10 mg 7.58 +/- 1.89; 20 mg 7.11 +/-2.99; 40 mg 5.51 +/- 1.04; 80 mg 5.02 +/- 0.69. HDL: placebo 1.13 +/- 0.19; 2.5 mg 1.12 +/- 0.18; 5mg 0.89 +/- 0.13; 10 mg 1.02 +/- 0.18; 20 mg 1.34 +/-0.17; 40 mg 1.06 +/- 0.25; 80 mg 1.10 +/- 0.19.TG: placebo 1.49 +/- 0.50; 2.5 mg 1.71 +/- 0.89; 5mg 1.27 +/- 0.44; 10 mg 1.33 +/-0.44; 20 mg 1.26 +/-0.54; 40 mg 1.16 +/- 0.45; 80 mg 0.92 +/- 0.48. When the log of simva dose was plotted against the percentage change in LDL after 4 weeks there was a highly significant correlation (r=-0.74, p<0.001).	Unknown	No subjective side effects were noted. No lab values above 200% of normal were noted.	It appears that simva versus placebo is effective in reducing TC and LDL in FH patients. This small study did not find increased efficacy using the 80 mg dose.	The groups in this study were very small and the follow up period was only four weeks. Unable to generalise based on this study.	Yes	Yes	
Expanded-dose simvastatin is effective in homozygous familial hypercholesterolaemia	Raal FJ; Pilcher GJ; Illingworth DR; Pappu AS; Stein EA; Laskarzewski P; Mitchel YB; Melino MR;	1997	Group 1: Baseline TC 16.2 (1.3), 80 mg 12.3 (1.0) and 160 mg 11.4 (1.0); Baseline TG 1.41 (0.16), 80 mg 1.11 (0.15) and 160 mg 1.03 (0.10); Baseline HDL 0.84 (0.06), 80 mg 0.89 (0.07) and 160 mg 0.86 (0.06); Baseline LDL 14.8 (1.3), 80 mg 10.9 (1.0) and 160 mg 10.1 (1.0); Baseline VLDL 0.64 (0.07), 80 mg 0.51 (0.06) and 160 mg 0.47 (0.04); Baseline Apo B 415 (32), 80 mg 340 (26) and 160 mg 323 (27); Baseline Lp (a) 91 (23), 80 mg 101 (24) and 160 mg 111 (27); Baseline	Merck	No serious adverse clinical or biochemical effects occurred.	This study of HFH patients does address the question of high dose statin use in this very high risk patients.	Although the methodology is acceptable, the study is not adequately powered.	Unknown	Comparisons are direct.	Extent of CV morbidity differed; baseline medication different

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			TC 16.2 (1.3), 80 mg 12.3 (1.0) and 160 mg 11.4 (1.0); Baseline Apo E 15.3 (1.1), 80 mg 5.9 (1.0) and 160 mg 7.5 (0.3). Group 2: Baseline TC 14.5 (1.8), 40 mg 12.8 (1.8) and 40 mg tid 12.7 (1.2); Baseline TG 0.83 (0.03), 40 mg 0.81 (0.13) and 40 mg tid 0.78 (0.10); Baseline TC 14.5 (1.8), 40 mg 12.8 (1.8) and 40 mg tid 12.7 (1.2); Baseline HDL 0.73 (0.13), 40 mg 0.80 (0.14) and 40 mg tid 0.85 (0.10); Baseline LDL 13.4 (1.7), 40 mg 11.7 (1.7) and 40 mg tid 11.5 (1.1); Baseline VLDL 0.38 (0.02), 40 mg 0.36 (0.04) and 40 mg tid 0.35 (0.04); Baseline Apo B 406 (62), 40 mg 347 (43) and 40 mg tid 359 (28); Baseline Lp(a) 44 (22), 40 mg 53 (28) and 40 mg tid 49 (25); Baseline Apo E 13.1 (1.0), 40 mg 6.0 (0.6) and 40 mg tid 7.6 (0.3). In group 1 LDL levels were reduced by 25% t the 80 mg dose and by 31% at the 160 mg dose. However, the range of individual responses varied widely from an 8% increase to a 58% reduction in LDL at the 160 mg dose. In group 2 LDL fell by 14% at the 40 mg dose.							
Treatment of Primary Hypercholesterolemia with Pravastatin - Efficacy and Safety Over 3 Years	Simons LA; Nestel PJ; Clifton P; Janus ED; Simons J; Parfitt A;	1992	TC: Group I baseline 9.40 mmol/l +/- 1.42; Week 12 -20% +/- 19% percent change; Group II baseline 10.33 mmol/l +/- 1.5.; -24% +/-7%. LDL: Group I baseline 7.35 mmol/l +/- 1.59; Week 12 -26% +/- 14% percent change; Group II baseline 8.27 mmol/l +/- 1.63.; -30% +/-8%. HDL: Group I baseline 1.32 mmol/l +/- 0.47; Week 12 8% +/- 20% percent change; Group II baseline 1.20 mmol/l +/- 0.43.; 18% +/-7%. TG: Group I baseline 1.59 mmol/l +/- 0.77; Week 12 2% +/- 25% percent change; Group II baseline 2.04 mmol/l +/- 0.99; 45% +/63%. Total and LDL cholesterol levels were significantly reduced by all treatments over the period (p<0.001). The reduction in TC with pravastatin 20 mg/day (20%) was NS; the reduction of	Bristol Meyers Squibb	Of the 42 subjects receiving pravastatin, five (12%) developed CNS symptoms, three (7%) developed GI symptoms and on (2%) developed knee and shoulder pain. One subject (male, aged 33 years) taking pravastatin 40 mg/day developed an acute hepatiic reaction within one week of starting therapy. Aside from this subject, two participants developed transient and minor increases in ALT in two subjects.	This study does provide information on doses of pravastatin.	The power was adequate and patients were randomised to treatment. If protocols were followed at each centre, comparisons should be accurate.	Yes	It is unclear how many of the patients in this study were FH versus FCH patients.	The long term aspect of this study is not considered as the researchers are not specific about the drugs which were used to supplement statins in this phase of the study.

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			TC with pravastatin 40 mg/day (24%) was significant (p<0.03). The reduction in LDL cholesterol level did not differ significantly between the treatment groups (range 26% - 34%). The HDL cholesterol level increased significantly with all treatments (range 8%-18%, p<0.001), there being no differences between the treatment groups in this response. There was a significant difference in the response of plasma triglyceride levels between the various treatments over the 12 weeks (p<0.001).							
Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial.[see comment]	Smilde TJ; van W; Wollersheim H; Trip MD; Kastelein JJ; Stalenhoef AF;	2001	The overall baseline IMT combining the measurements of the common and internal carotid artery and the carotid bifurcation on both sides, was 0.93mm (SD 0.22) and 0.92mm (0.21) in the atorva and simva groups, respectively. After treatment with atorva for 2 years, IMT decreased (-0.031 mm [CI -0.007 to -0.055]; p=0.0017), whereas in the simva group it increased (0.036 [0.014-0.058]; p=0.0005). The change in thickness differed significantly between the two groups (p=0.0001). Atorva showed significantly greater reductions in TC (5.73 [1.31] vs 6.71[1.38] mmol/l; p=0.0001) and LDL-C concentrations (3.88 [1.21] vs 4.81[1.38] mmol/l; p=0.0001) than did simvastatin. There was also a significant difference in triglycerides (p=0.0023) and in apo B levels (0.0001)."	Unknown	The clinical event rate was low and included muscle ache(which was never accompanied by increase in CPK) and mild abdominal complaints.	Although the primary outcome measure of this study was carotid IMT the reporting of comparative lipid levels in an FH population of 280 individuals after two years of therapy aids the evaluation of high dose therapy in this population.	Yes	Yes	Yes	
Comparison of rosuvastatin versus atorvastatin in patients with heterozygous familial hypercholesterolemia	Stein EA; Strutt K; Southworth H; Diggle PJ; Miller E; HeFH S;	2003	Absolute values not provided. Change from baseline: LDL at 6 weeks on 20 mg rosuvastatin -47.1% (0.8) and -38.0% (1.0) on 20 mg atorvastatin; at 12 weeks on 40 mg rosuvastatin -53.9% (0.8) and -46.0% (1.1) on 40 mg atorvastatin; at 18 weeks on 80 mg rosuvastatin -57.9% (0.9) and -50.4% (1.2) on 80 mg atorvastatin. TC at 6 weeks on 20 mg rosuvastatin -37.4% (0.6) and -31.2% (0.8) on	Unknown	Treatment emergent drug related clinical adverse events occurring in >2% of patients: abdominal pain Rosuvastatin 3% and atorvastatin 1%; headache Rosuvastatin 2% and atorvastatin 3%; hypertonia Rosuvastatin 1% and atorvastatin 3%; insomnia Rosuvastatin	This study compares two statins and various doses in FH patients and appears to favor rosuvastatin to atorvastatin.	Good methodology and adequate sample size. It would have been helpful to see absolute values for all results.	Yes	Yes	

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			20 mg atorvastatin; at 12 weeks on 40 mg rosuvastatin -43.1% (0.7) and -38.0% (0.9) on 40 mg atorvastatin; at 18 weeks on 80 mg rosuvastatin -46.4% (0.8) and -42.1% (1.0) on 80 mg atorvastatin. HDL at 6 weeks on 20 mg rosuvastatin +11.7% (0.9) and +5.3% (1.2) on 20 mg atorvastatin; at 12 weeks on 40 mg rosuvastatin + 10.4% (0.9) and +2.7% (1.3) on 40 mg atorvastatin; at 18 weeks on 80 mg rosuvastatin +12.4% (1.0) and 2.9% (1.3) on 80 mg atorvastatin. TG at 6 weeks on 20 mg rosuvastatin -22.9% (1.4) and -22.1% (1.9) on 20 mg atorvastatin; at 12 weeks on 40 mg rosuvastatin -25.2% (1.5) and -24.8% (2.0) on 40 mg atorvastatin; at 18 weeks on 80 mg rosuvastatin -27.8% (1.5) and -31.6% (2.0) on 80 mg atorvastatin. Apo B at 18 weeks on 80 mg rosuvastatin - 50.2% (0.9) and -44.4% (1.1) on 80 mg atorvastatin. Apo B at 18 weeks on 80 mg rosuvastatin +5.9% (0.9) and -2.3% (1.2) on 80 mg atorvastatin. All doses of rosuvastatin resulted in significantly greater (p<0.001) reductions in LDL than atorvastatin. Mean values for LDL at week 18 were 125 +/- 45.4 and 144.9 +/- for the rosuvastatin and atorvastatin respectively.							
Comparison of therapy with simvastatin 80 mg and atorvastatin 80 mg in patients with familial hypercholesterolaemia.	Wierzbicki AS; Lumb PJ; Chik G; Crook MA;	1999	"Results reported in mmol/l. TC: Baseline 11.2 +/- 1.65 mmol/litre; atorva 6.81 +/- 1.26 mmol/litre; simva 6.60 +/- 0.96 mmol/litre; TG: Baseline 1.93 mmol/litre; atorva 1.25 mmol/litre; simva 1.53 mmol/litre; HDL: Baseline 1.20 +/- 0.35 mmol/litre; atorva 1.17 +/- 0.29 mmol/litre; simva 1.28 +/- 0.23 mmol/litre; LDL: Baseline 9.02 +/- 1.52 mmol/litre; atorva 5.00 +/- 1.21 mmol/litre; simva 4.63 +/- 0.84 mmol/litre; Apo A1: Baseline 1.42 +/- 0.42 grams/litre; atorva 1.39 +/- 0.32grams/litre; simva 1.43 +/- 0.20 grams/litre; Apo	Unknown	Clinical side effects, which were mostly gastrointestinal or myalgia were reported in 4% and 16% of atients with simvastatin and atorvastatin therapy respectively The rate of side effects was significantly greater in the atorva group.	ConclKQQ3-9 The study compares two statin regimes in FH patients.	This study was not adequately powered to show a statistically meaningful association and there are methodological concerns which are not addressed in the study report	Unknown	Yes	This trial is an open crossover trial format. Of concern are the following: 1. possible carry over effect 2. There is no data on the patient status after the washout period to indicate if the patients returned to baseline

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			A2: Baseline 0.52 +/- 0.13 grams/litre; atorva 0.46 +/- 0.12 grams/litre; simva 0.37 +/- 0.12 grams/litre; Apo B: Baseline 2.33 +/- 0.36 grams/litre; atorva 1.56 +/- 0.36 grams/litre; simva 1.43 +/- 0.29 grams/litre; Lp (a): Baseline 0.51 grams/litre; atorva 0.52 grams/litre; simva 0.34 grams/litre. The study was too small for the difference between the two drug regimens to be significant."							

Question 8: What is the effectiveness of monotherapy in improving outcome in individuals with FH?

Study descriptions

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
Statin treatment for children and adolescents with heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis	Arambepola,C.; Farmer,A.J.; Perera,R.; Neil,H.A.W.	2007	SR	1+	RCTs and case series								
Treatment of hypercholesterolemia with the HMG CoA reductase inhibitor, simvastatin	Berger GM; Marais AD; Seftel HC; Baker SG; Mendelsohn D; Welsh NH; Joffe BI;	1989	RCT	1+	44 total; 22 in each centre	All patients had a primary elevation of plasma LDL while on a lipid lowering diet in the absence of coexisting factors. Potentially fertile women were excluded. Patients with cardiac disease or using hepato-toxic drugs were excluded.	Capetown: Average age 50.8 years; 18 males and 4 females; 11 with CAD; baseline LDL 6.26 mmol/l (1.63); baseline TC 8.15 mmol/l (1.70) Johannesburg: Average age 44.6 years; 14 males and 8 females; 4 with CAD; baseline LDL 7.77 mmol/l (1.00); baseline TC	Unknown	Two medical centres in South Africa	4 week placebo treatment followed by Phase 1 double blind active treatment phase during which patients were randomly assigned to medication or placebo. Phase 2II open extension trial to titrate the dose response profile of individual subjects did not meet inclusion criteria.	Placebo or simvastatin 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg, or 80 mg.	4 weeks of placebo then 4 weeks of placebo or active treatment	Primary: LDL-C; Secondary: HDL and triglycerides
Treatment of familial hypercholesterolaemia. United Kingdom lipid clinics study of pravastatin and cholestyramine	Betteridge DJ; Bhatnager D; Bing RF; Durrington PN; Evans GR; Flax H; Jay RH; Lewis-Barned N; Mann J; Matthews DR; et a;	1992	RCT	1+	128 - 43 placebo; 43 pravastatin; 42 cholestyramine.	Patients with FH including elevated TC, LDL and tendon xanthomas or family history. Participants were men and post menopausal or surgically sterile women aged 18-70 who had no other primary or secondary causes of hyperlipidaemia and no significant renal problems.	92 men/36 women; lipid and lipoprotein concentrations were similar in the three groups.	Patients were recruited from six specialist lipid clinics in England.	6 lipid clinics in England	12 week comparison of the pravastatin, cholestyramine, and placebo treated groups.	Treatment and placebo	12 weeks	TC, TG, LDL, HDL, LDL/HDL ratio
Effects of fenofibrate on plasma lipids. Double-blind, multicenter study in patients with type IIA or IIB hyperlipidemia	Brown WV; Dujovne CA; Farquhar JW; Feldman EB; Grundy SM; Knopp RH; Lasser NL; Mellies MJ; Palmer RH;	1986	RCT	1+	116 fenofibrate; 110 placebo	Type II hyperlipoproteinemia but otherwise in good health. Not over 65, either males or postmenopausal females not receiving estrogen.	Mean age 51.8. 153 males/74 females. 202/227 Caucasians	Previously diagnosed Type II hyperlipoproteinemia at 11 centers.	11 lipid centers in the USA	Fibrates to reduce cholesterol	Fibrates versus placebo	24 weeks	TC, LDL, HDL and TG

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
	Samuel P;												
Rosuvastatin for the treatment of patients with hypercholesterolemia.	Chong PH; Yim BT;	2002	SR	1-	Clinical trials and in vitro studies								
Treatment of childhood hypercholesterolemia with HMG-CoA reductase inhibitors	Duplaga BA;	1999	SR	1-	RCT and time series; case series								
The effects of colestipol hydrochloride on serum lipoprotein lipid and apolipoprotein B and A-I concentrations in children heterozygous for familial hypercholesterolemia	Groot PH; jkhuis-Stoffelsma R; Grose WF; Ambagtsheer JJ; Fernandes J;	1983	RCT	1+	14 patients completed the study in each arm	Diagnosis of FH in children aged 7-15	All of the children consumed a diet low in total fat and cholesterol and high in linoleic acid.	Not described.	Sophia Children's Hospital	Children received either colestipol or a placebo.	The study was a double blind cross over design in which group I started with colestipol and switched to placebo after 8 weeks. Group II received the medication in the reverse order. The dose was 5 g bid if under 40kg and 10 g qam and 5 g q pm if over 40	16 weeks	TC, HDL, LDL + VLDL, TG and Apo B and Apo A
Growth during treatment of familial hypercholesterolemia	Hansen D; Michaelsen KF; Skovby F;	1992	COH	3	30	Children with FH	The median age at the start of the study was 3.0 years in the diet only group and 5.0 years in the diet and colestipol group. The median duration of treatment was 8.5 years in 13 children on diet only and 5.5 years in 17 children treated with diet followed by diet and colestipol.	Unknown	Lipid clinic	Diet or diet and colestipol	Growth rates	Median time 8.5 years	height/age and weight/age
Treatment of patients with familial defective apolipoprotein B-100 with pravastatin and gemfibrozil: a two-period cross-over study	Hansen PS; Meinertz H; Gerdes LU; Klausen IC; Faergeman O;	1994	COH	2+	30 children divided into two groups: group 1 (8 girls and 5 boys) and group 2 (8 girls and 9 boys)	Children with FH (1-12 years of age) followed in Danish pediatric lipid clinic; diagnosis was on basis of lipid levels in children and relatives.	Details not provided other than Median age at start of treatment (4.5 with range of 1-12 years) and duration of treatment.	These children were patients at Rigs Hospitalet, Copenhagen	Danish lipid clinic	Growth following long term diet and colestipol	Difference in children who were treated with diet only and those treated with diet and colestipol	Up to 6 years	Weight/age and height/age; TC
Efficacy and Safety of Pravastatin in Patients with Primary Hypercholesterolemia .2. Once-Daily Versus Twice-Daily Dosing	Hunninghake DB; Mellies MJ; Goldberg AC; Kuo PT; Kostis JB; Schrott HG; Insull W; Pan HY;	1990	RCT	1+	184 total;4 treatment groups - placebo n=46, pravastatin 40 mg qam n=48, 40 mg qpm	Patients had primary hypercholesterolemia, were between 20-72 years. Patients were excluded if they were using concomitant medication potentially	135 men and 49 post menopausal or surgically sterilized women; mean age ranged from 52.6 to 54.0 years. There were no significant	Unknown	6 lipid clinics in USA	Treatment with placebo vs pravastatin 40 mg qam; prava 40 mg qpm and prava 20 mg bid.	Lipid levels after treatment with fluvastatin	8 weeks	Total cholesterol; LDL-C were primary outcomes. HDL and TG were

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
					n=43 and 20 mg bid n=47.	affecting lipid metabolism.	differences with regard to baseline demographic and lipid and lipoprotein variables among the treatment groups.						secondary outcome measures.
Ciprofibrate in the therapy of type II hypercholesterolemia. A double-blind trial	Illingworth DR; Olsen GD; Cook SF; Sexton GJ; Wendel HA; Connor WE;	1982	RCT	1+	20; 9 received 100 mg, 7 received 50 mg and 4 received placebo	All had primary phenotypic type II hypercholesterolemia. All had normal renal, hepatic and athyroid function and none was taking estrogens or any other prescription medications.	There were 13 females and 7 males. The study was based at the Lipid Disorders Clinic Oregon Health Sciences University, USA	Unknown	Lipid clinic, USA	Ciprofibrate to lower cholesterol	Ciprofibrate 50 mg and 100 mg versus placebo	12 weeks	TC, LDL, HDL and TG
Simvastatin (MK 733) in heterozygous familial hypercholesterolemia: a two-year trial	Leclercq V; Harvengt C;	1989	RCT	1-	19	All patients had a diagnosis of heterozygous familial hypercholesterolemia	Mean age 47; mean height 172; mean weight 72; mean total cholesterol 457; mean triglycerides 174.	Unknown	Medical centre in Brussels	8 week lipid lowering drug withdrawal then 2 weeks of placebo and a 4 week dose response study in which placebo or simvastatin ranging from 2.5 mg to 80 mg given.	Comparison between placebo and treatment levels of simvastatin	12 weeks	Serum total cholesterol, LDL-C, HDL-C, triglycerides measured in mg/dl.
A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia	Marks D; Thorogood M; Neil HA; Humphries SE;	2003	SR	1++	RCTs, cohort and epidemiological studies were included.								
Simvastatin in Severe Hypercholesterolemia - A Placebo Controlled Trial	Mcdowell IFW; Smye M; Trinick T; Shortt JA; Archibald MP; Trimble ER; Nicholls DP;	1991	RCT	1+	27	All had primary hypercholesterolaemia. Exclusions: age >70 and < 18 years; potential childbearing women; hx of MI or CABG within 3 months; diabetes; liver impairment.	Not described; baseline TC placebo group 11.7 +/- 0.6 mmol/l; LDL 9.5 +/- 0.6 mmol/l; baseline TC simva group 11.4 +/-0.6 mmol/l; LDL 9.1 +/- 0.6 mmol/l/	Not described	Royal Victoria Hospital, Belfast	Patients had 8 week placebo period and were then randomised on a double blind basis to receive simva10 mg daily or matching placebo from Week 0. The dose of simva was increased monthly to 20 mg in second month and 40 mg in the third month.	Placebo.	12 weeks	Total cholesterol, LDL cholesterol, VLDL cholesterol, HDL cholesterol, Triglycerides in mmol/l
Clinical evidence for use of acetyl salicylic acid in control of flushing related to nicotinic acid treatment	Oberwittler H; Baccara-Dinet M;	2006	SR	1+	'Clinical trial' without specific description of study types								
Efficacy and safety of cholestyramine therapy in peripubertal and prepubertal children with familial	Tonstad S; Knudtzon J; Sivertsen M; Refsum H; Ose L;	1996	RCT	1+	36 children in treatment group and 36 in placebo group	Children with FH; prepubertal who had completed an initial medical evaluation and dietary session and who	Ages 6-11; tanner stage 1	Unknown	Lipid Clinic, National Hospital, Oslo,	8 gm of cholestyramine in children with FH versus placebo after	Treatment versus placebo	One year	LDL, TC and HDL and height velocity

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
hypercholesterolemia.[see comment]						had a parent who understood the diet			Norway	one year of diet based on the National Cholesterol Education Program diet and vitamin supplements as normal.			
Low-dose simvastatin treatment in patients with moderate-grade familial hypercholesterolemia	Valerio G; Vigna GB; Vitale E; Romagnoni F; Fellin R;	1990	RCT	1+	12 - 4 placebo and 8 randomly treated in a double blind manner	inclexcl3-2-1 All patients with total cholesterol from 240-260 mg/dl. All had history of increased cholesterol levels in other blood relatives. Excluded: lactation, pregnancy, use of drugs known to interfere with lipid metabolism, important organ or system disease	Five men and seven women; age range, 25 to 63 years. No comorbidities reported.	Unknown	University of Padua, Italy	Simvastatin 10 mg v placebo	Treatment v placebo	8 weeks	Total cholesterol; LDL-C; HDL-C; TC/HDL-C; TG; Apo A1 and Apo B.
Treatment of familial hypercholesterolaemia: a controlled trial of the effects of pravastatin or cholestyramine therapy on lipoprotein and apolipoprotein levels.[see comment]	Wiklund O; Angelin B; Fager G; Eriksson M; Olofsson SO; Berglund L; Linden T; Sjoberg A; Bondjers G;	1990	RCT	1+	120;40 in each arm	Patients with a diagnosis of FH per study criteri8a, including laboratory values, tendon xanthomata and family history	62 men and 58 women with mean age of 50.6 years; premenopausal women and patients with diabetes, hepatic dysfunction, severe hypertension or excessive obesity were excluded from the study.	From two lipid centers in Sweden	Sahlgren Hospital and Huddinge University, Sweden	Pravastatin v placebo, dose of 40 mg week 6-12 ; cholestyramine v placebo, dose 24 gm and placebo alone	Comparison between treatments and placebo	12 weeks	TC, TG, LDL, VLDL, HDL, Apo A and Apo B

Study results

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
Statin treatment for children and adolescents with heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis	Arambepola,C.; Farmer,A.J.; Perera,R.; Neil,H.A.W.	2007		Unknown		This review reports about 1,150 person years follow up of statin treatment in childhood and adolescence. They conclude that current evidence supports treatment of children and adolescents at highest CV risk with statins. Statin monotherapy is efficacious, attenuates progression of carotid medial thickness, improves endothelial function and is well tolerated in the short term. Concerns: The pooled data in this review includes children of widely varying ages (8-18) and				This review is comprehensive and has utilized the Jadad scale to quality assess the literature. The case series studies which are reported (7) are not included in the pooled analysis. Five of eight RCTs which reported the efficacy of statin therapy as r

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
						trials of different types and dosages of statins. Heterogeneity is significant."				
Treatment of hypercholesterolemia with the HMG CoA reductase inhibitor, simvastatin	Berger GM; Marais AD; Seftel HC; Baker SG; Mendelsohn D; Welsh NH; Joffe BI;	1989	OutcomesQ3-7 Q2-9a. Percent change in LDL-C after 4 weeks therapy in entire study population: Placebo, -4.6%; Simva 2.5mg -14.9%; Simva 20 mg, -31.7%; Simva 40 mg -44.6% and Simva 80 mg -46.5%. Q2-9b. Triglyceride levels fell by 40% and the mean HDL-C concentration rose by 15.5% on the full dose of 80 mg/day (data not shown)	Merck, Sharp & Dohme	No serious adverse effects encountered	The study shows a substantial decrease in plasma LDL-C in FH patients when statin use is compared to placebo in the same patient. The changes observed were uniform across both study centres and in spite of some differences in population. The results are	The statistical power of this study is low due to small sample size and the inclusion of some non FH patients. However, there is good consistency with other studies of statins in non FH populations and extrapolation is reasonable.	There is good consistency with other studies of statins in non FH populations and extrapolation is reasonable.	Yes there is a direct comparison.	The average age of the Capetown group was 6.2 years older than the Johannesburg group. There were also more men than women in the study (32 and 12 respectively). Seven patients were non FH and 37 were diagnosed with FH
Treatment of familial hypercholesterolaemia. United Kingdom lipid clinics study of pravastatin and cholestyramine	Betteridge DJ; Bhatnager D; Bing RF; Durrington PN; Evans GR; Flax H; Jay RH; Lewis-Barned N; Mann J; Matthews DR; et a;	1992	OutcomesQ3-7 TC percentage change from baseline (absolute values not provided): TC placebo -2% (-7 to 4); pravastatin -25% (-29 to -21); cholestyramine -23% (-28 to -19). TG placebo 2% (-13 to 15); pravastatin -14% (-24 to -2); cholestyramine 18% (3 to 36). LDL placebo -2% (-9 to 4); pravastatin -30% (-35 to -25); cholestyramine -31% (-36 to -26). HDL placebo -6% (-14 to 3); pravastatin 0% (-9 to 10); cholestyramine 4% (-6 to 15). LDL/HDL placebo -4% (-9 to 18); pravastatin -30% (-38 to -20); cholestyramine -34% (-43 to -25).	Unknown	No serious adverse drug reactions occurred during the study.	Yes, pravastatin seems to be an effective, well tolerated compound for treating FH. Cholestyramine when tolerated at high dose is also highly effective.	Yes, the effect appears to be due to the treatment.	Yes	Yes	
Effects of fenofibrate on plasma lipids. Double-blind, multicenter study in patients with type IIA or IIB hyperlipidemia	Brown WV; Dujovne CA; Farquhar JW; Feldman EB; Grundy SM; Knopp RH; Lasser NL; Mellies MJ; Palmer RH; Samuel P;	1986	OutcomesQ3-7 In FH (Type IIa) patients: TC in fenofibrate arm 6.4 mmol/l; TC in placebo arm 8.0mmol/l. LDL in fenofibrate arm 4.5 mmol/l; TC in placebo arm 5.7 mmol/l. HDL in fenofibrate arm 1.4 mmol/l; TC in placebo arm 1.2 mmol/l. T\G in fenofibrate arm 1.3 mmol/l; TC in placebo arm 2.3 mmol/l. The units have been changed from g/dl to mmol/l. Standard errors	Unknown	The global incidence of patients experiencing some form of adverse reaction was 26% for fenofibrate and 20% for placebo.	This study shows the effectiveness of fibrates to lower cholesterol	The effect appears to be due to treatment	Yes	Yes	

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			were not provided by the authors. Fenofibrate significantly (p<0.01) reduced mean plasma concentrations of TC (18%), LDL (20%), VLDL (38%) and TG (38%). Mean plasma HDL increased (11%) significantly (p<0.01).							
Rosuvastatin for the treatment of patients with hypercholesterolemia.	Chong PH; Yim BT;	2002		Unknown		This review concludes that rosuvastatin reduced LDL-C and other lipid parameters to a greater degree in FH patients than currently available agents. No summary statistics were provided. This conclusion was based upon two presentation abstracts by Stein				There was no description of quality assessment in this systematic review and abstracts were included.
Treatment of childhood hypercholesterolemia with HMG-CoA reductase inhibitors	Duplaga BA;	1999		Unknown		The review looks at 6 studies of varying quality re the use of statins in children with hypercholesterolaemia. Their FH status is not always made clear. The conclusion is that adding lovastatin, pravastatin or simvastatin to diet therapy in children over 10 years of age may be effective when diet therapy alone has failed to reduce LDL. The use of statins during childhood and adolescence is concluded to be safe but large, long term studies are recommended.				A quality assessment protocol was not provided. The review included case series (3) as well as RCTs (3). These studies were all included in the Arambepola et al review from Simon Broome.
The effects of colestipol hydrochloride on serum lipoprotein lipid and apolipoprotein B and A-I concentrations in children heterozygous for familial hypercholesterolemia	Groot PH; jkhuis-Stoffelsma R; Grose WF; Ambagtsheer JJ; Fernandes J;	1983	OutcomesQ3-7 "Treatment effect: Colestipol v placebo: TC -.89 (p<0.001); LDL + VLDL -0.91(p<0.001); HDL 0.02 (NS); TG -0.10 (NS); Apo B -0.18 (p<0.001); Apo A 0.02 (NS). Percent change: TC -12.8%; LDL + VLDL -15.7%; HDL 1.7%; TG -9.3%; Apo B -13.5% and Apo A 1.7%."	Netherlands Heart Foundation.	5 children did not complete the study because of aversion to the sandy tasting medication. There were no other complaints.	It appears that resins significantly lower LDL + VLDL in children with FH but some children had difficulty tolerating the medicine.				This is a crossover design and there is concern about residual effect of previous treatment
Growth during treatment of familial hypercholesterolemia	Hansen D; Michaelsen KF; Skovby F;	1992	OutcomesQ3-7 The decision to prescribe colestipol was based upon the concentrations of serum lipids and the response to dietary measures, the age and sex of the child and the family history of early	Unknown	No	This study raises the question of dietary safety in children with FH	No - this study does not have an adequate sample size	No	Yes	This is actually a case series of FH children on diet or diet and colestipol

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			ischemic heart disease. The scores for both height/age and weight/age decreased by approximately 0.4 during dietary treatment (p<0.05), but were not affected by treatment with colestipol.							
Treatment of patients with familial defective apolipoprotein B-100 with pravastatin and gemfibrozil: a two-period cross-over study	Hansen PS; Meinertz H; Gerdes LU; Klausen IC; Faergeman O;	1994	OutcomesQ3-7 "When all 30 children were analyzed as one group, there was a statistically significant decrease in both scores of approximately 0.4 mean (SD score) during dietary treatment: Before treatment : height/age 0.43; after treatment 0.06, p=0.02. Before treatment: Weight/age -0.12; after treatment -0.55, p=0.0009. The addition of colestipol to the dietary regime of 17 children did not cause any statistically significant change of growth: After dietary treatment: height/age 0.15; after colestipol treatment 0.27. After dietary treatment: weight/age -0.56, ns; after colestipol treatment -0.22, ns."	Danish Medical Research Council	Possible inhibition of growth due to low fat diet.	This study provides a small amount of long term data about diet restriction in children with FH. Colestipol does not appear to change this effect although there is no information about colestipol on its own.	Small study from which conclusions cannot be drawn. Further research required.	No other studies	Yes	There was no blinding reported in this study and standardization of methods of weighing and measuring height were not discussed.
Efficacy and Safety of Pravastatin in Patients with Primary Hypercholesterolemia .2. Once-Daily Versus Twice-Daily Dosing	Hunninghake DB; Mellies MJ; Goldberg AC; Kuo PT; Kostis JB; Schrott HG; Insull W; Pan HY;	1990	OutcomesQ3-7 Significant reductions in both total and LDL cholesterol were observed in all 3 prava treatment groups (p<0.001) versus placebo at all times. The level in the placebo group were unchanged. At week 8 mean reductions from placebo ranged from 23-27% for TC (placebo 8.29[0.24] prava 6.11 [0.21]) and from 30-34% for LDL cholesterol (placebo 6.40 [0.24] prava 4.23 [0.20]). The differences in effects among prava regimes were not statistically significant. HDL levels were increased with all 3 prava regimes with 40	Squibb Institute for Medical Research	No discontinuations due to clinical symptoms and no statistically significant changes in laboratory results for liver enzymes.	This study indicates that pravastatin versus placebo is effective in reducing TC and LDL in patients with primary FH	The effect of lipid lowering appears to be related to statin use in this study.	This study is consistent with other studies of statins in patients with severe FH.	This study does directly apply to the population of interest.	

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			mgm and 20 mg bid regimes yielding significant elevations compared with placebo (p<0.05). Mean reductions in triglycerides in all 3 prava groups were significant compared with baseline. Mean TC/HDL ration was reduced 26-32% at the end of 8 weeks (p<0.001).							
Ciprofibrate in the therapy of type II hypercholesterolemia. A double-blind trial	Illingworth DR; Olsen GD; Cook SF; Sexton GJ; Wendel HA; Connor WE;	1982	OutcomesQ3-7 Placebo: TC 8 mmol/l +/- .82; LDL 6.1 mmol/l +/- 1.05; HDL 1.07 mmol/l +/- .25; TG 1.87mmol/l +/- 1.22. 50 mg ciprofibrate: TC 7.2 mmol/l +/- .49; LDL 5.3 mmol/l +/- .44; HDL 1.38 mmol/l +/- .29; TG 3.15 mmol/l +/- .56. 100 mg ciprofibrate: TC 6.9 mmol/l +/- 1.3; LDL 5.1 mmol/l +/- 1.3; HDL 1.43 mmol/l +/- .31; TG .78 mmol/l +/- .56. Percent change 50 mg ciprofibrate: TC -11.1% (+5 to -32), p<0.05; LDL -13% (+9 to -25), p<0.025; HDL +8% (-9 to +27), p<0.01; TG -22% (-5 to -30), p<0.025. Percent change 100 mg ciprofibrate: TC -19.7% (-9 to -24), p<0.005; LDL -24.4% (-4 to -29), p<0.005; HDL +9.8% (-14 to +27), p<0.01; TG -30% (-4 to -57), p<0.05. All percent changes were significant.	Unknown	Ciprofibrate was well tolerated by all patients. Routine laboratory tests did not show any consistent changes.	This study indicates that ciprofibrate is effective in lowering LDL cholesterol levels and increasing HDL levels.	This study was small and stopped prematurely but ciprofibrate does appear to be effective in this group of patients	Yes	Yes	The study was stopped because of evidence that ciprofibrate caused hepatic adenomas and carcinomas in rats and because of concern over the results of the WHO trial with clofibrate. Ciprofibrate has since been re-released for clinical trials.
Simvastatin (MK 733) in heterozygous familial hypercholesterolemia: a two-year trial	Leclercq V; Harvengt C;	1989	OutcomesQ3-7 Q2-9a. Group 1 (n=4) identified 'good responders': Mean total cholesterol Week 0 - 358 +/- 26; Week 12 - 216 +/- 13; mean LDL Week 0 - 276 +/- 28; Week 12 - 138 +/- 10; mean HDL Week 0-46 +/- 4; Week 12 - 45 +/- 4; mean Triglycerides Week 0 - 182 +/- 20; Week 12 - 164 +/- 30. Group 2 (n=15) identified 'poor responders': Mean total cholesterol Week 0 - 483	Merck, Sharp and Dohme	Simvastatin was not withdrawn in any patients because of side effects. Alterations in lab results and any symptom complaints were transient.	The placebo v simvastatin phase of this study showed significant reductions in total cholesterol and LDL levels.	Randomisation and allocation concealment were not described and the study sample was very small. Results should be confirmed.	There is good consistency with another study reviewed for this guideline and also with the non FH literature.	Yes, this study is directly applicable to FH patients.	More than half the study participants were men (12/19); co-morbidities not described.

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			+/- 26; Week 12 - 329 +/- 17; mean LDL Week 0 - 405 +/- 22; Week 12 - 257 +/- 15; mean HDL Week 0- 44 +/- 4; Week 12 - 52 +/- 5; mean Triglycerides Week 0 - 172 +/-19; Week 12 - 115 +/- 7. The change in total cholesterol and LDL cholesterol from Week 0 to Week 12 was significant (p<0.05) in both groups.							
A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia	Marks D; Thorogood M; Neil HA; Humphries SE;	2003		NHS R&D HTA Programme		No clinical trials were identified in FH patients which studied the effectiveness of statins in preventing coronary morbidity and mortality. However, the Simon Broome cohort of FH patients in the UK provides information on the changes in mortality after				This review is based upon searches done for the HTA 'Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost-effectiveness analysis.' Treatment was not included in the HTA but is addressed
Simvastatin in Severe Hypercholesterolemia - A Placebo Controlled Trial	Mcdowell IFW; Smye M; Trinick T; Shortt JA; Archibald MP; Trimble ER; Nicholls DP;	1991	OutcomesQ3-7 Q2-9a.Q2-9a. Results reported in mmol/l. Placebo group (n=12) : Mean total cholesterol Week 0 - 11.7 +/- 0.6; Week 12 - 11.7 +/- 0.6; mean LDL Week 0 - 9.5 +/- 0.6; Week 12 - 9.5 +/- 0.6; mean VLDL 0.73 +/0.15; Week 12 0.66 +/- 0.11; mean HDL Week 0- 1.46 +/- 0.09; Week 12 - 1.53 +/- 0.09; mean Triglycerides Week 0 - 2.0 +/- 0.5; Week 12 - 2.0 +/- 0.4; mean Apo B Week 0 - 1.69 +/- 0.13; Week 12 1.66 +/- 0.09; Apo A1 Week 0 - 1.45 +/- 0.07; Week 12 1.40 +/- 0.06;Apo (a) Week 0 - 445 +/- 107; Week 12 448 +/- 110; Simva group (n=15) : Mean total cholesterol Week 0 - 11.4 +/- 0.6; Week 12 - 7.7 +/- 0.5; mean LDL Week 0 - 9.1 +/- 0.6; Week 12 - 5.6 +/- 0.4;mean VLDL 0.93 +/0.17; Week 12 0.53 +/- 0.06; mean HDL Week 0- 1.36 +/- 0.11; Week 12 - 1.64 +/- 0.12; mean	Merck Sharp and Dohme	Side effects were transient and liver transaminases did not change.	Simva appears to be effective in lowering LDL cholesterol in severe Type II hypercholesterolaemia and is well tolerated in the short term	Although the study is small it appears that there is a statistically significant reduction in LDL with the use of simva v placebo	The results are consistent with other small Merck studies and with the larger literature on statins in non FH patients	Yes, this study directly applies to the population of interest	14/27 patients were classified as definite FH; all had severe hypercholesterolaemia

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			Triglycerides Week 0 - 2.6 +/- 0.5; Week 12 - 1.6 +/- 0.2; mean Apo B Week 0 - 1.55 +/- 0.11; Week 12 1.13 +/- 0.09; Apo A1 Week 0 - 1.41 +/- 0.07; Week 12 1.43 +/- 0.05;Apo (a) Week 0 - 402 +/- 109; Week 12 492 +/- 149; The change in total cholesterol and LDL cholesterol from Week 0 to Week 12 was significant (p<0.05) in the simva group for total cholesterol and LDL cholesterol (p<0.05)							
Clinical evidence for use of acetyl salicylic acid in control of flushing related to nicotinic acid treatment	Oberwittler H; Baccara-Dinet M;	2006		Unknown		The review supports the use of aspirin both physiologically and clinically to treat flushing due to nicotinic acid. It is not clear if the review is RCT based; the search could have been broader and a meta analysis done of the aspirin trials.				It may have been possible to combine the four studies which specifically explored the utility of aspirin in preventing flushing
Efficacy and safety of cholestyramine therapy in peripubertal and prepubertal children with familial hypercholesterolemia.[see comment]	Tonstad S; Knudtzon J; Sivertsen M; Refsum H; Ose L;	1996	OutcomesQ3-7 "Percent change reported; absolute values not given. After one year of treatment: TC decreased 11.5% after 12 months in the cholestyramine versus 0-3% in placebo group (p<0.001). LDL decreased 16.9%-18.6% after 12 months in the cholestyramine versus 0-1.5% in placebo group (p<0.0001), and HDL increased by 8.2%-13.4% versus 2.4%-8.8% (not significant). Mean triglyceride remained unchanged in both groups. APO B was reduced from 2.1 +/- 0.4 gm/l to 1.8 +/- 0.4 gm/l. Mean height velocity standard deviation scores during 1 year for the children in the cholestyramine and placebo groups who had not started puberty were 0.24 +/- 1.14 and 0.11 +/- 0.68, respectively (not significant).In the cholestyramine group, mean levels of 25-	Funded in part by Bristol-Myers Squibb	Unpalatability of the drug caused 21 withdrawals. Abdominal pain and/or loose stools or nausea were reported in 3 placebo and 5 treatment patients. One case of intestinal obstruction in one boy after taking two doses of cholestyramine was reported.	This study indicates that significant reductions in LDL are achievable with cholestyramine and that growth is not adversely affected. However tolerability is a problem and vitamin D supplements may be required.	This study is small with a high drop out rate. Further research is required.	Yes	Yes	

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			hydroxyvitamin D decreased."							
Low-dose simvastatin treatment in patients with moderate-grade familial hypercholesterolemia	Valerio G; Vigna GB; Vitale E; Romagnoni F; Fellin R;	1990	OutcomesQ3-7 Simva treatment: TC Week 0 288 +/- 21mg/dl (7.4mmol/l +/- .54); Week 8 212 +/- 16 (-26%)mg/dl (5.4 mmol/l +/-.4; LDL-C Week 0 213 +/- 17 mg/dl (5.46 mmol/l +/- .44; Week8 139 +/- 13(-35%) mmol/l (3.56 mmol/l +/- .33; HDL-C Week 0 52 +/- 14mg/dl (1.44 mmol/l+/- .03); Week 8 50 +/- 14(-4%)(1.28 mmol/l +/- .35); TC/HDL-C Week 0 5.9 +/- 1.4 mg/dl \9.15 mmol/l +/- 0.4); Week 8 4.4 +/- 1.3(-25%)mg/dl (.11 mmol/l +/- .03); TG Week 0 116 +/- 46 mg/dl (1.3 mmol/l +/- .52); Week 8 97 +/- 43(-16%) mg/dl (1.09 mmol/l +/-.48) ; Apo A1 Week 0 156 +/- 28; Week 8 154 +/- 27; Apo B Week 0 195+/- 16; Week 8 134 +/- 15 (-31%). Changes in Total cholesterol, LDL-C, TC/HDL-C and Apo B were significant at P<0.001.The four patients treated with placebo did not show any significant variation in any of the lipid parameters examined.	Unknown	In both groups of patients, clinical and laboratory safety parameters including SGOT, SGPT, AP, and CPK showed no changes. No eye changes were evidenced and no adverse reactions were observed.	This study compares simvastatin to placebo and answers question 8. Simvastatin 10mg significantly lowers total cholesterol, LDL-C, TC/HDL-C and Apo B in patients with 'slight to mild' FH.	Although this was a randomised, double blinded study the sample size was too small to be generalisable.	This study is consistent with other studies of high dose statins in patients with severe FH.	This study does directly apply to the population of interest.	
Treatment of familial hypercholesterolaemia: a controlled trial of the effects of pravastatin or cholestyramine therapy on lipoprotein and apolipoprotein levels.[see comment]	Wiklund O; Angelin B; Fager G; Eriksson M; Olofsson SO; Berglund L; Linden T; Sjoberg A; Bondjers G;	1990	OutcomesQ3-7 At 12 weeks: TC with Pravastatin 7.64 +/- 1.53 mmol/l; with Cholestyramine 7.27 +/- 1.73 mmol/l; with placebo 10.09 +/- 2.15 mmol/l. TG with Pravastatin 1.62 +/- 0.88 mmol/l; with Cholestyramine 1.52 +/- 0.77 mmol/l; with placebo 1.71 +/- 0.84 mmol/l. LDL with Pravastatin 5.86 +/- 1.52 mmol/l; with Cholestyramine 5.55 +/- 1.76 mmol/l; with placebo 8.26 +/- 2.26 mmol/l. VLDL with Pravastatin 0.46 +/- 0.39 mmol/l; with Cholestyramine 0.47 +/-	Swedish Heart Lund Foundation; the Swedish Medical Research Council, the King Gustaf V and Queen Victoria Foundation and a grant from E.R Squibb & Sons	The overall frequency of side effects was 35% for pravastatin 53% for cholestyramine and 30% for placebo. The significantly higher frequency in the cholestyramine group was mainly due to GI symptoms (p=0.032).	ConclKQQ3-9 Yes, it is concluded that pravastatin at 40 mg daily was as effective as cholestyramine in lowering LDL cholesterol and increasing HDL in patients with FH. Since the frequency of side effects was higher with cholestyramine , pravastatin should offer a promising alternative treatment.	The effect appears to be the result of treatment	Yes	Yes	

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			0.36 mmol/l; with placebo 0.60 +/- 0.52 mmol/l. HDL with Pravastatin 1.34 +/- 0.88 mmol/l; with Cholestyramine 1.27 +/- 0.77 mmol/l; with placebo 1.23 +/- 0.84 mmol/l. Apo B with Pravastatin 1.64 +/- 0.41 mmol/l; with Cholestyramine 1.54 +/- 0.40 mmol/l; with placebo 2.03 +/- 0.43 mmol/l. Apo A with Pravastatin 1.55 +/- 0.32 mmol/l; with Cholestyramine 1.47 +/- 0.36 mmol/l; with placebo 1.40 +/- 0.31 mmol/l. The differences between the treatment groups were not significant.							

Question 9: What is the effectiveness of the following adjunctive pharmacotherapy with statins in individuals with FH: statins with any of resins, fibrates, niacin, fish oils, nicotinic acid and ezetimibe (alone or in combination)?

Study descriptions

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
Comparative efficacy and safety of pravastatin, nicotinic acid and the two combined in patients with hypercholesterolemia	Davignon J; Roederer G; Montigny M; Hayden MR; Tan MH; Connelly PW; Hegele R; McPherson R; Lupien PJ; GagnÚ C;	1994	RCT	1+	154 were included in short term ITT population; pravastatin alone n=39; pravastatin plus nicotinic acid n=30; placebo alone n=40; placebo plus nicotinic acid n=30.	Women were postmenopausal or surgically sterile and represented only 28% of study population. 76% of patients had heterozygous FH; 14% had FCH; and 11% had polygenic hypercholesterolaemia. Excluded comorbidities metabolic, renal, hepatic, endocrine or CV.	Other exclusion criteria included use of steroids or other lipid lowering agents. Mean age was 48.8 and 95% were Caucasian.	Unknown	Multicentre study in USA	Patients were randomised to placebo, pravastatin alone, pravastatin plus nicotinic acid, placebo plus nicotinic acid.	Treatments were compared to baseline levels.	8 weeks	LDL, HDL, total cholesterol and TG
Clinical experience with simvastatin compared with cholestyramine	Erkelens DW; Baggen MG; Van Doormaal JJ; Kettner M; Koningsberger JC; Mol MJ;	1988	RCT	1-	60;20 received cholestyramine and 40 received simvastatin. All received combination therapy.	Patients with heterozygous familial hypercholesterolaemia between 24 and 70	29 male and 31 female; age 49.3	Unknown	This is the Dutch section of an international stud	Colestyramine 8-16 g; simva 20 mg for 6 weeks then 40 mg for six weeks. After 12 weeks all patients received combination therapy of 40 mg simvastatin and 8-16 g cholestyramine.	Comparisons are between treatments	12 weeks on single drug and 8 more weeks on the combination	TC, LDL, HDL, TG, Apo A and ApoB
Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia	Gagne C; Gaudet D; Bruckert E; Ezetimibe S;	2002	RCT	1+	16 patients were randomized to ezetimibe 10 mg plus statin-40 (either atorva or simva); 17 patients were randomized to ezetimibe plus statin-80 and 17 to statin-80.	Adults and children at least 12 years old or body weight > or equal to 40kg with HoFH determined by genetic testing or clinical criteria	Median age of ezetimibe groups was 32 +/- 3 and statin group 33 +/- 4; age greater than or equal to 18 was 85% in ezetimibe groups and 88% in statin group. 71% of statin group was female and 52% of ezetimibe group was female.	Unknown	Montreal Canada; 2 sites in Quebec;1 site in Paris	Statin (atorva or simva) 80 versus ezetimibe 10 mg plus statin 40 mg or ezetimibe 10 mg plus statin 80 mg	Treatments are compared	12 week study phase	LDL-C (direct and calculated); total cholesterol; apo B, HDL-C; TG
The efficacy and safety of pravastatin, compared to and in combination with bile acid binding resins, in familial hypercholesterolaemia.	Hoogerbrugge N; Mol MJ; Van D; Rustemeijer C; Muls E; Stalenhoef AF; Birkenhager JC;	1990	RCT	1+	62 patients with 40 in pravastatin group and 22 in placebo/resin group	All patients had heterozygous FH. The women were post menopausal or had been surgically sterilized. FH was diagnosed on the basis of family history, tendon xanthomata and serum lipid concentrations.	38 men and 24 women with mean age of 44-45 years.	Recruited at 5 centres.	Holland and Belgium	Pravastatin versus placebo; follow on study of resins and resins plus pravastatin compared to placebo lipid levels	Comparisons are made between treatments and between treatments versus placebo	10-24 weeks	TC, LDL, HDL, TG
Comparative Efficacy	Knopp RH;	1993	RCT	1+	311 adults.	Patients with primary	There were 216 men	Unknown	9 lipid	Pravastatin was	Pravastatin	8 weeks	LDL, TC,

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
and Safety of Pravastatin and Cholestyramine Alone and Combined in Patients with Hypercholesterolemia	Brown WV; Corder CN; Dobs AS; Dujovne CA; Goldberg AC; Hunninghake DB; Insull W; Mellies MJ; Smith DA; Stein EA;				Placebo: n=60; Cholestyramine 12 g bid n=61; pravastatin 20 mg bid n=63; pravastatin 40 mg bid n=63; and pravastatin 20 mg bid plus cholestyramine 12 g bid n=64.	hypercholesterolaemia were included. Excluded were premenopausal women unless surgically sterile and patients with DM, impaired hepatic or renal function, angina, obesity and on drugs which interfered with lipid metabolism.	and 95 women. Nearly all were white. Otherwise subject characteristics did not differ significantly among the five treatment groups. Mean age was 52 years.		research clinics in the USA	studied at doses of 20 or 40 mg twice daily alone or 20 mg twice daily with cholestyramine, 12 g twice daily vs placebo	with versus placebo		HDL
Efficacy and safety of a combination fluvastatin-bezafibrate treatment for familial hypercholesterolemia: comparative analysis with a fluvastatin-cholestyramine combination	Leitersdorf E; Muratti EN; Eliav O; Meiner V; Eisenberg S; Dann EJ; Sehayek E; Peters TK; Stein Y;	1994	RCT	1+	38 total; 18 in Group 1 and 20 in Group 2	Patients with heterozygous FH who had been recruited and participated in a previous study. Further details not provided in this report.	Mean age Group 1 42.7 and Group 2 47; 61% of Group 1 was male and 40% of Group 2 was male. 70% of Group[1 smoked and 45% of group 2 smoked. The differences between groups were not statistically significant.	Patients had been recruited for a previous study.	Hadassah University Hospital, Jerusalem	Treatment with 40 mg fluvastatin plus either 400 mg/d of bezafibrate or 8 g per day cholestyramine	Comparison between treatments is made	Patients took combination therapy during weeks 13-18 of this study.	LDL, HDL, TC and TG
Effectiveness of Low-Dose Lovastatin Combined with Low-Dose Colestipol in Moderate to Severe Primary Hypercholesterolemia	Tonstad S; Ose L; Gorbitz C; Harrison EM; Gans HJD;	1993	RCT	1+	57 participants. 19 per group	Age 18-65 years with BMI<35 kg per m2. No clinically significant endocrine, renal, hepatic or GI disease and absence of MI or major surgery within 6 months of the study or secondary hyperlipidaemia. No lipid lowering drugs or possibility of pregnancy.	Mean age 51.7 years. Seven men and five women smoked at least 10 cigarettes daily. The median frequency of alcohol consumption was once a week. Mean BMI was 24.9 kg per m2.	Unknown	Lipid Clinic, Rikshospitalet, Oslo, Norway	Effect of lovastatin and colestipol (resin) on lipid lowering	Treatment versus placebo	8 weeks	TC, LDL, TG, HDL, Apo A and Apo B
Comparison of pravastatin alone and with cholestyramine in the treatment of hypercholesterolemia	Tsai CH; Ding YA; Hao KL;	1995	RCT	1-	30 patients with 15 in each group	All patients had primary hypercholesterolemia with a fasting serum total cholesterol of 250-350 mg/dl (6.4 mmol/l-9.0mmol/l) and a fasting TG of less than 350 mg/dl (3.9 mmol/l).	5 males and 25 females with ages from 30-60 years. Patients with heart disease, renal failure, hepatic disease, diabetes or secondary hypercholesterolemia were excluded.	Unknown	Taiwan	Pravastatin 20 mg versus pravastatin10 mg with cholestyramine 8g/day	Treatment versus treatment	24 weeks	TC, LDL, HDL and TG
Pravastatin and Gemfibrozil Alone and in Combination for the Treatment of Hypercholesterolemia	Wiklund O; Angelin B; Bergman M; Berglund L; Bondjers G; Carlsson A; Linden T; Miettinen T; Odman B; Olofsson SO; Saarinen I; Sipila R; Sjostrom P; Kron B; Vanhanen H; Wright I;	1993	RCT	1+	266 patients: pravastatin n=64; gemfibrozil n=68; combination n=65 and placebo n=69.	Ambulatory men and women with no childbearing potential. All patients had primary hypercholesterolemia. Homozygous FH patients and type I, III, IV or V were excluded. Patients with significant CV, renal, hepatic disease or metabolic or GI disorders war	There were 177 males and 89 females; mean age 53.9 years.	Unknown	5 centers in Sweden and 2 in Finland	Pravastatin and gemfibrozil also and in combination for treatment of hypercholesterolemia	Treatments to placebo and in comparison to each other	12 weeks	TC, LDL, VLDL, TG, HDL, Apo A and Apo B.

Study results

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
Comparative efficacy and safety of pravastatin, nicotinic acid and the two combined in patients with hypercholesterolemia	Davignon J; Roederer G; Montigny M; Hayden MR; Tan MH; Connelly PW; Hegele R; McPherson R; Lupien PJ; GagnÚ C;	1994	8 week results: Placebo: NS change from baseline; Nicotinic acid: LDL -16.11%; HDL 12.20%; TC -11.25%; TG -11.43%. Pravastatin: -32.72%; HDL 13.46%; TC -23.08%; TG -14.38%. Combination of prava and nicotinic acid: LDL -41.50%; HDL 16.14%; TC -31.62%; TG -34.85%. There were significant differences between the pravastatin and pravastatin and nicotinic acid combination (p<0.05).	Bristol Myers Squibb	Of 158 patients randomized to treatment, 5 discontinued treatment due to adverse events in the first 8 weeks, 4 in the nicotinic acid group and 1 in the combination group. No patient receiving pravastatin alone discontinued treatment.	This study indicates that a combination of nicotinic acid and pravastatin is significantly more effective than either treatment on its own.				Not clear why 12 patients did not participate.
Clinical experience with simvastatin compared with cholestyramine	Erkelens DW; Baggen MG; Van Doormaal JJ; Kettner M; Koningsberger JC; Mol MJ;	1988	TC baseline 12mmol/l; percent change with simva -36%, cholestyramine -23% and combination -45%. LDL baseline 10mmol/l; percent change with simva -43%, cholestyramine -30% and combination -64%.HDL baseline 1.11mmol/l; percent change with simva +16%, cholestyramine +9% and combination +20%.TG baseline 1.85 mmol/l; percent change with simva -21%, cholestyramine +11% and combination -17%. Apo A baseline 99mmol/l; percent change with simva +21%, cholestyramine +9% and combination +15%. Apo B baseline 303 mmol/l; percent change with simva -47%, cholestyramine -32% and combination -64%.	Unknown	Clinical adverse effects were primarily GI symptoms in the cholestyramine group. Eleven patients could not tolerate cholestyramine. Transaminase increases were observed with both drugs and CPK increases occurred in the simva group only.	The study indicates that the combination of simva and cholestyramine has an additive effect.	It appears that the effect is due to the treatment.	Yes	Yes	
Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia	Gagne C; Gaudet D; Bruckert E; Ezetimibe S;	2002	Changes in lipid levels from baseline simva 40 (mmol/l): Direct LDL absolute change 0.5 statin-80 and 1.7 in ezetimibe plus statin 40/80 (p =0.007); TC absolute change .49 statin-80 and 1.9 in ezetimibe plus statin 40/80 (p<0.01) . There were no other significant differences between the two treatment groups. There were reductions of at least 14% to 20.5% in LDL-C when ezetimibe was coadministered with a moderate (40 mg) or maximal (80 mg) dose statin therapy compared with maximal therapy with statins alone. Ezetimibe plus statin 80 reduced LDL 26.6% compared to	Schering-Plough Research Institute and Merck/Schering-Plough Pharmaceuticals	Two patients in the ezetimibe group discontinued treatment - one due to epigastric and chest pain and another due to increase liver enzymes. There were no significant differences between treatment groups on another other measures of safety.	It appears that ezetimibe is an effect lipid lowering agent in the HoFH population	This study appears to be well designed and the results are plausible.	No other studies	Yes	There may be differences between sites

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			statin 80 reduction of 5.6% from baseline of simva 40.							
The efficacy and safety of pravastatin, compared to and in combination with bile acid binding resins, in familial hypercholesterolaemia.	Hoogerbrugge N; Mol MJ; Van D; Rustemeijer C; Muls E; Stalenhoef AF; Birkenhager JC;	1990	Changes in serum lipid concentrations (%): TC: placebo group week 8 -2 +/-9; Resins week 24 -17 +/- 12; pravastatin week 8 -28 +/- 7. LDL: placebo group week 8 -2 +/-9; Resins week 24 -22 +/- 15; pravastatin week 8 -33 +/- 8. HDL: placebo group week 8 -5 +/-14; Resins week 24 7 +/- 15; pravastatin week 8 8 +/- 13. TG: placebo group week 8 4 +/38; Resins week 24 17 +/54; pravastatin week 8 -14 +/30. When pravastatin was supplemented with resins, there was an additional reduction in TC of 8% by week 24 ($p<0.01$) and 12% in LDL ($p<0.01$).	Unknown	None of the patients had to discontinue medication because of side effects Symptomatic adverse effects or major abnormalities of laboratory values did not occur.	The mean reduction in LDL cholesterol after 8 weeks of treatment with pravastatin was 33%; with resins was 22% and by 42% with pravastatin and resin combination.	The results appear to be due to treatment. There were two resins used but the researchers assumed that these reduced cholesterol levels to the same extent and by the same mechanism.	Yes	Yes	
Comparative Efficacy and Safety of Pravastatin and Cholestyramine Alone and Combined in Patients with Hypercholesterolemia	Knopp RH; Brown WV; Corder CN; Dobs AS; Dujovne CA; Goldberg AC; Hunninghake DB; Insull W; Mellies MJ; Smith DA; Stein EA;	1993	Pravastatin 20 mg bid: TC - baseline 7.9 +/- 0.14; week 8 6.0 +/- 0.14; -24% +/- 1.2. LDL - baseline 6.1 +/- 0.13; week 8 4.2+/- 0.13; -31.3 % +/- 1.6. Pravastatin 40 mg bid: TC - baseline 8.0 +/- 0.15; week 8 5.7 +/- 0.12; -28.7% +/- 1.2. LDL - baseline 6.1 +/- 0.14; week 8 3.8 +/- 0.11; -37.7% +/- 1.5. Cholestyramine 12 g bid: TC - baseline 8.1 +/- 0.17; week 8 6.3 +/- 0.18; -22.0% +/- 1.3. Cholestyramine 12 g bid + pravastatin 20 mg bid: LDL - baseline 6.1 +/- 0.17; week 8 4.2 +/- 0.17; -32.1% +/- 1.7. Placebo: TC - baseline 8.0 +/- 0.16; week 8 7.9 +/- 0.18.LDL - baseline 6.0 +/- 0.15; week 8 5.9 +/- 0.18; -2.3% +/- 2.4."	Bristol Meyers Squibb	Frequencies of adverse experiences attributable to the drugs were similar in all treatment groups. The most common adverse reaction were gastrointestinal. Mean levels of liver enzymes remained within the normal range throughout the trial.	This study indicates that both pravastatin, cholestyramine and cholestyramine and pravastatin in combination are effective treatments for cholesterol and LDL.				Only about half of the patients had FH.
Efficacy and safety of a combination fluvastatin-bezafibrate treatment for familial hypercholesterolemia: comparative analysis with a fluvastatin-cholestyramine combination	Leitersdorf E; Muratti EN; Eliav O; Meiner V; Eisenberg S; Dann EJ; Sehayek E; Peters TK; Stein Y;	1994	Percent change from baseline was reported in both groups. Total cholesterol in Group 1 changed by 23.9% + 10.7 and in Group 2, 28.6% +11.7; TG increased in Group 1 by 14.2 % +35.8 and decreased in Group 2, 25.1% + 29.7; HDL increased in Group 1 2.9 % + 11.0 and in Group 2 13.0% + 13.4; LDL decreased by 21.3% + 7.9 in Group 1 and 25.0% + 13.5. There was no significant difference in total cholesterol or LDL between groups; however, there were significant differences	Sandoz	None of the patients discontinued the study because of adverse events. GI events occurred in five cases from Group 1 and four from Group 2. No notable abnormalities were observed in laboratory values.	This study demonstrates that the addition of fibrates or resins did not result in a significant difference in LDL or TC but that fibrates were more effective in treating TG and HDL levels.				

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			between triglyceride and HDL levels (p<0.001 and p<0.05 respectively).							
Effectiveness of Low-Dose Lovastatin Combined with Low-Dose Colestipol in Moderate to Severe Primary Hypercholesterolemia	Tonstad S; Ose L; Gorbitz C; Harrison EM; Gans HJD;	1993	Mean baseline values (SD): TC mmol/l -Placebo 7.6 (0.9); lovastatin 20 mg & 5 g colestipol 5.8 (0.7): lovastatin 20 mg and 10 g colestipol 5.5 (0.9); LDL mmol/l -Placebo 5.6 (0.7); lovastatin 20 mg & 5 g colestipol 3.9 (0.7): lovastatin 20 mg and 10 g colestipol 3.6 (0.); TG - Placebo 1.5 (0.7); lovastatin 20 mg & 5 g colestipol 1.4 (0.7): lovastatin 20 mg and 10 g colestipol 1.2 (0.4); HDL - Placebo 1.3 (0.3); lovastatin 20 mg & 5 g colestipol 1.3 (0.4): lovastatin 20 mg and 10 g colestipol 1.4 (0.3); Apo A- Placebo 1.2 (0.1); lovastatin 20 mg & 5 g colestipol 1.2 (0.2): lovastatin 20 mg and 10 g colestipol 1.3 (0.2);Apo B - Placebo 1.2 (0.3); lovastatin 20 mg & 5 g colestipol .9 (0.2): lovastatin 20 mg and 10 g colestipol .9 (0.1). Compared to placebo 20 mg lovastatin and 5 g and 10 g of colestipol reduced TC significantly (p<0.0001), Apo B levels(p<0.01), LDL levels (p<0.0001). There was a 34% and 35% reduction in LDL levels at 8 weeks with 5 g and 10 g colestipol respectively.	Unknown	The incidence of GI events possibly or probably attributed to drug treatment was 32% and 30% in the lovastatin 5 g colestipol and 10 g groups respectively and 50% in the placebo group (p>0.05). Six of the 39 participants (15%) on active therapy reported abdominal side effects that lasted 3 weeks or longer. There were no clinically significant changes in lab safety tests.	The combination of low dose lovastatin with low dose colestipol in this study resulted in significant reductions in total cholesterol, LDL and Apo B levels.	Yes, it appears that the treatment was responsible for the effect.	Yes	Yes	
Comparison of pravastatin alone and with cholestyramine in the treatment of hypercholesterolemia	Tsai CH; Ding YA; Hao KL;	1995	TC % change at 24 weeks: Pravastatin 5.5 mmol/l +/- .26; pravastatin + cholestyramine 5.4 mmol/l +/- .31; p value NS. LDL % change at 24 weeks: Pravastatin 3.5 mmol/l +/- .28; pravastatin + cholestyramine 3.13 mmol/l +/- .33; p <0.01. HDL % change at 24 weeks: Pravastatin 1.4 mmol/l +/- .15; pravastatin + cholestyramine 1.4 mmol/l +/- .26; p value NS. TG % change at 24 weeks: Pravastatin 2.1 mmol/l +/- .24; pravastatin + cholestyramine 2.5 mmol/l +/- .20; p <0.01.	Sankyo Company and Bristol Myers Squibb	No serious adverse drug reactions occurred during the study. No patients withdrew due to side effects.	The reduction of LDL of 24% with pravastatin alone is in line with results obtained in a dose response study on primary hypercholesterolemia. There was a higher reduction in LDL (32%) with low dose pravastatin and cholestyramine. The low dose of cholestyramine reduced side effects and improved compliance.	The effect appears to be due to the treatment	Yes	Yes	
Pravastatin and Gemfibrozil Alone and in Combination for the Treatment of Hypercholesterolemia	Wiklund O; Angelin B; Bergman M; Berglund L; Bondjers G; Carlsson A; Linden T; Miettinen T;	1993	TC: Placebo 7.13 mmol/l (0.12), -1.72% change; pravastatin 5.44 mmol/l (0.11), -26.25% change; gemfibrozil 6.20 mmol/l (0.12),- 15.18% change; combination 5.10 mmol/l (0.12), -28.98%	Swedish Medical Research Council, the Swedish Heart and Lung Foundation, the King Gustav V and Queen	Safety3-11 A total of 93 patients reported 162 adverse events. The overall frequency did not differ significantly between the	This study shows that when compared with placebo, pravastatin, gemfibrozil and their combination significantly (p<0.01) reduced TC, LDL, VLDL and TG and also	The effect appears to be due to the intervention.	Yes	Yes	It appears that no account was taken of the 24 drop outs.

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
	Odman B; Olofsson SO; Saarinen I; Sipila R; Sjostrom P; Kron B; Vanhanen H; Wright I;		change. LDL: Placebo 5.02 mmol/l (0.13), -1.88% change; pravastatin 3.44 mmol/l (0.11), -33.54% change; gemfibrozil 4.29 mmol/l (0.11),-16.80% change; combination 3.17 mmol/l (0.10), -37.06% change. VLDL: Placebo 0.65 mmol/l (0.05), +2.17% change; pravastatin .49 mmol/l (0.04), -21.85% change; gemfibrozil 0.32 mmol/l (0.02),-49.06% change; combination 0.32 mmol/l (0.03), -49.43 % change. TG: Placebo 1.83 mmol/l (0.10), +1.87% change; pravastatin 1.53 mmol/l (0.08), -14.17% change; gemfibrozil 1.03 mmol/l (0.05),-42.16% change; combination 1.01 mmol/l (0.06), -41.68 %change. HDL: Placebo 1.16 mmol/l (0.03), -4.44% change; pravastatin 1.32 mmol/l (0.04), -5.93% change; gemfibrozil 1.39 mmol/l (0.04),15.21% change; combination 1.46 mmol/l (0.05), 16.81% change. Apo A : Placebo 1.37 mmol/l (0.04), -2.82% change; pravastatin 1.50 mmol/l (0.04), -3.33% change; gemfibrozil 1.49 mmol/l (0.04),5.07% change; combination 1.53 mmol/l (0.05), 5.73 change. Apo B: Placebo 1.61 mmol/l (0.06), -1.81% change; pravastatin 1.13 mmol/l (0.04), -28.76% change; gemfibrozil 1.37 mmol/l (0.04),-15.29% change; combination 1.06 mmol/l (0.04), -31.61% change.	Victoria Foundation and the Bristol Myers Squibb Company	groups. 13 patients left the study because of clinical adverse events or asymptomatic elevations in CK (2 patients both receiving combination therapy).	increased HDL significantly (p<0.01). C more (p<0.01) than gemfibrozil alone and reduced TG and VLDL and increased HDL (p<0.01) more than pravastatin.				

Question 10: What is the effectiveness of the following interventions to reduce LDL cholesterol and improve outcome in people with either heterozygous FH or homozygous FH: apheresis alone; apheresis and drugs, plasmapheresis, surgery?

Study descriptions

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
Treatment of severe hyperlipidemia: six years' experience with low-density lipoprotein apheresis	Bambauer R; Schiel R; Latza R; Klinkmann J;	1996	COH	2+	30 patients	FH resistant to diet and maximum lipid lowering drugs	13 males; 17 females; aged 44.2 +/- 14.8; range 21-67. 29 were heterozygous and 1 was homozygous; 23 of 30 suffered from CHD.	Unknown	Germany	Efficacy, clinical utility and safety of LDL apheresis in long term treatment	Before and after treatment	Up to 6 years	Lipid levels
LDL apheresis in clinical practice: long-term treatment of severe hyperlipidemia	Bambauer R; Schiel R; Latza R; Klinkmann J; Schneidewind JM;	1997	COH	2+									
LDL-apheresis as long-term treatment in severe hyperlipidemia using differing methods	Bambauer R; Schiel R; Latza R; Schneidewind JM;	1999	COH	2+	34 were studied	34FH patients who were regarded as refractory to conventional thereapy	Women/men 16/18; age 46.7 +/- 14.9 years	Unknown	Germany	Effect of different LDL apheresis systems on lipid levels	Comparison of before and after lipid levels and of four different apheresis systems	72.8 + 43.2 months	TC, LDL, HDL and TG. Fibrinogen was also reported.
Three different schedules of low-density lipoprotein apheresis compared with plasmapheresis in patients with homozygous familial hypercholesterolemia	Berger GM; Firth JC; Jacobs P; Wood L; Marais AD; Horak A;	1990	COH	3	2	Homozygous FH	Both were 17 year old females one of whom had been treated for severe CHD at age 8 with CABG surgery	Unknown	South Africa	Lipid levels	Pre and post treatment levels on three differing schedules of apheresis (twice per week, once per week and every two weeks) and after plasmapheresis (biweekly)	Each patient was treated for 8 or more procedures	LDL, HDL, TC, Apo B
Results of an open, longitudinal multicenter LDL-apheresis trial	Borberg H;	1999	COH	2+	25 patients were evaluated	Homozygous FH patients and heterozygous patients with organ involvement, e.g. xanthomatosis, general atherosclerosis, CHD	Average 43.2 years (15-63); 19 women and 13 men	Patients were carefully screened & pretreated with diet and drugs for 6 months. No lipid lowering drugs were used during the trial however.	University of Kohl	prevention and regression of coronary heart disease and decrease in lipid levels	Before and after apheresis	3 years	Lipid levels and degree of stenosis
Long term effect of LDL	Donner MG;	1997	COH	2+	34 patients	Heterozygous FH and	21 men and 13	Unknown	Germany	Long term	Before and after	3.5 years +/-	LDL, TC, HDL

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
apheresis on coronary heart disease	Richter WO; Schwandt P;					angiographically proven coronary heart disease	women with mean age of 47 +/- 9 years			lipoprotein changes and result of coronary angiograms	values are compared as well as reults by treatment modality	2.5 years	and change score of coronary arteries
Long-term effects of low-density lipoprotein apheresis using an automated dextran sulfate cellulose adsorption system. Liposorber Study Group	Gordon BR; Kelsey SF; Dau PC; Gotto AMJ; Graham K; Illingworth DR; Isaacsohn J; Jones PH; Leitman SF; Saal SD; Stein EA; Stern TN; Troendle A; Zwiener RJ;	1998	COH	2-	Thre were initially 54 heterozygous patients and 10 homozygous patients in this study	All had LDL cholesterol levels above 4.10 mmol.l despite diet and maximum tolerated combination drug therapy.	The characteristics of the population were previously published and not included in this report.	Not reported	Cornell Medical Centre, New York	Long term (5 year) safety, lipid lowering and rate of cardiovascular events	In the long term phase this is essentially a before and after study and long term changes in laboratory values, rates of cardiovascular events and adverse clinical experiences are reported	5 years	TC, LDL and cardiovascular event rates
Angiographic and pathological studies on regression of coronary atherosclerosis of FH patients who received LDL-apheresis treatment	Koga N; Iwata Y; Yamamoto A;	1992	COH	2+	37 patients treated by 13 institutions register as member of the Japan LARS group consisting of 7 homozygous FH and 25 heterozygous FH 2 familial combined hyperlipidemia and 3 patients with high cholesterol not confirmed as FH	Acceptance into the LARS study - criteria not provided	22 men and 15 women with mean age of homozygotes of 44 years and of the rest of the sample was 55 years. Most of the patients were treated with a cholesterol lowering drug such as probucol, pravastatin and cholestylamine in combination with apheresis.	Unknown	Japan	Regression of CHD	Before and after apheresis	Angiography was performed at intervals of 49 months for homozygotes and 32 months for heterozygotes	Percentage change in stenosis of coronary arteries
Long-term effects of LDL apheresis on carotid arterial atherosclerosis in familial hypercholesterolaemic patients	Koga N; Watanabe K; Kurashige Y; Sato T; Hiroki T;	1999	COH	2+	In the LDL apheresis group there were 2 homozygotes and 9 heterozygotes; the 'control' group on drugs alone consisted of 10 heterozygotes	The treatment group consisted of 11 'severe' FH patients with 2 homozygotes whose average LDL was 16.0 +.- 3.60 mmol.l and 9 heterozgotes with average LDL of 11.5 +/- 2.46 mmol/l and 10 'mild' FH patients with baseline LDL of 4.81+/- 1.36 mmol/l	There were 10 women and 11 men; the average age of the homozygotes was 35 years; of the severe heterozygotes was 41 +/- 7.2 and of the controls was 63 +/- 10 years ($p<0.001$). There were no other significant differences between groups.	Unknown	Japan	LDL apheresis plus pravastatin 10-20 mg in all and probucol (750-1000 mg) for 10 patients; in the drug treatment group pravastatin 10-20 mg in 8 and probucol in 7 patients.	The two groups were compared for the development or progression of carotid atherosclerosis	4 years	Ultrasonographic changes of atheromatous plaque of the combined common carotid artery and carotid bifurcation and the annual progression rate of early carotid atherosclerosis by IMT.
LDL-apheresis atherosclerosis regression study (LAARS) - Effect of aggressive versus	Kroon AA; Aengevaeren WRM; vanderWerf T; Uijen GJH;	1996	RCT	1+	21 apheresis plus simvastatin 40 mg/d and 21 simvastatin 40	Elevated TC or LDL and TG <5.0 mmol/lon diet alone with extensive CAD. Excluded were patients	Dutch men, aged between 30-67 years; 16 patients in each group were heterozygous for	All patients underwen diagnostic coronary angiography	The Netherlands	apheresis plus simvastatin and simvastatin only	Treatment and usual care	2 years	Quantitative analysis of coronary angiograms during 2 years of

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
conventional lipid lowering treatment on coronary atherosclerosis	Reiber JHC; Bruschke AVG; Stalenhoef AFH;				mg only	with ejection fraction <0.35; acute MI, PTCA or CABG within 3 months, impaired hepatic or renal function, hypertension, diabetes, severe obesity, homozygous FH,	FH (76% of study population).All patients had severe coronary atherosclerosis	for angina pectoris					treatment are described and related to the lipid and lipoprotein levels
Long-term efficacy of low-density lipoprotein apheresis on coronary heart disease in familial hypercholesterolemia. Hokuriku-FH-LDL-Apheresis Study Group	Mabuchi H; Koizumi J; Shimizu M; Kajinami K; Miyamoto S; Ueda K; Takegoshi T;	1998	COH	2+	87 patients received intensive drug therapy and 43 patients received medical therapy and LDL apheresis	130 Fh patients with clinically significant coronary artery stenosis (>75%) by angiography were accepted for study. 43 patients whose serum cholesterol levels remained >3.4 mmol/l despite medical therapy received LDL apheresis and 87 others received inte (to complete?)	Except for smoking (p=0.024) there were no significant differences in age, gender, or co-morbidities in the two study groups. Ages ranged from 56-59 years +/- 10-13 years. The male to female ratio was approximately 3:1.	Unknown	Japan	Long term safety and efficacy of LDL apheresis combined with cholesterol lowering drugs on the incidence of coronary atherosclerotic events compared with intensive cholesterol lowering therapy with drugs in the management of heterozygous FH patients with	LDL apheresis is compared with aggressive drug therapy which included `10-20 mg/day pravastatin or 5-10 mg/day simvastatin and then 500 1000 mg/day of probucol and or 4-12 g/day of cholestyramine or 400 mg/day of benzafibrate.	6 years	End points were total mortality, major coronary events including MI, CABG or angioplasty
Low density lipoprotein apheresis for the treatment of familial hypercholesterolemia	Moga C; Harstall C;	2004	SR	1+	Controlled studies were selected								
Effects of intensive lipid lowering by low-density lipoprotein apheresis on regression of coronary atherosclerosis in patients with familial hypercholesterolemia: Japan Low-density Lipoprotein Apheresis Coronary Atherosclerosis Prospective Study (L-CAPS)	Nishimura S; Sekiguchi M; Kano T; Ishiwata S; Nagasaki F; Nishide T; Okimoto T; Kutsumi Y; Kuwabara Y; Takatsu F; Nishikawa H; Daida H; Yamaguchi H;	1999	RCT	2+	25 apheresis patients and 11 controls	inclexcl3-2-1 Age below 70 with clinical features compatible with heterozygous FH and scheduled for coronary angiography. Exclusion criteria included CHF, MI within one month after onset, angioplasty within 6 months or bypass surgery within 1 year, severe diabetes	Average age 51 years; 17 males and 8 females. No significant differences in disease history or risk factors for heart disease	Multi centre recruitment	Japan	apheresis vs drug therapy and the effect on progression or regression of heart disease	comparisons are made between treatments	28 months	Primary end point was a difference in frequency of definite progression and regression coronary artery stenosis. Lipid levels were also reported.
Reappraisal of partial ileal bypass for the treatment of familial hypercholesterolemia	Ohri SK; Keane PF; Swift I; Sackier JM; Williamson RC; Thompson GR; Wood CB;	1989	COH	2-	11	Eleven adult heterozygous FH patients were selected for ileal bypass because of failure to control serum cholesterol levels with conventional	Mean age 42.5 years; 6 men and 5 women	Unknown	Department of Surgery, Hammersmith Hospital London	Effect of ileal bypass on lipid levels	Before and after lipid levels	60 months (only 3 patients follwed out to 60 months)	TC, HDL, , HDL/LDL ratio

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
						management which included a low fat and high fiber diet.							
Long-term effects of LDL apheresis in patients with severe hypercholesterolemia	Sachais BS; Katz J; Ross J; Rader DJ;	2005	COH	2+	34 FH patients	Treated with LDL apheresis every two weeks	Mean age was 50 years with 62% being male.	This was a retrospective chart review of clinical and laboratory data as well as cardiovascular outcomes to determine the safety and efficacy of long term LDL apheresis	USA	Safety and clinical efficacy of long term LDL apheresis	Change in laboratory values and ardiovascular events before and fater treatment	Up to 7 years (average 2.5 years)	Adverse reactions; blood chemistries; lipoprotein levels; cardiovascular events
The Help-Ldl-Apheresis Multicenter Study, An Angiographically Assessed Trial on the Role of Ldl-Apheresis in the Secondary Prevention of Coronary Heart-Disease .2. Final Evaluation of the Effect of Regular Treatment on Ldl-Cholesterol Plasma-Concentration	Schuffwerner P; Gohlke H; Bartmann U; Baggio G; Corti MC; Dinsenbacher A; Eisenhauer T; Grutzmacher P; Keller C; Kettner U; Kleophas W; Koster W; Olbricht CJ; Richter WO; Seidel D; Schoppenthau M; Schlierf G; Marburger C; Zollner N; Suhler K; Schwandt P;	1994	COH	2+	Data from 39 of 51 patients could be evaluated	Patients with angiographically documented CAD and severe hypercholesterolaemia were included. Exclusion criteria were haemorrhagic diathesis, neoplasm, liver disease, severe cardiac insufficiency, cardiac valvular disease, apoplexy, dementia.	34 males and 17 females recruited with mean age of 44.4 years (9.2)	Unknown	10 centres in Germany	Effect of regular LDL apheresis on LDL-C and course of coronary heart disease	Before and after treatment	2 years	LDL-C and results of angiography
The HELP-LDL-apheresis multicentre study, an angiographically assessed trial on the role of LDL-apheresis in the secondary prevention of coronary heart disease. I. Evaluation of safety and cholesterol-lowering effects during the first 12 months. HELP Stud	Seidel D; Armstrong VW; Schuff-Werner P;	1991	COH	2+	46 patients completed 12 months of regular treatment	All patients had severe CHD and type IIa hypercholesterolaemia. A distinction between patients with heterozygous and homozygous FH is not made.	Ages 28-65 years; 33 males and 13 females	Ten centres in Germany recruited patients	Germany	Long term effects of regluar HELP LDL apheresis on plasma lipoproteins and coronary status. Also assessment of safety of long term apheresis.	Before and after comparisons of lipid levels are made in this report. Coronary status to be evaluated by angiography after two years of therapy.	This was a two year study. This paper reports the first year results.	LDL-C, TC, TG and HDL are reported in this study. Fibrinogen and plasminogen were also reported.
Familial Hypercholesterolaemia Regression Study: a randomised trial of low-density-lipoprotein apheresis.	Thompson GR; Maher VM; Matthews S; Kitano Y; Neuwirth C; Shortt MB;	1995	RCT	1+	39 patients with 20 in apheresis group and 19 in drugs only group	Inclusion: TC 8.0mmol/l or more plus tendon xanthomata in patient or first degre relative family history of heart disease and	No significant differences in age sex or risk factors. Age mean 49 years; sex 28 males and 11	Attended local lipid clinics and were recruited on the basis of inclusion	Wales and London	LDL apheresis fortnightl plus 40 mg simvastatin daily or cholestipol 20	Before and after serum lipids and quantitative coronary angiography	mean of 2.1 years after initiating treatment	Changes in lipid levels, Percent diameterstenosis of lesions in angiogram; and the mean lumen

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
	Davies G; Rees A; Mir A; Prescott RJ; et a;					evidence of heart disease in patient on angiogram. Exclusion: CABG, diabetes, HTN, premenopusal or HRT, illial bypass.	females	criteria.		g plus simvastatin daily			diamenter of segments and mean minimum lumen diameter of lesions
The effect of ezetimibe on serum lipids and lipoproteins in patients with homozygous familial hypercholesterolemia undergoing LDL-apheresis therapy	Yamamoto A; Harada-Shiba M; Endo M; Kusakabe N; Tanioka T; Kato H; Shoji T;	2006	COH	3	5 patients	Receptor negative homozygous FH on LDL apheresis. These patients were also being treated with a range of other cholesterol lowering drugs including atorvastatin at varying doses and probucol 500 mg or 1000 mg/day.	3 females and 2 males ages 24,26,28,63 and 66	Unknown	Japan	Effect of ezetimibe on lipid levels among homozygous patients on apheresis	Before and after levels of TC, LDL-C, HDL-C and TG	16 weeks	TC, LDL-C, HDL-C and TG
The effect of atorvastatin on serum lipids and lipoproteins in patients with homozyous familial hypercholesterolemia undergoing LDL-apheresis therapy	Yamamoto A; Harada-Shiba M; Kawaguchi A; Oi K; Kubo H; Sakai S; Mikami Y; Imai T; Ito T; Kato H; Endo M; Sato I; Suzuki Y; Hori H;	2000	COH	3	5 receptor negative homozygous FH patients and 4 receptor defective homozygous patients	Homozygous FH on LDL apheresis once every week or two	5 male and 4 female; ages 16-60.Seven of nine patients were under 23 years old.	Unknown	Japan	Response to addition of atorvastatin to apheresis regime. Atorvastatin was given in escalating doses from 10-40 mg to nine homozygous FH patients.	Before and after adding atorvastatin	44 weeks	TC, DL-C, HDL-C and TG
A 5-Year Follow-Up of Low-Density-Lipoprotein Apheresis in Patients with Familial Hypercholesterolemia - A Multicenter Study	Yamamoto K; Nakashima Y; Koga N; Sasaki J; Takagi M; Kobori S; Ageta M; Hori H; Arima S; Toma S;	1995	COH	2+	37 patients - there were 4 homozygouts and 33 heterozygotes	These were patients enrolled in K-LAS-I study for a mean duration of 2.4 years.	21 males and 16 females; age 13-71 with a mean age of 51 +/- 14	Through the K-LAS study	Japan	5 year follow up of lipid levels and secondary prevent of CHD	Before and after treatment with apheresis over time. Treatments were performed once every 1, 2, 3, or 4 weeks depending on plasma cholesterol levels.	5 years	Percent further reduction in lipid levels from K-LAS-I to K-LAS-II; frequency of cardiovascular events

Study results

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
Treatment of severe hyperlipidemia: six years' experience with low-density lipoprotein apheresis	Bambauer R; Schiel R; Latza R; Klinkmann J;	1996	Baseline treatment value / Under % change / p TC mmol/l 5.5 +/-1.5 / 10.4 +/-1.9 / -47.2 / <0.0001 LDL 3.8 +/-1.67 / 7.42+/-1.95 / -48.7	Unknown	Minor side effectgs were noted during 447 treatment sessions. Severe side effects such as shock symptoms or allergic reactions were very rare	This study concludes that LDL apheresis is an efficient and safe method for lowering lipid levels.	The results appear to be plausible.	Yes	Yes	See also Bambauer 1997.

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			<0.0001 HDL 1.050 +/-0.02 1.16 +/-0.29 +10.5 <0.0001 TG 5.63 3.4 -39.8 <0.0001 Fibrinogen dropped by 25.6% (p<0.001)"		(0.55%).					
LDL apheresis in clinical practice: long-term treatment of severe hyperlipidemia	Bambauer R; Schiel R; Latza R; Klinkmann J; Schneidewind JM;	1997								See Bambauer et al, 1996 for details of study. This report extends the original study for 57 additional apheresis treatments. The results are not essentially changed.
LDL-apheresis as long-term treatment in severe hyperlipidemia using differing methods	Bambauer R; Schiel R; Latza R; Schneidewind JM;	1999	Baseline treatment Under Mean % change TC(mmol/l) 10.5 +/-1.92 5.42 +/-1.52 - 51.9% LDL-C(mmol/l) 7.42 +/-1.95 3.70 +/-1.72 - 49.8% HDL-C(mmol/l) 1.05 +/-0.19 1.10 +/-0.33 +4.4% TG(mmol/l) 5.63 3.26 - 57.8% Fibrinogen decreased by 73.3%"	Unknown	Minor side effects were noted in 16.3% of treatments. Serious but not life threatening side effects were observed in 14 treatments (0.5%) and included shock symptoms during five treatments and allergic reactions during nine treatments.	This study shows that lipid levels can be lowered in refractory patients using LDL apheresis	This is a small study but results are plausible	Yes	Yes	
Three different schedules of low-density lipoprotein apheresis compared with plasmapheresis in patients with homozygous familial hypercholesterolemia	Berger GM; Firth JC; Jacobs P; Wood L; Marais AD; Horak A;	1990	'Quasi steady state' values, i.e. the values just bfore every procedure representing the least favorable lipoprotein values in the course of therapy, were reported. Absolute numbers were not reported. Graphs showed a profound reduction in the quasi steady state levels of plasma cholesterol, LDL and Apo B in schedules 1 and 2 of apheresis. In patient 1 the LDL/HDL ratio fell by 74% on schedule 1 (bi weekly treatment), 68% on schedule 2	Unknown	One incident of reversible hypotension	These two cases demonstrate the safety and efficacy of LDL apheresis on an accelerated protocol. There was no significant difference between apheresis and plasmaphersis when schedules were equivalent (every two weeks).	This is a case study of two patients and therefore further research is required. It appears that the length of time between treatments and severity of disease influenced outcomes.	Yes	Yes	This is a case study of two homozygous patients which compares plasmapheresis to apheresis. It was selected as a rare comparison of these two methods of treatment

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			(weekly) and 37% on schedule 3 (every two weeks) and 46% on plasmapheresis. A similar although less dramatic trend was noted in patient 2 but in neither was there a significant difference in these ratios comparing schedule 3 of apheresis with plasmapheresis (p value not given). Other laboratory paramenters remained stable except for iron and hemoglobin levels which were reduced with both procedures."							
Results of an open, longitudinal multicenter LDL-apheresis trial	Borberg H;	1999	Before treatment After treatment AverageTC mmol/l 8.35 (7.13-10.9) 3.54 (2.72-5) AverageLDL-C mmol/l 6.36 (4.77-9.51) 2.10 (1.13-3.31) AverageHDL-C mmol/l 1.13 (0.67-1.92) 0.87 (0.51-1.41) Quantitative measurement of 111 circumscribed coronary stenoses showed a mean stenosis degree of 45 +/-26% at entry and 43+/-22% at final cineangiofilm demonstrating no significant change. Eight localized stenoses showed a regression of more than 10% and 11 a progression of more than 10%. The panel consensus evaluation for overall coronary atherosclerosis resulted in regression in no patients, no change in 16, debatable progression in 3 and undecided in one."	A grant of the Deutsche jVErsuchsanstalt fur Luft und Raumfahrttechnik	None	Overall regression of CHD could not be observed in any of the patients in this study. However it was possible to demonstrate that secondary prevention or at least a slowing of progression could be obtained using LDL apheresis as the only lipid lowering therapy	The results of this study appear to be plausible.	No, this study does not reflect others which have shown regression. The fact that no lipid lowering drugs were used during the study may have affected the outcome	Yes	
Long term effect of LDL apheresis on coronary heart disease	Donner MG; Richter WO; Schwandt P;	1997	Immunoadsorption Dextran sulfate adsorption HELP apheresis TC mmol/l Baseline 7.69 +/-3.07 7.79+/-1.82 9.43+/-1.84 Mean of final 5 treatments 5.02+/-0.87 4.95+/-1.12 5.33+/-0.53 LDL mmol/l Baseline 6.63 +/-1.41 5.92+/-2.02	Unknown	None	This study concludes that in the long term LDL apheresis combined with hypolipidemic drug ttreatment may improve the prognosis of patients with severe heterozygous familial hypercholesterolemia.	The results of this study are plausible.	Yes	Yes	This study is primarily a comparison of three methods of apheresis and combined results are not provided.

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			6.51+/-1.43 Mean of final 5 treatments 3.17+/-0.58 3.25+/-0.68 3.56+/-0.51 HDL mmol/l Baseline 1.05 +/-0.31 1.05+/-0.12 0.99+/-0.15 Mean of final 5 treatments 1.28+/-0.25 1.18+/-0.18 1.23+/-0.21 In 3 of 23 patients followed up for more than 2 years there was a regression of coronary atherosclerosis in 3 patients and in all other cases there was a stop in progression of coronary lesions (that is, no change).Three patients died of coronary complicationsafter 6 and 9 months of therapy; one after 6 years. One patient suffered a non fatal MI."							
Long-term effects of low-density lipoprotein apheresis using an automated dextran sulfate cellulose adsorption system. Liposorber Study Group	Gordon BR; Kelsey SF; Dau PC; Gotto AMJ; Graham K; Illingworth DR; Isaacsohn J; Jones PH; Leitman SF; Saal SD; Stein EA; Stern TN; Troendle A; Zwiener RJ;	1998	Results for patients with data at the 2 and 4 year follow-up time points (n=29). Controls received apheresis only after the initial controlled phase of the study ended at 18 weeks Homozygotes Heterozygotes n=7 Treated n=19 Control n=3 LDL baseline mmol/l 12.31 6.23 6.18 2 years 10.51 5.54 5.18 4 years 9.03 5.95 6.21 p value 0.059 0.22 HDL baseline 0.46 0.49 1.54 2 years 0.52 0.48 0.63 4 years 0.55 0.48 0.58 p value 0.33 0.82 A total of 24 unique cardiovascular events occurred during the 5 years before initiation of LDL apheresis whereas only 7 events occurred during the period of treatment with LDL apheresis, a drop of 44% from 6.3 events per 1000 patient-	Unknown	There were no clinically important changes in labortory values over time. Hypotension was the most common adverse event in 0.9% of procedures. One episode of blood loss with anemia occurred.	This study provides data on long term clinical effectiveness and safety	The high drop out rate is problematic in this study	Unknown	Yes	Entire protocol not reported as it was included in a previous publication. High drop out rate. No confidence intervals

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			months to 3.5 per 1000 patient months. There were no clinically important changes in labortory values over time. Hypotension was the most common adverse event in 0.9% of procedures. One episode of blood loss with anemia occurred."							
Angiographic and pathological studies on regression of coronary atherosclerosis of FH patients who received LDL-apheresis treatment	Koga N; Iwata Y; Yamamoto A;	1992	The evaluation of regression of no change and of progression in a lesion for each patient was defined as follows: patients with at least one regressed segment and without any progressed segment were represented as regression; patients with only unchanged segments were represented as no change; and patients with at least one progressed segment and without any regressed segment were reprresented as progression. Such representation led to the following results: regression occurred in 14 of 37 patients (37.8%); no change, in 18 patients (48.6%) and progression occurred in 5 patients (13.5%).	Unknown	None	The results of this study showed that regression of coronary artery stenosis in FH patients can be induced by treatment with LDL apheresis in combination with cholesterol lowering drugs.	The results of this study are plausible.	Yes	Yes	
Long-term effects of LDL apheresis on carotid arterial atherosclerosis in familial hypercholesterolaemic patients	Koga N; Watanabe K; Kurashige Y; Sato T; Hiroki T;	1999	LDL apheresis group Homozygous Baseline Time average value Change TC mmol/l 17.0+/-3.95 7.42+/-0.40 56.4% LDL mmol/l 16.0+/-3.60 6.43 +/- 0.07 60.5% Heterozygous Baseline Time average value Change TC mmol/l 12.9+/-2.47 5.63+/-1.26 56.5% LDL mmol/l 11.5+/-2.46 4.32 +/- 1.20 56.8% Control Baseline On Treatement Change TC mmol/l 7.18+/-1.14 5.62+/-0.79 21.7% LDL mmol/l 4.81+/-1.26 3.71 +/- 0.58 22.9% In the LDL apheresis progression of plaques occurred in nine of the 11 patients; one patient remained unchanged and one patient	Unknown	None	This study suggests that LDL apheresis may induce regression of heart disease as well as slow progression.	The study is very small and the sample is variable with degree of severity of disease. This should be repeated in a larger sample	Yes	Yes	The sample contains 2 homozygotes and 19 heterozygotes. Results may not be comparable. There is no blinding or randomisation for logistic and ethical reasons

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			showed regression. In the control group all patients showed progression. The difference between the two groups was not statistically significant. The annual progression rate of mean maximum IMT was a mean of 0.0002 mm/year in the LDL apheresis group. This was significantly lower than the mean of 0.0251 years in the control group (p<0.005). In the LDL apheresis group the mean maximum IMT in heterozygous FH patients was -0.0023 mm/year. Although progression occurred in the homozygous patients it was markedly slower than in the control group. (no p level given)."							
LDL-apheresis atherosclerosis regression study (LAARS) - Effect of aggressive versus conventional lipid lowering treatment on coronary atherosclerosis	Kroon AA; Aengevaeren WRM; vanderWerf T; Uijen GJH; Reiber JHC; Bruschke AVG; Stalenhoef AFH;	1996	A constant reduction of 63% of LDL-C was found in the apheresis group to an interval mean level of 2.95 +/- 1.13 mmol/l. TC, LDL-C and Apo B showed the same course and were significantly lower in comparison to the medication group. Apheresis (n=21) Medication only (n=21) Pvalue TC mmol/l Basal 9.72+ 1.84 9.85+ 2.17 After/mean 2.06+ 0.46 5.95+ 1.6 % change -52.6+ 6.6 -39.5+ 7.7 .005 LDL mmol/l Basal 7.78+ 1.86 7.85+ 2.34 After/mean 0.82+ 0.41 4.13+ 1.58 % change -62.9+ 8.3 -47.4+ 8.1 .01 There was no significant difference in the number of clinical events. The mean change per patient in percent stenosis was not different for both groups. However in the apheresis group the total number of lesions was decreased as the result of the disappearance (<20%) of 40 minor stenoses versus 20 in the medication group (p=0.005)whereas 23 versus 32 new stenoses were found	Dutch Heart Foundation	No serious treatment side effects were reported. All side effects were transient and non life threatening.	The study showed that the addition of biweekly LDL apheresis to lipid lowering treatment with a statin improved the ischemic threshold whereas an equal effect in angiographically derived measures for coronary atherosclerosis was observed in both groups in whom progression of disease would be usual.	The results are plausible.	There is some inconsistency in studies with regard to regression of heart disease with apheresis. However, it certainly appears that progression is slowed with this treatment.	Yes	Randomization was stratified for the level of TC and Lp(a), age and CABG status

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			respectively (p=.19). By categorical approach, 9 patients in the apheresis group and 11 patients in the medication group were classified as progressors. Two and 5 patients were regressors respectively and the remaining men showed stable disease. Exercise tolerance was significantly improved in the apheresis group by bicycle exercise tests(p<0.001 for time)"							
Long-term efficacy of low-density lipoprotein apheresis on coronary heart disease in familial hypercholesterolemia. Hokuriku-FH-LDL-Apheresis Study Group	Mabuchi H; Koizumi J; Shimizu M; Kajinami K; Miyamoto S; Ueda K; Takegoshi T;	1998	Using time averaged concentrations of LDL because the rebound curves of TC and LDL after apheresis are not linear, it was shown that LDL apheresis significantly reduced LDL cholesterol from 7.42 + 1.73 to 3.13 + 0.80 mmol/l (58%) compared with group taking drug therapy, from 6.03 + 1.32 to 4.32 + 1.53mmol/l (28%) (p<0.0001). TC decreased by 53% from baseline levels (9.28 +/- 1.71 mmol/l to 4.40 +/- 0.78mmol/l) with LDL apheresis and by 25% (from 7.94 +/- 1.24 to 5.92 +/- 1.58 mmol/l) with drug therapy (p<0.0001). The proportion of patients without any coronary events was significantly higher in the LDL apheresis group (90%) than in the drug therapy group (64%) by 72% (p=0.0088)."	Scientific research grants from Education Ministry of Japan and grants for Primary Hyperlipidemia Research Projects of the Welfare Ministry of Japan and a grant from the Ono Medical Foundation.	The LDL apheresis procedure was well tolerated by patients and all patients were safely treated without requiring supplemenmtation with any plasma constituents.	This study directly compares apheresis and drug therapy. Although it is not randomised or blinded these features are not possible in such a study due to logistic and ethical reasons.	The results of this study appear to be robust.	Yes	Yes	This study is not blinded or randomised. These features are not possible either logistically or ethically.
Low density lipoprotein apheresis for the treatment of familial hypercholesterolemia	Moga C; Harstall C;	2004		Alberta Heritage Foundation for Medical Research, Canada		Weak evidence suggested that the DSC Liposorber system in combination with lipid lowering drug therapy lowered LDL cholesterol levels in older patients (>50 years of age) with severe FH when they were treated at least once every two weeks for a minimum of one year. The mean percent decrease in LDL-C ranged from 34%-81%. However, the use of a combined therapy meant that the contribution of LDL apheresis to the treatment effect is unclear. The included studies were: Matsuzaki et al2002;Nishimura et al 1999; Mabuchi et al 1998;				Although a thorough search of the literature was done and strict inclusion and exclusion criteria were applied there is no description of the quality assessment of the literature. Also, only two apheresis systems were included and no studies with mixed h

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
						Koga et al 1999; Gordon et al 1998; Thompson et al 1995; Ritcher et al 1999 and Julius et al 2002. A meta analysis was not done."				
Effects of intensive lipid lowering by low-density lipoprotein apheresis on regression of coronary atherosclerosis in patients with familial hypercholesterolemia: Japan Low-density Lipoprotein Apheresis Coronary Atherosclerosis Prospective Study (L-CAPS)	Nishimura S; Sekiguchi M; Kano T; Ishiwata S; Nagasaki F; Nishide T; Okimoto T; Kutsumi Y; Kuwabara Y; Takatsu F; Nishikawa H; Daida H; Yamaguchi H;	1999	Mean minimum lumen diameter increased significantly in the LDL apheresis group and decreased in the control group.l For percent diameter stenosis though the direction of changed in both groups diverged there was no statistical significance. Progression occurred in 64% of controls and 8% of apheresis group. Regression was found in 16% of the apheresis group and in no controls. There was a significant difference in frequency of patients with progression, unchanged and regression between the two groups (p<0.004). Three patients in the apheresis group had clinical coronary events and four patients in the control group had an event. Ithe differences between the groups averaged over the follow up period were TC -17% (5.07 +/- 0.92mmol/l versus 6.10 +/- 1.87;p<0.05) and LDL-C -18% (3.59 +/-0.78 versus 4.36 +/- 1.49;p<0.05).	Unknown	None	The combination of LDL apheresis and drugs was more effective in this study than drugs alone in reducing LDL-C over 28 months and in effecting regression and stabilization of coronary lesions.	The results of this study are plausible.	Yes	Yes	This is a controlled trial with the apheresis group self selecting this treatment.
Reappraisal of partial ileal bypass for the treatment of familial hypercholesterolemia	Ohri SK; Keane PF; Swift I; Sackier JM; Williamson RC; Thompson GR; Wood CB;	1989	TC fell by 26% at one month butrose slightly over the next 20-24 months to 20% below preoperative values and this was maintained at 60 months (p<0.01). HDL rose by 21% (p<0.05) over the first 24 months and the HDL/LDL ration increased by 62% (p<0.05). Mean absolute values were not provided but graphically it appears that mean TC 20 months after surgery was >8mmol.l Five patients had refreactory hypercholesterolemia and were treated with lovastatin. One was reated with lovastatin and LDL apheresis."	Unknown	No operative mortality. Two patients developed wound infection. All patients had diarrhoea postopertively. Two patients with refractory gas bloat syndrome had the bypass reversed at 28 and 80 months. One patient died from MI at 55 months post op.	This study provides some information regarding	This is a small study, done before the wide use of statin therapy. Absolute values are not provided but it appears from the graphic representation that despite a percentage decrease in cholesterol levels mean TC still remained considerably above normal.	No other studies	Yes	This is a small observational study in which mean absolute changes are not reported. Only percentage changes are reported.
Long-term effects of LDL apheresis in patients with severe hypercholesterolemia	Sachais BS; Katz J; Ross J; Rader DJ;	2005	Adverse reactions were rare. The most common reactions were lightheadedness (1.5%), nausea/vomiting (1.2%), hypotension (0.73%), and chest pain (0.58%). Examination of BUN, creatinine, AST, ALT, total	Unknown	See results	This study provides evidence of the long term safety and efficacy of LDL apheresis	The results are plausible	Yes		This was a retrospective study of 34 patients who were treated with LDL apheresis from 1996-2003.

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			protein, albumin and PT, PTT revealed that all values were withinn normal range and none was significantly altered by long term treatment. All patients had markedly decreased LDL-C and triglycerides after each treatment without a significant change in HDL-C. All patients had decreased time averaged LDL-C. (Values not provided) After treatment with LDL apheresis for an average of 2.5 years, patients had a 3.2 fold decrease in cardiovascular events and over 20 fold decrease in cardiovascular interventiions.Subjectively, patients reported decreased episodes of angina symptoms and improved quality of life.							
The Help-Ldl-Apheresis Multicenter Study, An Angiographically Assessed Trial on the Role of Ldl-Apheresis in the Secondary Prevention of Coronary Heart-Disease .2. Final Evaluation of the Effect of Regular Treatment on Ldl-Cholesterol Plasma-Concentration	Schuffwerner P; Gohlke H; Bartmann U; Baggio G; Corti MC; Dinsenbacher A; Eisenhauer T; Grutzmacher P; Keller C; Kettner U; Kleophas W; Koster W; Olbricht CJ; Richter WO; Seidel D; Schoppenthau M; Schlierf G; Marburger C; Zollner N; Suhler K; Schwandt P;	1994	The mean pre/post apheresis LDL-C levels decreased from 7.33/3.10 mmo./l at first apheresis treatment to 5.21/1.97 mmol/l after 1 year to 5.26/1.97 mmol/l after 2 years. The angiographies from 33 patients obtained before and after 2 years of regular treatment were evaluated blindly and the mean degree of stenosis of all segments decreased from 32.5% (SD=16) to 30.6% (SD=16.8) over the 2 years. A regression >8% was observed in 50/187 (26.7%) segments whereas 29/187 (15.5%) segments showed progression. In 108 /187 (57.8%) segments the lesions were stable (<8% deviation) over 2 years.	Grant from Bundesministerium fur Forschung und Technologie	Adverse clinical reactions were reported in only 2.9% of treatments and the rections were generally of minor clinical relevance. No major life threatening complications occurred during treatment.	This study demonstrates that regular treatment with LDL apheresis is able to stabilize progressive atherosclerotic disease and to induce almost twice as much regression as progression of atherosclerotic lesions.	The presults of this study are plausible	Yes	Yes	This is the final evaluation of a previously reviewed study
The HELP-LDL-apheresis multicentre study, an angiographically assessed trial on the role of LDL-apheresis in the secondary prevention of coronary heart disease. I. Evaluation of safety and cholesterol-lowering effects during the first 12 months. HELP Stud	Seidel D; Armstrong VW; Schuff-Werner P;	1991	Baseline 12 months p value TC (mmol/l) Pre apheresis 9.18(2.3) 7.10(1.05) p<0.001 Post apheresis 4.62(1.46) 3.51(0.67) LDL-C (mmol/l) Pre apheresis 7.26(2.2) 5.21(1.05) p<0.001 Post apheresis 3.08(1.36) 1.95(0.62) HDL (mmol/l) Pre apheresis 1.04(0.28)	A grant from the Bundesministerium fur Forschung und Technologie	Adverse clinical reactions were reported in 2.9% of treatments and the reactions were generally of a minor nature. No major life threatening complications occurred during treatment. There was a general improvement in angina symptoms of patients.	The study shows a significant decrease in lipid level in these very high risk patients	The effect appears to be plausible	Yes	Yes	

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			1.24(0.28)) p<0.001 Post apheresis 0.94(0.36)) 1.06(0.31) TG (mmol/l) Pre apheresis 2.07(1.46) 1.66(0.01) p<0.05 Post apheresis 1.69 1.38 Fibrinogen levels fell 19-24% over the course of therapy and plaminogen concentrations were unchanged."							
Familial Hypercholesterolaemia Regression Study: a randomised trial of low-density-lipoprotein apheresis.	Thompson GR; Maher VM; Matthews S; Kitano Y; Neuwirth C; Shortt MB; Davies G; Rees A; Mir A; Prescott RJ; et a;	1995	Apheresis n=20 Drugs only n=19 Interval mean TC mmol.l 5.2 (0.7) 5.3 (1.) NS HDL 1.1 (0.2) 1.15 (0.3) NS LDL 3.2 (0.8) 3.4 (1.1) p=0.03 The interval means between apheresis procedures did not differ significantly from the mean values in the drug group for TC and HDL. The LDL value was significantly lower in the apheresis group (p=0.03) Aperhesis n=20 Drugs only n=19 Diameter stenosis % per patient -1.8(4.0) -2.2(5.5) NS Diameter stenosis % lesion change -1.91 (9.38) -2.06(9.21) NS The mean changes in % diameter stenosis after 2 years treatment did not differ significantly between the apheresis and drug groups on either a per patient basis or per lesion basis Two MI and one angioplasty occurred in the drug group during the study and one angioplasty in the apheresis group."	British Heart Foundation and Upjohn and Bristol Myers-Squibb and Merck, Sharpand Dohme for drugs.	One patient developed hepatotoxicity on simvastatin and dose was reduced withou further complication	The researchers conclude that although LDL apheresis combined with simvastatin was more effective hand colestipol llus simvastatin in reducing LDL cholesterol it was less beneficial in influencing coronary atherosclerosis and should be reserved for patients unresponsive to drugs.				
The effect of ezetimibe on serum lipids and lipoproteins in patients with homozygous familial hypercholesterolemia undergoing LDL-	Yamamoto A; Harada-Shiba M; Endo M; Kusakabe N; Tanioka T; Kato H; Shoji T;	2006	Changes in lipid levels following treatment with ezetimibe LDL-C TC TG HDL-C Pretreatment mmol/l 10.04+/-	Unknown	Slight to mild adverse event occurred in more than one patient including nausea, fatigability, cough and	Although the effect was not very strong, exetimibe nevertheless appeared to be a useful drug in combination with statins forreceptor negative	This is a small case series but the results appear to be plausible	No other studies identified	Yes	This is a case series but was included because it provides the only information on the treatment of

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
apheresis therapy			1.11 12.17+/-1.73 1.21+/-0.59 0.79+/-0.22 Post-treatment mmol/l 9.09+/-1.22 11.09+/-2.03 1.28+/-0.69 0.72+/-0.19 Percent change -9.57 -9.07 18.78 -7.58 95% CI -14.11to -5.03 -17.43 to -0.72 -42.51 to 80.06 -18.98 to 3.82 With the exception of one patient, significant decreases in LDL-C and TC at 2 weeks after each apheresis procedure were obtained during the period from 4-12 weeks of treatment (p values not given)."		albuminuria.	homozygous FH patients undergoing LDL apheresis				homozygous FH patients on apheresis with ezetimibe
The effect of atorvastatin on serum lipids and lipoproteins in patients with homozyous familial hypercholesterolemia undergoing LDL-apheresis therapy	Yamamoto A; Harada-Shiba M; Kawaguchi A; Oi K; Kubo H; Sakai S; Mikami Y; Imai T; Ito T; Kato H; Endo M; Sato I; Suzuki Y; Hori H;	2000	Effect of atorvastatin-apheresis therapy compared with regular treatment Regular treatment Combined treatment P value TC mmol/l Negative 11.87+/-0.27 12.1+/-2.54 NS Defective 7.49+/-2.06 6.54+/-2.31 p<0.05 LDL-C mmol/l Negative 10.08+/-2.16 10.28+/-2.15 NS Defective 6.38+/-1.91 5.44+/-2.22 NS HDL-C mmol/l Negative 1.00+/-0.11 1.08+/-0.13 NS Defective 0.77+/-0.02 0.87+/-0.09 NS TG mmol/l Negative 1.76+/-1.03 3.49+/-2.42 NS Defective 0.74+/-0.32 0.52+/-0.19 p<0.05"	Unknown	There were no serious adverse effects resulting in any patients stopping treatments.	Five of nine patients responded well to atorvastatin (20.6% decrease in LDL-C); four of these patients were receptor defective . Of the five receptor negative patients only one showed good response (14.9% decrease in LDL-C). Combination therapy may increase the efficacy of apheresis treatment in patients withreceptor-defective homozygous FH.	This case series is a weak study design but results are plausible	No other similar studies found	Yes	This is a case series of 9 homozygous patients and was included because stdies of this patient group are rare and a comparison of apheresis to apheresis plus statins is also rare.
A 5-Year Follow-Up of Low-Density-Lipoprotein Apheresis in Patients with Familial Hypercholesterolemia - A Multicenter Study	Yamamoto K; Nakashima Y; Koga N; Sasaki J; Takagi M; Kobori S; Ageta M; Hori H; Arima S; Toma S;	1995	There were no significant differences between mean pre-treatment levels of TC, HDL-C, LDL-C, TG from the end of the phase 1 study and the end of phase 2. The change in Lp(a) was p=0.052 and was considered significant. Phase 1	Unknown	None	Comparison with studies of mortality and morbidity in patients with hypercholesterolemia without severe CHDwho took lipid lowering drugs indicates that long term agreessive LDL apheresis treatment is effective in the secondary preventaion of				

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			Phase 2 % change p Value TC mmol/l mean pretreatment 7.18 +/-1.64 6.79+/-1.56 -5.4 p=0.071 HDL mmol/l mean pretreatment 0.87 +/-0.28 0.79+/-0.22 -8.8 p=0.112 TG mmol/l mean pretreatment 1.43 +/-0.87 1.40+/-0.92 -1.6 p=0.255 LDL-C mmol/l mean pretreatment 5.4 +/-1.5 5.13+/-1.38 -5.3 p=0.156 As a whole 7 (18%, 7/38) cardiovascular events were observed during a mean of 5 years of LDL apheresis. One additional patient experienced new unstable angina"			coronary heart disease in FH patients				

Question 11: What are the appropriate indications for i-combined heart and liver transplantation or ii- liver transplantation alone in homozygous FH?

Study descriptions

Title	Author(s)	Year	Study Type	Grading	Details
Heart-liver transplantation in a child with homozygous familial hypercholesterolemia		1985	CSER	3	See narrative for details
Liver transplant combined with heart transplant in severe heterozygous hypercholesterolemia: report of the first case and review of the literature. [Review] [11 refs]	Alkofer BJ; Chiche L; Khayat A; Deshayes JP; Lepage A; Saloux E; Reznik Y;	2005	CSER	3	See narrative for details
Normal levels of lipoproteins including lipoprotein(a) after liver-heart transplantation in a patient with homozygous familial hypercholesterolaemia	Barbir M; Khaghani A; Kehely A; Tan KC; Mitchell A; Thompson GR; Yacoub M;	1992	CSER	3	See narrative for details
Role of orthotopic liver transplant in the treatment of homozygous familial hypercholesterolemia	Castilla Cabezas JA; Lopez-Cillero P; Jimenez J; Fraga E; Arizon JM; Briceno J; Solorzano G; De la Mata M; Pera C;	2000	CSER	3	See narrative for details
Metabolic effects of liver replacement in homozygous familial hypercholesterolemia	Cienfuegos JA; Pardo F; Turrion VS; Ardaiz J; Mora NP; Escartin P; Garrido A; Barrios C; Cuervas-Mons V;	1988	CSER	3	See narrative for details
Liver transplantation for treatment of cardiovascular disease: comparison with medication and plasma exchange in homozygous familial hypercholesterolemia	Hoeg JM; Starzl TE; Brewer HBJ;	1987	CSER	3	See narrative for details
Liver transplantation in patients with homozygotic familial hypercholesterolemia previously treated by end-to-side portocaval shunt and ileal bypass	Lopez-Santamaria M; Migliazza L; Gamez M; Murcia J; az-Gonzalez M; Camarena C; Hierro L; De l; Frauca E; Diaz M; Jara P; Tovar J;	2000	CSER	3	See narrative for details
Homozygous familial hypercholesterolaemia presenting with cutaneous xanthomas: response to liver transplantation	Moyle M; Tate B;	2004	CSER	3	See narrative for details
Plasma exchange and heart-liver transplantation in a patient with homozygous familial hypercholesterolemia	Offstad J; Schrumpf E; Geiran O; Soreide O; Simonsen S;	2001	CSER	3	See narrative for details
Liver transplantation for homozygous familial hypercholesterolaemia	Revell SP; Noble-Jamieson G; Johnston P; Rasmussen A; Jamieson N; Barnes ND;	1995	CSER	3	See narrative for details
Long-term outcome of liver transplantation for familial hypercholesterolemia	Shrotri M; Fernando BS; Sudhindran S; Delriviere L; Watson CJ; Gibbs P; Alexander GJ; Gimson AE; Jamieson NV;	2003	CSER	3	See narrative for details
Liver transplantation for familial hypercholesterolemia before the onset of cardiovascular complications	Sokal EM; Ulla L; Harvengt C; Otte JB;	1993	CSER	3	See narrative for details
Heart-liver transplantation in a patient with familial hypercholesterolaemia	Starzl TE; Bilheimer DW; Bahnson HT; Shaw BWJ; Hardesty RL; Griffith BP; Iwatsuki S; Zitelli BJ; Gartner JCJ; Malatack JJ; et a;	1984	CSER	3	See narrative for details
Lipids and lipoprotein changes after heart and liver transplantation in a patient with homozygous familial hypercholesterolemia	Valdivielso P; Escolar JL; Cuervas-Mons V; Pulpon LA; Chaparro MA; Gonzalez-Santos P;	1988	CSER	3	See narrative for details

Question 12: What is the effectiveness of investigations to assess the degree of atherosclerosis to improve outcome in people with heterozygous FH?

Study descriptions

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
Arterial mechanical changes in children with familial hypercholesterolemia	Aggoun Y; Bonnet D; Sidi D; Girardet JP; Brucker E; Polak M; Safar ME; Levy BI;	2000	COH	2+	Heterozygous FH male children (n=30) compared with male normocholesterolemic controls (n=27).	Heterozygous FH male children (n=30) compared with male normocholesterolemic controls (n=27) matched for age and blood pressure. Homozyotes were excluded	Average age 11.1 and witht 39-40 lbs.	Unknown	Paris	The geometric and mechanical properties of large arterial vessels in young children with FH	Arterial properties compared with IMT results	This is a cross sectional study	Non invasive ultrasonic measurements were performed of the CCA luminal systolic and diastolic diameters and IMT. Brachial artery diameters were measured after reactive hyperemia and nitroglycerine treatment.
Supravalvular aortic stenosis and coronary ostial stenosis in familial hypercholesterolemia: two-dimensional echocardiographic assessment	Beppu S; Minura Y; Sakakibara H; Nagata S; Park YD; Nambu S; Yamamoto A;	1983	CSER	3		See narrative for details							
Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis	Celermajer DS; Sorensen KE; Gooch VM; Spiegelhalter DJ; Miller OI; Sullivan ID; Lloyd JK; Deanfield JE;	1992	CSER	3		See narrative for details							
Increased carotid intima-media thickness in children-adolescents, and young adults with a parental history of premature myocardial infarction	Cuomo S; Guarini P; Gaeta G; De Michele M; Boeri F; Dorn J; Bond MG; Trevisan M;	2002	CSER	3		See narrative for details							
Coronary angiographic characteristics in Japanese patients with heterozygous familial hypercholesterolemia	Genda A; Nakayama A; Shimizu M; Nunoda S; Sugihara N; Suematzu T; Kita Y; Yoshimura A; Koizumi J;	1987	CSER	3		See narrative for details							

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
	Mabuchi H; et a;												
Quantification of coronary artery calcification in patients with FH using EBCT.[see comment]	Hoffmann U; Bodlaj G; Derfler K; Bernhard C; Wicke L; Herold CJ; Kostner K;	2001	CSER	3		See narrative for details							
Relation of peripheral flow-mediated vasodilatation and coronary arterial calcium in young patients with heterozygous familial hypercholesterolemia	Hoffmann U; Dirisamer A; Heher S; Kostner K; Widhalm K; Neunteufl T;	2002	COH	2+	13 FH patients and 13 healthy controls	Young heterozygous FH patients with an LDL cholesterol level >95 percentile for age and a family history. Patients on a cholesterol lowering medication were excluded.	4 mailes and 9 females in each group; no HTN or DM in either group	Through the Dept of Pediatrics at the University Hospital of Vienna	Vienna	Comparison of endothelial dysfunction and coronary artery calcium	Presence of pathology by method of detetection was compared	This is a cross sectional study	Measurements of the brachial artery done by scan and calcium scoring of the amount of calcium of the aortic root and the coronary vessel wall were the primary outcomes as calculated by Agatston score.
Evaluation of coronary risk factors in patients with heterozygous familial hypercholesterolemia	Hopkins PN; Stephenson S; Wu LL; Riley WA; Xin Y; Hunt SC;	2001	CSER	3		See narrative for details							
Association of coronary heart disease with age-adjusted aortocoronary calcification in patients with familial hypercholesterolaemia	Jensen JM; Gerdes LU; Jensen HK; Christiansen TM; Brorholt-Petersen JU; Faergeman O;	2000	COH	2+	80 individuals with molecularly defined FH; 24 had CHD and 56 were presumedto be disease free.	Adults above 18 years of hage and heterozygous for one of three diferent mutations.	Thre were significant differences between the CHD and non CHD groups in age (55.3[11.7] in former and 38.8 [10.6] in latter; p<0.001) in smoking % (83.3% in former and 53.5 in latter; p<0.02)	Lipid Clinic at Aarhus Amtssygehus University Hospital	Denmark	Four CHD diagnostic models for CAD were compared	Model A - traditional risk factors including age, sex, cholesterol, hypertension, smoking and BMI; Model B- cholesterol year score and Model C,D - aortic & coronary calcium measured by spiral computed tomography (CT).	This is a cross sectional study	A logistic regression model was used to obtain predicted probabilitiesof CHD for each model and these were used to construct an ROC curve.
Carotid intima-media thickness in young patients with familial hypercholesterolaemia	Lavrencic A; Kosmina B; Keber I; Videcnik V; Keber D;	1996	CSER	3		See narrative for details							
Development of coronary heart disease in familial hypercholesterolemia	Mabuchi H; Koizumi J; Shimizu M; Takeda R;	1989	CSER	3		See narrative for details							
Exercise testing in asymptomatic patients with heterozygous familial	Michaelides AP; Fourlas CA; Pitsavos C; Andrikopoulos	2004	CSER	3		See narrative for details							

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
hypercholesterolaemia	GK; Skoumas I; Kartalis A; Katsaros A; Stougiannos P; Stefanadis CI;												
Cross sectional echocardiographic assessment of the aortic root and coronary ostial stenosis in familial hypercholesterolaemia	Ribeiro P; Shapiro LM; Gonzalez A; Thompson GR; Oakley CM;	1983	CSER	3		See narrative for details							
Echocardiographic changes in patients with heterozygous and homozygous familial hypercholesterolemia: correlation with clinical findings	Tato F; Keller C; Schewe S; Pinter W; Wolfram G;	1991	CSER	3		See narrative for details							
Risk factors related to carotid intima-media thickness and plaque in children with familial hypercholesterolemia and control subjects	Tonstad S; Joakimsen O; Stensland-Bugge E; Leren TP; Ose L; Russell D; Bonaa KH;	1996	CSER	3		See narrative for details							
Intima-media thickness after cholesterol lowering in familial hypercholesterolemia. A three-year ultrasound study of common carotid and femoral arteries	Wendelhag I; Wiklund O; Wikstrand J;	1995	CSER	3		See narrative for details							
Differences in intima-media thickness in the carotid and femoral arteries in familial hypercholesterolemic heterozygotes with and without clinical manifestations of cardiovascular disease	Wittekoek ME; de G; Prins MH; Trip MD; Buller HR; Kastelein JJ;	1999	CSER	3		See narrative for details							

Study results

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
Arterial mechanical changes in children with familial hypercholesterolemia	Aggoun Y; Bonnet D; Sidi D; Girardet JP; Brucker E; Polak M; Safar ME; Levy BI;	2000	In patients with FH there was significant reduction of systodistolic variations in diameter of the CCA (by 20%, p<0.001) without a significant difference in IMT. The wall stiffness was larger in FH subjects than in controls (by 27%, p=0.003). The flow mediated dilation of the brachial artery was smaller in the FH subjects (4.2 +/- 2.9%) than in controls (9.0 +/- 3.1%, p<0.001). No correlation was evident between the carotid incremental modulus and either IMT or LDL-C.	Unknown	None	ConclKQQ3-9 These results indicate that increased stiffness of the CCA wall in children with FH could be related to endothelial dysfunction. Thus alterations in CCA wall mechanics could be early and easily measurable markers of atheromatous changes in the arterial wall.	This is a small study;validity of measurement techiques should be explained.	Yes	Yes	

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
Supravalvular aortic stenosis and coronary ostial stenosis in familial hypercholesterolemia: two-dimensional echocardiographic assessment	Beppu S; Minura Y; Sakakibara H; Nagata S; Park YD; Nambu S; Yamamoto A;	1983	See narrative for details							
Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis	Celermajer DS; Sorensen KE; Gooch VM; Spiegelhalter DJ; Miller OI; Sullivan ID; Lloyd JK; Deanfield JE;	1992	See narrative for details							
Increased carotid intima-media thickness in children-adolescents, and young adults with a parental history of premature myocardial infarction	Cuomo S; Guarini P; Gaeta G; De Michele M; Boeri F; Dorn J; Bond MG; Trevisan M;	2002	See narrative for details							
Coronary angiographic characteristics in Japanese patients with heterozygous familial hypercholesterolemia	Genda A; Nakayama A; Shimizu M; Nunoda S; Sugihara N; Suematzu T; Kita Y; Yoshimura A; Koizumi J; Mabuchi H; et a;	1987	See narrative for details							
Quantification of coronary artery calcification in patients with FH using EBCT.[see comment]	Hoffmann U; Bodlaj G; Derfler K; Bernhard C; Wicke L; Herold CJ; Kostner K;	2001	See narrative for details							
Relation of peripheral flow-mediated vasodilatation and coronary arterial calcium in young patients with heterozygous familial hypercholesterolemia	Hoffmann U; Dirisamer A; Heher S; Kostner K; Widhalm K; Neunteufl T;	2002	Baseline vessel diameter was significantly smaller in patients with FH compared to controls (3.2 =/- 0.3 mm, range 2.7 to 3.6 vs 3.5 +/- 0.4 mm, range 3.0 to 4.3; p<0.02, respectively). Flow mediated dilation was significantly reduced in patients with FH compared with controls (10.7 +/- 5.3%, range 4.5% to 17.2% vs 17.3 +/- 4.6%, range 7.7% to 25.0%; p=0.002). None of the FH patients or controls showed calcium of the aotic root or the roximal coronary areteries, resulting in an Agatston score of 0 in every patient. For the whole group (n=26) total cholesterol and LDL-C were inversley correlated with flow mediated dilation, p=0.0003 and p=0.003 respectively	Unknown	None	This study indicates that peripheral FMD, a precursor of atherosclerosis, is altered in young heterozygous patients with FH. This alteration occurs before coronary arterial or aortic root calcium can be detected by MDCT and is is independently related to hypercholesterolemia.	This is a small study and results of calcium of the aortic root are a calculated score. Validity of this method was not discussed.	Yes	Yes	There was a significant difference between groups on age (p=0.000010 with FH group 17.9 years +/- 3.4 and control group 26.5 +/- 2.6
Evaluation of coronary risk factors in patients with heterozygous familial hypercholesterolemia	Hopkins PN; Stephenson S; Wu LL; Riley WA; Xin Y; Hunt SC;	2001	See narrative for details							
Association of coronary heart disease with age-adjusted aortocoronary calcification in patients with familial hypercholesterolaemia	Jensen JM; Gerdes LU; Jensen HK; Christiansen TM; Brorholt-Petersen JU; Faergeman O;	2000	The following variables from models A and B were significantly associated with CHD in individuals with FH: Age p<0.001 Treated Cholesterol p<0.05 (BMI borderline) p<0.06 Smoking p<0.02 Models C and D were highly significant: Coronary calcium p<0.001 Aortic calcium p<0.001 The age adjusted ROC curves for coronary calcium score was significantly greater than those for traditional risk factors (p<0.002) cholesterol year score	Danish Heart Foundations and multiple research funding organisations	None	Yes. The four diagnostic models are only moderately accurate but age adjusted coronary calcium appeared to be the best indicator	Yes	No other studies	Yes	

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			(p<<0.0001) and age adjusted aortic calcium score (p<0.0004)."							
Carotid intima-media thickness in young patients with familial hypercholesterolaemia	Lavrencic A; Kosmina B; Keber I; Videcnik V; Keber D;	1996	See narrative for details							
Development of coronary heart disease in familial hypercholesterolemia	Mabuchi H; Koizumi J; Shimizu M; Takeda R;	1989	See narrative for details							
Exercise testing in asymptomatic patients with heterozygous familial hypercholesterolaemia	Michaelides AP; Fourlas CA; Pitsavos C; Andrikopoulos GK; Skoumas I; Kartalis A; Katsaros A; Stougiannos P; Stefanadis CI;	2004	See narrative for details							
Cross sectional echocardiographic assessment of the aortic root and coronary ostial stenosis in familial hypercholesterolaemia	Ribeiro P; Shapiro LM; Gonzalez A; Thompson GR; Oakley CM;	1983	See narrative for details							
Echocardiographic changes in patients with heterozygous and homozygous familial hypercholesterolemia: correlation with clinical findings	Tato F; Keller C; Schewe S; Pinter W; Wolfram G;	1991	See narrative for details							
Risk factors related to carotid intima-media thickness and plaque in children with familial hypercholesterolemia and control subjects	Tonstad S; Joakimsen O; Stensland-Bugge E; Leren TP; Ose L; Russell D; Bonaa KH;	1996	See narrative for details							
Intima-media thickness after cholesterol lowering in familial hypercholesterolemia. A three-year ultrasound study of common carotid and femoral arteries	Wendelhag I; Wiklund O; Wikstrand J;	1995	See narrative for details							
Differences in intima-media thickness in the carotid and femoral arteries in familial hypercholesterolemic heterozygotes with and without clinical manifestations of cardiovascular disease	Wittekoek ME; de G; Prins MH; Trip MD; Buller HR; Kastelein JJ;	1999	See narrative for details							

Question 13: What is the effectiveness of dietary interventions to improve outcome in adults, children and young people with FH?

Study descriptions

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
Plant stanols do not restore endothelial function in pre-pubertal children with familial hypercholesterolemia despite reduction of low-density lipoprotein cholesterol levels	Jakulj L; Vissers MN; Rodenburg J; Wiegman A; Trip MD; Kastelein-John JP;	2006	RCT	1+	41 children	Inclusion: FH diagnosis; between the ages of 7-12 years	22 males; 19 females; average 9.8 years (1.5). At the start of the study none of the girls had reached menarche	Outpatient lipid clinic at Emma Children's Hospital in Amsterdam.	Out patient	Subjects were randomised to either a low fat plant stanol containing yogurt (2g of stanol) or a low fat yogurt without plant stanol	This is a comparison between treatments	Two consecutive 4 week interventiion periods (cross over design)	LDL-C, HDL-C, TC and TG and flow mediated dilation for endothelial function
Non-cholesterol sterols in serum, lipoproteins, and red cells in statin-treated FH subjects off and on plant stanol and sterol ester spreads	Ketomõki A; Gylling H; Miettinen TA;	2005	RCT	1+	18 adults	Inclusion: FH diagnosis Exclusion: diabetes or kidney, liver or thyroid diseases	6 males; 12 females; mean age of 48 +/- 2 years	Outpatient Lipid Clinics, Department of Medicine, University of Helsinki	Out patient	Stanol and sterol dietary consumption	Lipid levels and plant stanol levels in serum	Two consecutive 4 week intervention periods	TC, LDL-C, HDL-C, TG and plant sterol levels
Phytosterols/stanols lower cholesterol concentrations in familial hypercholesterolemic subjects: a systematic review with meta-analysis	Moruisi KG; Oosthuizen W; Opperman AM;	2006	SR	1+	RCT								
Comparison of efficacy of plant stanol ester and sterol ester: short- term and longer-term studies	O'Neill FH; Sanders-Tom AB; Thompson GR;	2005	RCT	1+	139 subjects divided into three treatment groups randomised to receive plant sterol (Flora Pro Activ) or plant stanol (Benecol spread or Benecol cereal bar).	Individuals with FH and unaffected individuals	Randomisation resulted in 3 well matched groups with respect to numbers, age, ratio of FH to unaffect subjects, baseline serum lipids. No other information is provided.	Two centres in West London	Out patient	Comparison of plant sterol (Flora Pro Activ) or plant stanol (Benecol spread or Benecol cereal bar) in relation to lipid lowering	Effects on lipid lowering and lipid/cholesterol synthesis	2 months	LDL-C and plant sterol levels
Dietary treatment for familial hypercholesterolaemia	Poustie VJ; Rutherford P;	2001	SR	1+	RCT								

Study results

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
Plant stanols do not restore endothelial function in pre-pubertal children with	Jakulj L; Vissers MN; Rodenburg J;	2006	Variables Stanol Placebo Mean change		None	This study demonstrates that plant stanols reduce LDL-C concentrtions in children with FH without improving	This is a very small study but appears to be	Yes	Yes	

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
familial hypercholesterolemia despite reduction of low-density lipoprotein cholesterol levels	Wiegman A; Trip MD; Kastelein-John JP;		TC 6.47+/-1.35 7.00+/-1.49 -0.53(-0.79 to 0.28) LDL-C 4.77+/-1.32 5.24+/-1.45 -0.48(-0.69 to 0.27) HDL-C 1.35+/-0.24 1.38+/-0.27 -0.03(-0.13 to 0.06) TG 0.61+/-0.51-0.84 0.57+/-0.51-0.93 -0.05(-0.18 to 0.08) FMD%) 10.5(+/-5.1) 10.5(+/-5.1) 0.05(-2.40 to 2.51) Changes in TC and LDL-C were significant compared to placebo p<0.001 Plant sterols were decreased in serum, lipoproteins and red cells by about 25% with stanols and increased from 37-80% with sterols, especially with high statin doses."			endothelial function	concordant with other studies in this field.			
Non-cholesterol sterols in serum, lipoproteins, and red cells in statin-treated FH subjects off and on plant stanol and sterol ester spreads	Ketomõki A; Gylling H; Miettinen TA;	2005	Variables Baseline Stanols Sterols TC 6.30+/-0.24 5.65+/-0.22 5.71+/-0.21 LDL-C 4.50+/-0.21 3.81+/-0.18 3.86+/-0.19 HDL-C 1.26+/-0.05 1.32+/-0.04 1.37+/-0.04 TG 1.19+/-0.10 1.16+/-0.12 1.05+/-0.09 Changes in TC and LDL-C were significant from baseline p<0.05 Changes in HDL-C and TG were significant from baseline p<0.01 Plant sterols were decreased in serum, lipoproteins and red cells by about 25% with stanols and increased from 37-80% with sterols, especially with high statin doses."	Finnish Heart Research Foundation, Finnish Medical Society Duodecim, Research Foundation of Orion, Biomedicum Helsinki Foundation, Finnish Cultural Foundation, Ida Montin Foundation, Helsinki University Central Hospital	None	Stanols and sterols both reduce LDL-C but sterols increase serum, lipoprotein and red cell plant sterol levels in statin treated FH subjects while all the respective values are decreased with stanols. There is some evidence that elevated serum plant sterols pose an increased coronary risk and the authors therefore state that increases of serum plant sterol levels should be avoided, especially in atherosclerosis prone individuals such as subjects with FH.	This is a very small study but apppears to be concordant with other studies in the field	Yes	Yes	No placebo control in this study
Phytosterols/stanols lower cholesterol concentrations in familial hypercholesterolemic subjects: a systematic review with meta-analysis	Moruisi KG; Oosthuizen W; Opperman AM;	2006		Unknown		The results of the SR of 6 studies showed LDL-C reduction of 14-15% and TC reduction of 11% in children with the highest dosages of 2.3 g/day plant sterol and 2.8 g/day plant stanol enriched spreads. Intake of 1.6 g/day plant sterol enriched spread by ch ConclKQQ3-9 "The results of the SR of 6 studies showed LDL-C reduction of 14-15% and TC reduction of 11% in children with the				This SR included only controlled, randomized, double blind studies with good compliance and sufficient statistical power. Six trials from 1976 to 2004 qualified to be in the review. Four

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
						highest dosages of 2.3 g/day plant sterol and 2.8 g/day plant stanol enriched spreads. Intake of 1.6 g/day plant sterol enriched spread by children resulted in reductions of 10.2% in LDL-C and 7.4% in TC concentrations. In the adult group, 2.5 g/day plant sterol enriched spread caused a reduction of 10% in LDL-C and 8% in TC concentrations. The results of the meta analysis of 124 subjects on 2.3 +/- 0.5 g phytosterols/stanols/day for 6.5 +/- 1.9 weeks were as follows: TC reducedby 0.65 mmol/l (95% CI -0.88 to -0.42 mmol/l, p<0.00001) and LDL-C by 0.64 mmol/l (95% CI -0.86 to -0.43 mmol/l, p<0.00001). I squared was 0%."				of these were included in the meta analysis.
Comparison of efficacy of plant stanol ester and sterol ester: short- term and longer-term studies	O'Neill FH; Sanders-Tom AB; Thompson GR;	2005	There was no statistical difference in the response to plant sterols or stanols between FH subjects taking statins and unaffected subjects. Decreases in LDL-C ranged from 4.8% to 6.6%. Changes in total cholesterol ranged from 3% to 7.5%. Decreases in both concentrations were more marked in the plant sterol group at 1 month and in the plant stanol group at 2 months. In the plant sterol group the decrease at 2 months was only half as great as at 1 month and was no longer significantly different from baseline. Changes in HDL-C were slight but there was a tendency for values to decrease by about 3% in each of the groups. Sterols: Increased serum plant sterols and a significant decrease in 7 alpha-hydroxy-4-cholesten-3-one a marker of bile acid synthesis Stanols: Lowered significantly both LDL-C and plant sterol levels and had no effect on bile acid synthesis"	Unknown	None	The findings suggest that absorption of dietary plant sterols downregulates bile acid synthesis which attenuates their cholesterol lowering efficacy. The authors conclude that plant stanos are preferable for the long term management of hypercholesterolemia	It would be interesting to evaluate this effect in a long term study	Yes	Yes	
Dietary treatment for familial hypercholesterolaemia	Poustie VJ; Rutherford P;	2001		Cochrane Collaboration		"Cholesterol lowering diet compared with no dietary intervention: One trial with 19 participants. NS difference. Cholesterol-lowering diet compared with all other dietary interventions: 5 trials with 80 participants. NS differences for ischaemic heart disease, death, TC, LDL-C, HDL-C, TG, Apo A and Apo B, Cholesterol-lowering diet compared with low fat diet: One trial with 16 participants. NS difference.				All seven eligible trials were randomised controlled cross over trials. All were short term trials with each arm of the trial lasting between one and three months.

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
						Cholesterol lowering diet compared with increase in plant stanols: One trial of 14 children with NS difference. Cholesterol lowering diet compared with increase in plant sterols: Two trials but one (Neil) failed to provide data from FH subgroup and the other found NS difference. Cholesterol lowering diet compared to high protein diet: Two trials were combined and NS difference was found on ischaemic heart disease, death, TC, LDL-C, HDL-C, TG. Author's conclusion: No conclusions can be made about the effectiveness of cholesterol lowering diets or other dietary interventions for FH due to lack of adequate data. An RCT is needed to investigate dietary treatment for FH."				

Question 14: What information/counselling should be provided to girls/women of child bearing potential with FH with respect to contraception?

Study descriptions

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis	Baillargeon JP; McClish DK; Essah PA; Nestler JE;	2005	MET	1-	14 case control studies								
Epidemiology of oral contraceptives and cardiovascular disease.	Chasan-Taber L; Stampfer MJ;	1998	SR	1+	All english language epidemiological studies								
Oral contraceptives use and the risk of myocardial infarction: a meta-analysis	Khader YS; Rice J; John L; Abueita O;	2003	MET	1-	19 case control; 4 cohort								
The effect of rosuvastatin on oestrogen & progestin pharmacokinetics in healthy women taking an oral contraceptive	Simonson SG; Martin PD; Warwick MJ; Mitchell PD; Schneck DW;	2004	COH	2+	18	Healthy volunteers; pre-menopausal; nonpregnant, nonbreastfeeding, nonsmoking between 18-40 with intact ovarian function who had received ortho tri cyclen throughout the previous 3 menstrual cycles. Exclusion criteria included elevated liver enzymes	Female, with mean age of 25, height 163 cm and weigh of 60kg.	Volunteers	Finland	Effect of rosuvastatin on estrogen and progestin metabolism.	Changes in hormone levels of estrogen, progestin FL, FSH, cortisol and TC, LDL-C, TG nd HDL.	Two menstrual cycles	Hormone concentrations and lipid levels
Myocardial infarction and third generation oral contraceptives: Aggregation of recent studies	Spitzer WO; Faith JM; MacRae KD;	2002	MET	1-	Case control								

Study results

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis	Baillargeon JP; McClish DK; Essah PA; Nestler JE;	2005		Fond de Rechereche en Sante du Quebec; National Institutes of Health Grants		In relation to MI the summary risk estimates associated with current use of low dose OCs was 1.84 (1.83-2.44) for MI. Second generation OCs were associated with a significant increased risk of MI OR 1.85 (1.03-3.32);MI for third generation OC use was not				The inherent bias of observational studies makes it difficult to combine studies and obtain a reliable summary statistic.

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
						significant 1.28 (0.78-2.10). This is a meta analysis of OC use in healthy women. The risk in women with FH or high lipid levels is not assessed."				
Epidemiology of oral contraceptives and cardiovascular disease.	Chasan-Taber L; Stampfer MJ;	1998		Ortho Pharmaceuticals		In relation to MI the summary risk estimates associated with current use of low dose OCs was 1.84 (1.83-2.44) for MI. Second generation OCs were associated with a significant increased risk of MI OR 1.85 (1.03-3.32);MI for third generation OC use was not significant 1.28 (0.78-2.10). This is a meta analysis of OC use in healthy women. The risk in women with FH or high lipid levels is not assessed."				The studies were done in basically healthy women
Oral contraceptives use and the risk of myocardial infarction: a meta-analysis	Khader YS; Rice J; John L; Abueita O;	2003		Unknown. Study conducted at Jordan University of Science and Technology		In relation to MI the summary risk estimates associated with current use of low dose OCs was 1.84 (1.83-2.44) for MI. Second generation OCs were associated with a significant increased risk of MI OR 1.85 (1.03-3.32);MI for third generation OC use was not significant 1.28 (0.78-2.10). This is a meta analysis of OC use in healthy women. The risk in women with FH or high lipid levels is not assessed."				Although a random effects model, sensitivity analysis and analysis for publication bias was done the meta analysis is essentially flawed by the combination of cohort and case control studies which do possess the methodological robustness of RCTs. The literature search was medline only. Studies vary in the formulations, doses and generations of Ocs."
The effect of rosuvastatin on oestrogen & progestin pharmacokinetics in healthy women taking an oral contraceptive	Simonson SG; Martin PD; Warwick MJ; Mitchell PD; Schneck DW;	2004	Co-administration of orthotricyclen and rosuvstatin did not result in lower exposures to the exogenous oestrogen or progetin components of the OC. LH and FSH were similar between cycles. There were no changes in the urinary excretion of cortisol. Rosuv	Astra zeneca	None	Rosuvastatin can be coadministered with orthotricyclen (a third generation OCP - norgestimate) without decreasing oral contraceptive steroid concentrations. The lipid regulating effect of the state does not appear to be altered.	Yes	Yes	Yes	This is an open label non radomised trial with 18 participants
Myocardial infarction and third generation oral contraceptives: Aggregation of recent studies	Spitzer WO; Faith JM; MacRae KD;	2002		Unknown		This is an overview of seven controlled observational studies (case control design). Summary statistics for MI events were calculated for users of second and third generation oral contraceptives. There were 6464 subjects accrued. Compared with non users the aggregated OR for 3gen OC was 1.13 (0.66-1.92) and for 2gen OC it was 2.18 (1.62-2.94).				A meta analysis of observational studies is subject to bias based upon study type. Therefore, results must be accepted with caution. The studies analysed are done in populations of generally healthy women.

Question 15: What information/care should be provided to (a) pregnant women with FH, or women with FH prior to pregnancy on lipid-modifying treatment or FH related complications in pregnancy/labour/delivery or (b) lactating women with FH taking lipid modifying drugs?

Study descriptions

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Inclusion/exclusion	Description of participants/studies	Recruitment	Setting	Aims	Comparisons	Length of study	Outcomes
Marked changes in plasma lipids and lipoproteins during pregnancy in women with familial hypercholesterolemia	Amundsen AL; Khoury J; Iversen PO; Bergei C; Ose L; Tonstad S; Retterstol K;	2006	COH	2+	22 pregnant women with FH and 149 pregnant non FH women	Excluded were any women with other diseases which could influence blood lipids and twin pregnancies.	Ages 29-31 years; education more than 12 years 77-79%; nulliparous 63-65%. Importantly 32% of FH group smoked and none of the reference group smoked.	Lipid clinic patients	Oslo, Norway	Lipid levels in pregnancy	Different levels of factors are compared	Throughout pregnancy	TC and LDL
Altered hemostatic balance and endothelial activation in pregnant women with familial hypercholesterolemia	Amundsen AL; Khoury J; Sandset PM; Seljeflot I; Ose L; Tonstad S; Henriksen T; Retterstol K; Iversen PO;	2007	COH	2+	22 pregnant women with FH and 149 healthy pregnant women	Excluded: women with other diseases which could affect lipid level; twin pregnancies	Age 29-31; education greater than 12 years 77%-79%; smoking before pregnancy 31% in FH and 0% in reference.	Lipid clinic	Oslo Norway	Changes in hemostatic and endothelial activation levels	Different levels of hemostatic and endothelial activation factors	Throughout pregnancy	Prothrombin and VCAM-1
Risk of congenital anomalies in pregnant users of statin drugs	Ofori B; Rey E; BÚrard A;	2007	CC	2-	288 pregnant women	The participants had to be between age 15 to 45 years from the first day of gestation; to be continuously insured by the RAMQ (Regie de l'Assurance Maladie du Quebec) drug plan for at least 12 months before the first day of gestation and during their preg	See inclusion criteria. The women were divided into three groups: Group A user of statins only before and during 1st trimester (n=153); Group B users of fibrates or nicotinic acid only before and during 1st trimester (n=29) and group C usrs of statins o	This is a retrospective review of a pregnancy register created by linking databases	Montreal	Congenital anomalies	Use of statins, fibrates or nicotinic acid before or during pregnancy	Not applicable. This is a cross sectional study	Congenital anomalies diagnosed in the first year of life
Pregnancy outcomes after maternal exposure to simvastatin and lovastatin	Pollack PS; Shields KE; Burnett DM; Osborne MJ; Cunningham ML; Stepanavage ME;	2005	COH	2-	477 reports. There were 386 prospective reports (received before the outcome of the pregnancy was known) and 91 retrospective reports (received after the outcome of the pregnancy was known).	Exposure to simvastatin and/or lovastatin during pregnancy	Maternal age was reported in 291 cases and the mean was 32+/- 6 years	This is a database review	Review of Merck data base carried out in the US	Frequency of adverse outcomes after maternal exposure to simvastatin and/or lovastatin during pregnancy	No comparisons are made. Pregnancies were evaluated for timing of exposure, outcome , congenital anomalies and other events	NA	Outcome rates

Study results

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
Marked changes in plasma lipids and lipoproteins during pregnancy in women with familial hypercholesterolemia	Amundsen AL; Khoury J; Iversen PO; Bergei C; Ose L; Tonstad S; Retterstol K;	2006	In 22 pregnant women with FH blood samples were collected at gestational weeks 17-20 (baseline), 24, 30 and 36 weeks and compared with a reference group of 149 women. Total cholesterol and LDL-C increased significantly between baseline and gestational week 36 by 29% to 11.6 +1.9mmol/l in the first instance and by 30% to 8.6 + 2.0 mmol/l in the case of LDL-C. The increases in the reference women were 25.4% increase in TC and 34.2% increase in LDL-C. The relative increases did not differ ($p<0.05$) but absolute values in FH women were markedly higher than in the reference group. Of note however is the relatively large number of pre-pregnancy smokers in the FH group (31% compared to 0% in the reference group). Pregnancy outcomes in the FH group did not differ significantly from those in the reference group.	Throne Holst Foundation and Health Region East of Norway	None	This study indicates that lipid levels continue to rise in pregnant FH women but these results may be affected by the smoking history of these women.	Yes	Yes	Yes	
Altered hemostatic balance and endothelial activation in pregnant women with familial hypercholesterolemia	Amundsen AL; Khoury J; Sandset PM; Seljeflot I; Ose L; Tonstad S; Henriksen T; Retterstol K; Iversen PO;	2007	The concentration of prothrombin fragments 1 + 2, a marker of thrombin generation was higher ($p<0.05$) in the FH group compared with the reference group. The baseline concentrations of the endothelial activation marker VCAM-1 were apparently similar ($p<0.05$) in the FH and reference groups, VCAM-1 rose markedly ($p<0.05$) during pregnancy by 120% in the FH group, whereas it remained unaltered in the reference group.	Throne Holst Foundation and Health Region East of Norway	None	This study provides support for the level of cardiac risk which may be present in women with FH who become pregnant. However, the results may be skewed by the large number of pre-pregnancy smokers in the FH group. It is possible however that enhanced en	Yes	No other studies	Yes	
Risk of congenital anomalies in pregnant users of statin drugs	Ofori B; Rey E; BÚrard A;	2007	Crude OR using Group B as reference group: Group A 0.18 (95% CI 0.03,1.01); Group C 0.43 (95% CI 0.10, 1.91) The first multivariate analysis of the entire study cohort, stratified by study group included the variables: maternal age at end of pregnancy, socioeconomic information and education, comorbidities and health services utilisation. The adjusted OR for congenital anomalies for group A was 0.79 (95% CI 0.10, 6.02) and for group C 1.74 (95% CI 0.27, 11.27). In the second multvariate analysis which included groups A and C, using group C as the reference group, the adjusted OR for group A was 0.36 (95% CI 0.06, 2.18) when compared with group C. No pattern of anomaly was evident in	Les Fonds de la Recherche en Sante du Quebec, the Reseau Quebecois de recherche sur l'usage des medicaments.	This study looks at the safety of statins in pregnancy	This study supports the position that there is no clear evidence of harm when statins are taken in early pregnancy. Termination should not be routinely recommended in these cases.	The study was underpowered, retrospective and included only live births and is therefore not adequate to be certain of effect.	Yes	Yes	This is a retrospective study of live births only

Title	Author(s)	Year	Results	Funding	Reported harms	Conclusions	Effect due to factor under investigation?	Consistent with other studies?	Applicable to guideline population?	Notes
			this study group."							
Pregnancy outcomes after maternal exposure to simvastatin and lovastatin	Pollack PS; Shields KE; Burnett DM; Osborne MJ; Cunningham ML; Stepanavage ME;	2005	There were 386 prospective reports (received before the outcome of the pregnancy was known) and 91 retrospective reports (received after the outcome of the pregnancy was known). The rate of congenital anomalies was 3.8% in the prospectively reported pregnancies and was slightly higher than the US background rate of 3.15% incidence of overall birth defects. Thirteen congenital anomalies (14%) were reported retrospectively. There was no specific pattern of congenital anomalies for either prospectively or retrospectively reported pregnancies.	Unknown	Congenital anomalies and other adverse events in pregnancy	Drugs should be used during pregnancy onlyif the benefits outweigh the risks. It was concluded by the authors that simvastatin and lovastatin remain contraindicated during pregnancy				This was a review of the Merck & Co pharmacovigilance database which contained study reports of serious adverse events from clinical trials and postmarketing studies as well as all spontaneous postmarketing reports related to product use from any source, including health care professionals, patients and regulatory agencies. Individual case reports from the literature were also included.

Question 16: What are the key components of assessment and review for individuals (adults and children) with homozygous or heterozygous FH including infromation & support regarding diet, exercise/regular physical activity and smoking cessation?

No studies were identified.

Question 17: What is the effectiveness of dietary interventions to improve outcome in the general population? (NOTE only agreed to include meta-analyses for corroboration)

See also Question 13.

Title	Author(s)	Year	Study Type	Grading	Participants or included studies	Funding	Conclusions	Notes
Dietary advice for reducing cardiovascular risk	Brunner EJ; Rees K; Ward K; Burke M; Thorogood M;	2007	MET	1++	RCTs of trials providing dietary advice to adults with a follow up of at least 3 months and no more than 20% loss to follow up. See also Chapter narrative for details.	Cochrane collaboration	This meta-analysis is of studies giving dietary advice. The studies included were ones which gave advice verbally and/or written to individuals and groups both in person and over the telephone; the advice given included reducing intake of "one or more of	
Reduced or modified dietary fat for preventing cardiovascular disease	Hooper L; Summerbell CD; Higgins JPT; Thompson RL; Clements G; Capps N; Davey SG; Riemersma RA; Ebrahim S;	2000	MET	1++	RCTs of dietary interventions to reduce or modify fat or cholesterol intake in adults with follow ups of at least 6 months. See also Chapter narrative for details.	Cochrane collaboration	This meta-analysis focuses on the effect of reducing or modifying dietary fats on the mortality (both cardiovascular and other) and cardiovascular morbidity. The interventions included were dietary advice, supplementation or a provided diet all of which i	L. Hooper (author) was employed as a dietition working in cardiac rehabilitation during the review. R Thompson and C Summerbell are also dietitions - potential conflicts of interest.
Plasma lipid and lipoprotein responses to dietary fat and cholesterol: a meta-analysis	Howell WH; McNamara DJ; Tosca MA; Smith BT; Gaines JA;	1997	MET	1+	Single group or multiple-group repeated-measures comparisons of dietary interventions in adults published between January 1966 and February 1994. See also Chapter narrative for details.	American Egg Board	This meta-analysis is of studies which have dietary interventions for adults over the age of 18. This study addresses the quality of the studies included in the meta-analysis very well. And showed that on average if patients in the high-risk range for LDL	This study is based on the typical American diet in 1994 (described as 385mg of cholesterol per day and 37% of the total energy coming from fat, of which 7% are polyunsaturated fatty acids, 17% are monounsaturated fatty acids and 7% from saturated fatty a

Excluded studies

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
2380	Diagnosis of familial hypercholesterolaemia using DNA probes for the low-density lipoprotein (LDL) receptor gene.	Armston AE; Iversen SA; Burke JF;	1988	Annals of Clinical Biochemistry	1	This is an old study which reflects early development of DNA and is not relevant to current practice.
270	The relationship among apolipoprotein(a) polymorphisms, the low-density lipoprotein receptor-related protein, and the very low density lipoprotein.	Benes P; Muzik J; Benedik J; Znojil V; Vacha J;	2002	Human Biology	1	Does not answer question
1169	Linkage Between Familial Hypercholesterolemia with Xanthomatosis and the C3-Polymorphism Confirmed.	Berg K; Heiberg A;	1978	Cytogenetics and Cell Genetics	1	No population data
5221	Genetic polymorphisms affecting the phenotypic expression of familial hypercholesterolemia.	Bertolini S; Pisciotta L; Di S; Langheim S; Bellocchio A; Masturzo P; Cantafora A; Martini S; Averna M; Pes G; Stefanutti C; Calandra S;	2004	Atherosclerosis	1	Within DNA positive group comparison
1550	Diagnosis and screening for familial hypercholesterolaemia, Finding the patients, finding the genes.	Bhatnagar D;	2006	Annals of Clinical Biochemistry	1	This is a narrative review

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
103	LDL receptor mutation genotype and vascular disease phenotype in heterozygous familial hypercholesterolaemia.	Brorholt-Petersen JU; Jensen HK; Jensen JM; Refsgaard J; Christiansen T; Hansen LB; Gregersen N; Faergeman O;	2002	Clinical Genetics	1	Did not answer question, wrong outcome measure
2602	Familial hypercholesterolemia, genetic, biochemical and pathophysiologic considerations.	Brown MS; Goldstein JL;	1975	Advances in Internal Medicine	1	Narrative review
1548	Clinical features of familial hypercholesterolemia in Japan in a database from 1996-1998 by the research committee of the ministry of health, labour and welfare of Japan.	Bujo H; Takahashi K; Saito Y; Maruyama T; Yamashita S; Matsuzawa Y; Ishibashi S; Shionoiri F; Yamada N; Kita T; Research C;	2004	Journal of Atherosclerosis & Thrombosis	1	Not a direct comparison of DNA positive and negative participants
1553	Detection of familial hypercholesterolemia in a cohort of children with hypercholesterolemia, Results of a family and DNA-based screening.	Campagna F; Martino F; Bifolco M; Montali A; Martino E; Morrone F; Antonini R; Cantafora A; Verna R; Arca M;	2006	Atherosclerosis	1	Did not answer question 1 - this is a study about screening
1126	Coexisting dysbetalipoproteinemia and familial hypercholesterolemia, Clinical and laboratory observations.	Carmena R; Roy M; Roederer G; Minnich A; Davignon J;	2000	Atherosclerosis	1	Within DNA positive group comparison
316	Association between the TaqIB polymorphism in the cholesteryl ester transfer protein gene locus and plasma lipoprotein levels in familial hypercholesterolemia.	Carmena-Ramon R; Ascaso JF; Real JT; Najera G; Ordovas JM; Carmena R;	2001	Metabolism, Clinical & Experimental	1	Within DNA positive group comparison

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
214	A common variant in the ABCA1 gene is associated with a lower risk for premature coronary heart disease in familial hypercholesterolaemia.	Cenarro A; Artieda M; Castillo S; Mozas P; Reyes G; Tejedor D; Alonso R; Mata P; Pocovi M; Civeira F; Spanish FH;	2003	Journal of Medical Genetics	1	Within DAN positive group study
1783	Improved detection of familial hypercholesterolemia by determining low density lipoprotein receptor expression in mitogen-induced proliferating lymphocytes.	Chan PC; Edwards A; Lafreniere R; Parsons HG;	1998	Journal of Lipid Research	1	This is a review of an assay which is expensive and time consuming and will not be considered in this review
62	Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia.	Civeira F; International P;	2004	Atherosclerosis	1	These guidelines do not provide the method of review but offer a good summary and background
62	Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia.	Civeira F; International P;	2004	Atherosclerosis	1	Method of review not provided
1549	FH clinical phenotype in Greek patients with LDL-R defective vs. negative mutations.	Dedoussis GV; Skoumas J; Pitsavos C; Choumerianou DM; Genschel J; Schmidt H; Stefanadis C;	2004	European Journal of Clinical Investigation	1	Not a direct comparison of DNA positive and negative participants
778	Different genes and polymorphisms affecting high-density lipoprotein cholesterol levels in Greek familial hypercholesterolemia patients.	Dedoussis GVZ; Maumus S; Choumerianou DM; Skoumas J; Pitsavos C; Stefanadis C; Visvikis-Siest S;	2002	Genetic Testing	1	Not a direct comparison of DNA positive and negative participants. Did not answer question.

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
5222	DNA polymorphisms of the apolipoprotein B gene (XbaI, EcoRI, and MspI RFLPs) in Norwegians at risk of atherosclerosis and healthy controls.	Delghandi M; Thangarajah R; Nilsen M; Grimsgaard S; Bonaa KH; Tonstad S; Jorgensen L;	1999	Acta Cardiologica	1	FH population not analysed separately
53	Update of the molecular basis of familial hypercholesterolemia in The Netherlands.	Fouchier SW; Kastelein JJ; Defesche JC;	2005	Human Mutation	1	Within DNA positive group comparison
2438	The diagnosis and management of hyperlipidemia.	Gotto AMJ; Jones PH; Scott LW;	1986	Disease-A-Month	1	Narrative review
1544	Genotype of the mutant LDL receptor allele is associated with LDL particle size heterogeneity in familial hypercholesterolemia.	Hogue JC; Lamarche B; Gaudet D; Tremblay AJ; Despres JP; Gagne C; Couture P;	2006	Atherosclerosis	1	Not a direct comparison of DNA positive and negative participants
2630	Studies in essential hypercholesterolemia and xanthomatosis, relationships between age, sex, cholesterol concentrations in plasma fractions, and size of tendinous deposits.	Hood B; Angervall G;	1959	American Journal of Medicine	1	This is not an FH specific population
1702	Type-Iii Dyslipoproteinemia in Patients Heterozygous for Familial Hypercholesterolemia and Apolipoprotein-E2 - Evidence for A Gene Gene Interaction.	Hopkins PN; Wu LL; Schumacher MC; Emi M; Hegele RM; Hunt SC; Lalouel JM; Williams RR;	1991	Arteriosclerosis & Thrombosis	1	DNA testing not done in all participants
1928	Genetic diagnosis of familial hypercholesterolemia in affected relatives using pedigree tracing.	Hsia SH; Connelly PW; Hegele RA;	1996	Clinical Biochemistry	1	Case study
2428	Familial hypercholesterolaemia as an example of early diagnosis of coronary artery disease risk by DNA techniques.	Humphries SE;	1986	British Heart Journal	1	This is an editorial

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
1710	The Application of Molecular-Biology Techniques to the Diagnosis of Hyperlipidaemia and Other Risk-Factors for Cardiovascular-Disease.	Humphries SE;	1993	Clinica Chimica Acta	1	Narrative for background use only
1883	Genetic testing for familial hypercholesterolaemia, practical and ethical issues.	Humphries SE; Galton D; Nicholls P;	1997	Quarterly Journal of Medicine	1	Narrative review
1542	Genetic causes of familial hypercholesterolaemia in patients in the UK, relation to plasma lipid levels and coronary heart disease risk.	Humphries SE; Whittall RA; Hubbart CS; Maplebeck S; Cooper JA; Soutar AK; Naoumova R; Thompson GR; Seed M; Durrington PN; Miller JP; Betteridge DJ; Neil HA; Simon B;	2006	Journal of Medical Genetics	1	
228	The molecular genetic basis and diagnosis of familial hypercholesterolemia in Denmark.	Jensen HK;	2002	Danish Medical Bulletin	1	This is a Ph.D. thesis which provides a narrative review of the genotype-phenotype relationship in Danish FH patients and of the clinical versus the DNA diagnosis in Danish FH patient
3315	Screening for familial hypercholesterolaemia, effective, safe treatments and DNA testing make screening attractive.	Kastelein JJP;	2000	British Medical Journal	1	Comment only - not study or trial
24	Low-density lipoprotein receptor genotype and response to pravastatin in children with familial hypercholesterolemia, substudy of an intima-media thickness trial.	Koeijvoets KC; Rodenburg J; Hutten BA; Wiegman A; Kastelein JJ; Sijbrands EJ;	2005	Circulation	1	Not a direct comparison of DNA positive and negative participants

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
2770	Genetic screening of patients with familial hypercholesterolaemia (FH), A New Zealand perspective.	Laurie AD; Scott RS; George PM;	2004	Atherosclerosis Supplements	1	Description of a programme - letter to the editor
555	Apolipoprotein E phenotype and lipoprotein(a) in familial hypercholesterolaemia, implication for lipoprotein(a) metabolism.	Lindahl G; Mailly F; Humphries S; Seed M;	1994	Clinical Investigator	1	Did not answer question
2460	Tracking of high- and low-density-lipoprotein cholesterol from childhood to young adulthood in a single large kindred with familial hypercholesterolemia	Mellies MJ; Laskarzewski PM; Tracy T; Glueck CJ;	1985	Metabolism, Clinical & Experimental	1	Case study of one family
1923	Clinically applicable mutation screening in familial hypercholesterolemia.	Nissen H; Guldberg P; Hansen AB; Petersen NE; Horder M;	1996	Human Mutation	1	Study does not answer the question - assessment of a screening assay
1800	Evaluation of a clinically applicable mutation screening technique for genetic diagnosis of familial hypercholesterolemia and familial defective apolipoprotein B.	Nissen H; Hansen AB; Guldberg P; Hansen TS; Petersen NE; Horder M;	1998	Clinical Genetics	1	Description of an assay
1714	An update on familial hypercholesterolaemia.	Ose L;	1999	Annals of Medicine	1	Narrative review
438	Familial hypercholesterolemia in children.	Rodenburg J; Vissers MN; Wiegman A; Trip MD; Bakker HD; Kastelein JJ;	2004	Current Opinion in Lipidology	1	Narrative review
1115	Screening for A Prevalent LDL Receptor Mutation in Patients with Severe Hypercholesterolemia.	Savolainen MJ; Korhonen T; Aaltosetala K; Kontula K; Kesaniemi YA;	1991	Human Genetics	1	Study of DNA assay. Out of date paper

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
3317	High risk/high priority, familial hypercholesterolemia--a paradigm for molecular medicine.	Schuster H;	2002	Atherosclerosis Supplements	1	Narrative review
1250	Familial hypercholesterolemia, a challenge of diagnosis and therapy.	Sibley C; Stone NJ;	2006	Cleveland Clinic Journal of Medicine	1	Narrative review
1489	DNA testing for familial hypercholesterolemia, improving disease recognition and patient care.	Vergopoulos A; Knoblauch H; Schuster H;	2002	American Journal of PharmacoGenomics	1	Narrative review
3331	Familial hypercholesterolaemia in Finland, common, rare and mild mutations of the LDL receptor and their clinical consequences. Finnish FH-group.	Vuorio AF; alto-Setala K; Koivisto UM; Turtola H; Nissen H; Kovanen PT; Miettinen TA; Gylling H; Oksanen H; Kontula K;	2001	Annals of Medicine	1	Not a direct comparison of DNA positive and negative participants
2105	Genetic basis of familial dyslipidemia and hypertension, 15-year results from Utah.	Williams RR; Hunt SC; Hopkins PN; Wu LL; Hasstedt SJ; Berry TD; Barlow GK; Stults BM; Schumacher MC; Ludwig EH; et a;	1993	American Journal of Hypertension	1	This paper discusses the general risk for HTN as an outcome
5327	Corneal arcus, case finding and definition of individual clinical risk in heterozygous familial hypercholesterolaemia.	Winder AF; Jolleys JC; Day LB; Butowski PF;	1998	Clinical Genetics	1	Study not written in English
1558	Relation between coronary artery disease, risk factors and intima-media thickness of carotid artery, arterial distensibility, and stiffness index	Alan S; Ulgen MS; Ozturk O; Alan B; Ozdemir L; Toprak N;	2003	Angiology	2	Not FH population

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
439	Families with familial combined hyperlipidemia and families enriched for coronary artery disease share genetic determinants for the atherogenic lipoprotein phenotype	Allayee H; Aouizerat BE; Cantor RM; linga-Thie GM; Krauss RM; Lanning CD; Rotter JI; Lusis AJ; de B;	1998	American Journal of Human Genetics	2	Not FH population
2612	High 'population attributable fraction' for coronary heart disease mortality among relatives in monogenic familial hypercholesterolemia	Austin MA; Zimmern RL; Humphries SE;	2002	Genetics in Medicine	2	Does not answer the question
318	The C766T low-density lipoprotein receptor related protein polymorphism and coronary artery disease, plasma lipoproteins, and longevity in the Czech population	Benes P; Muzik J; Benedik J; Elbl L; Vask A; Siskova L; Znojil V; Vacha J;	2001	Journal of Molecular Medicine	2	Does not answer question
678	Risk factor variability and coronary heart disease.	Berg K;	1990	Acta Geneticae Medicae et Gemellologiae	2	Report, not a trial
394	P1A1/A2 polymorphism of platelet glycoprotein IIIa and risk of acute coronary syndromes in heterozygous familial hypercholesterolemia	Cenarro A; Casao E; Civeira F; Jensen HK; Faergeman O; Pocovi M;	1999	Atherosclerosis	2	Study within DNA positive group
1545	Tendon xanthomas in familial hypercholesterolemia are associated with cardiovascular risk independently of the low-density lipoprotein receptor gene mutation	Civeira F; Castillo S; Alonso R; Merino-Ibarra E; Cenarro A; Artied M; Martin-Fuentes P; Ros E; Pocovi M; Mata P; Spanish F;	2005	Arteriosclerosis, Thrombosis & Vascular Biology	2	DNA testing not done in all participants
3297	Family history of coronary heart disease, evidence-based applications	Crouch MA; Gramling R;	2005	Primary Care, Clinics in Office Practice	2	Narrative review

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
3288	Family history of cardiovascular events and endothelial dysfunction in children with familial hypercholesterolemia	de Jongh S; Lilien MR; Bakker HD; Hutten BA; Kastelein JJ; Stroes ES;	2002	Atherosclerosis	2	Not all participants DNA tested
1465	Prevalence and significance of cardiovascular risk factors in a large cohort of patients with familial hypercholesterolaemia	de Sauvage Nolting PR; Defesche JC; Buirma RJ; Hutten BA; Lansberg PJ; Kastelein JJ;	2003	Journal of Internal Medicine	2	This study did not provide a comparison between mutation positive and mutation negative individuals
1369	Advanced method for the identification of patients with inherited hypercholesterolemia.	Defesche JC; Lansberg PJ; Umans-Eckenhausen MA; Kastelein JJ;	2004	Seminars in Vascular Medicine	2	Description of a model
2736	Genetic tests may have additional predictive power over and above the accepted risk factors in patients with severe hypercholesterolemia	Descamps OS;	2005	Louvain Medical	2	Not RCT
2002	Coronary artery disease in heterozygous familial hypercholesterolemia patients with the same LDL receptor gene mutation	Ferrieres J; Lambert J; Lussier-Cacan S; Davignon J;	1995	Circulation	2	DNA testing not done in all participants
1762	LDL receptor mutations and ApoB mutations are not risk factors for ischemic cerebrovascular disease of the young, but lipids and lipoproteins are	Frikke-Schmidt R; rlien-Soborg P; Thorsen S; Jensen HK; Vorstrup S;	1999	European Journal of Neurology	2	No FH patients
1741	Ethical issues in molecular screening for heterozygous familial hypercholesterolemia, the complexity of dealing with genetic susceptibility to coronary artery disease	Gaudet D; Gagne C; Perron P; Couture P; Tonstad S;	1999	Community Genetics	2	Does not answer the question asked

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
393	Contribution of receptor negative versus receptor defective mutations in the LDL-receptor gene to angiographically assessed coronary artery disease among young (25-49 years) versus middle-aged (50-64 years) men	Gaudet D; Vohl MC; Couture P; Moorjani S; Tremblay G; Perron P; Gagne C; Despres JP;	1999	Atherosclerosis	2	Not all participants tested for mutations
5223	Relative contribution of low-density lipoprotein receptor and lipoprotein lipase gene mutations to angiographically assessed coronary artery disease among French Canadians	Gaudet D; Vohl MC; Julien P; Tremblay G; Perron P; Gagne C; Bergeron J; Moorjani S; Despres JP;	1998	American Journal of Cardiology	2	Within DNA positive group comparison
666	Genetic and environmental factors affecting the incidence of coronary artery disease in heterozygous familial hypercholesterolemia	Hill JS; Hayden MR; Frohlich J; Pritchard PH;	1991	Arteriosclerosis & Thrombosis	2	Patients not DNA tested
1273	Lipoprotein(a) is an independent risk factor for cardiovascular disease in heterozygous familial hypercholesterolemia	Holmes DT; Schick BA; Humphries KH; Frohlich J;	2005	Clinical Chemistry	2	Did not answer question
1611	Evaluation of coronary risk factors in patients with heterozygous familial hypercholesterolemia	Hopkins PN; Stephenson S; Wu LL; Riley WA; Xin Y; Hunt SC;	2001	American Journal of Cardiology	2	DNA testing not done in all participants
2428	Familial hypercholesterolaemia as an example of early diagnosis of coronary artery disease risk by DNA techniques	Humphries SE;	1986	British Heart Journal	2	This is an editorial

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
99	Mutational analysis in UK patients with a clinical diagnosis of familial hypercholesterolaemia, relationship with plasma lipid traits, heart disease risk and utility in relative tracing	Humphries SE; Cranston T; Allen M; Middleton PH; Fernandez MC; Senior V; Hawe E; Iversen A; Wray R; Crook MA; Wierzbicki AS;	2006	Journal of Molecular Medicine (Berlin Germany)	2	Does not answer question asked
82	Genetic determinants of cardiovascular disease risk in familial hypercholesterolemia	Jansen AC; Van AC; Tanck MW; Cheng S; Fontecha MR; Li J; Defesche JC; Kastelein JJ;	2005	Arteriosclerosis, Thrombosis & Vascular Biology	2	
5224	Effect of common methylenetetrahydrofolate reductase gene mutation on coronary artery disease in familial hypercholesterolemia	Kawashiri M; Kajinami K; Nohara A; Yagi K; Inazu A; Koizumi J; Mabuchi H;	2000	American Journal of Cardiology	2	Not a direct comparison of DNA positive and negative participants
368	Paraoxonase gene polymorphisms are associated with carotid arterial wall thickness in participants with familial hypercholesterolemia	Leus FR; Wittekoek ME; Prins J; Kastelein JJ; Voorbij HA;	2000	Atherosclerosis	2	Does not answer the question, not a direct comparison of DNA positive and negative participants
325	PON2 gene variants are associated with clinical manifestations of cardiovascular disease in familial hypercholesterolemia patients	Leus FR; Zwart M; Kastelein JJ; Voorbij HA;	2001	Atherosclerosis	2	Not a direct comparison of DNA positive and negative participants
198	Apolipoprotein E genotype is not associated with cardiovascular disease in heterozygous participants with familial hypercholesterolemia	Mozas P; Castillo S; Reyes G; Tejedor D; Civeira F; Garcia-Alvarez I; Puzo J; Cenarro A; Alonso R; Mata P; Pocovi M; Spanish g;	2003	American Heart Journal	2	Did not answer the question

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
3316	Prevalence and significance of cardiovascular risk factors in a large cohort of patients with familial hypercholesterolaemia	Nolting PRWD; Defesche JC; Buirma RJA; Hutten BA; Lansberg PJ; Kastelein JJP;	2003	Journal of Internal Medicine	2	Outcome measures were not those identified by GDG
1445	Importance of LDL/HDL cholesterol ratio as a predictor for coronary heart disease events in patients with heterozygous familial hypercholesterolaemia, a 15-year follow-up (1987-2002)	Panagiotakos DB; Pitsavos C; Skoumas J; Chrysohoou C; Toutouza M; Stefanadis CI; Toutouzas PK;	2002	Current Medical Research & Opinion	2	DNA testing not done in all participants
106	Coronary artery disease prevention in childhood, Results of management of children with familial hypercholesterolemia	Rose V; Cullen-Dean G; Regelink-Helden E; Kay-Soroka S;	1991	Annals of the New York Academy of Sciences	2	Does not answer question
1081	Coronary Risk-Factors and the Severity of Angiographic Coronary-Artery Disease in Members of High-Risk Pedigrees	Sharp SD; Williams RR; Hunt SC; Schumacher MC;	1992	American Heart Journal	2	DNA testing not done in all participants
1575	Genetic and metabolic factors predicting risk of cardiovascular disease in familial hypercholesterolemia. [Review] [125 refs]	Smilde TJ; van W; Wollersheim H; Kastelein JJ; Stalenhoef AF;	2001	Netherlands Journal of Medicine	2	Narrative review
1552	Influence of LDL-receptor mutation type on age at first cardiovascular event in patients with familial hypercholesterolaemia	Souverein OW; Defesche JC; Zwinderman AH; Kastelein JJ; Tanck MW;	2006	European Heart Journal	2	Does not answer the question
3318	Identification and treatment of individuals at high risk of coronary heart disease. [Review] [30 refs]	Stein EA;	2002	American Journal of Medicine	2	Narrative review

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
2575	Plasma high-density lipoproteins and ischemic heart disease, studies in a large kindred with familial hypercholesterolemia	Streja D; Steiner G; Kwiterovich POJ;	1978	Annals of Internal Medicine	2	DNA testing not done in all participants
1098	Risk of Fatal Coronary Heart-Disease in Familial Hypercholesterolemia	Thorogood M;	1991	British Medical Journal	2	DNA testing not done in all participants
1454	Family history and cardiovascular risk in familial hypercholesterolemia, data in more than 1000 children	Wiegman A; Rodenburg J; de J; Defesche JC; Bakker HD; Kastelein JJ; Sijbrands EJ;	2003	Circulation	2	Patients were not all DNA tested
5283	Efficacy and safety of cholesterol-lowering treatment, prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins	Baigent C; Keech A; Kearney PM; Blackwell L; Buck G; Pollicino C; Kirby A; Sourjina T; Peto R; Collins R; Simes R;	2005	Lancet	3	Used for background only
1550	Diagnosis and screening for familial hypercholesterolaemia, Finding the patients, finding the genes	Bhatnagar D;	2006	Annals of Clinical Biochemistry	3	Narrative review
2409	Variables affecting apolipoprotein B measurements in 3- to 5-day-old babies, a study of 4491 neonates	Blades BL; Dudman NP; Wilcken DE;	1987	Pediatric Research	3	Not relevant population
2376	Screening for familial hypercholesterolemia in 5000 neonates, a recall study	Blades BL; Dudman NP; Wilcken DE;	1988	Pediatric Research	3	Not relevant population
1369	Advanced method for the identification of patients with inherited hypercholesterolemia.	Defesche JC; Lansberg PJ; Umans-Eckenhausen MA; Kastelein JJ;	2004	Seminars in Vascular Medicine	3	Narrative review

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
5284	A comprehensive description of muscle symptoms associated with lipid-lowering drugs	Franc S; Dejager S; Bruckert E; Chauvenet M; Giral P; Turpin G;	2003	Cardiovascular Drugs and Therapy	3	Used for background information only
26	Implementation of cascade testing for the detection of familial hypercholesterolaemia	Hadfield SG; Humphries SE;	2005 Aug	Current Opinion in Lipidology	3	Narrative review
5287	Genetic screening by DNA technology, a systematic review of health economic evidence.	Rogowski W;	2006	International Journal of Technology Assessment in Health Care	3	See health economics review
5288	Systematic family screening for familial hypercholesterolemia in Iceland	Thorsson B; Sigurdsson G; Gudnason V;	2003	Arteriosclerosis, Thrombosis & Vascular Biology	3	Does not answer the question
181	Screening for familial hypercholesterolaemia in relatives	Tonstad S; Vollebaek LE; Ose L;	1995	Lancet	3	Narrative review
5380	Child-parent screening for familial hypercholesterolaemia, screening strategy based on a meta-analysis	Wald DS; Bestwick JP; Wald NJ;	2007	British Medical Journal	3	Does not answer our question- the FH guideline is not evaluating population screening
217	Prevention of familial cardiovascular disease by screening for family history and lipids in youths	Williams RR; Hunt SC; Barlow GK; Wu LL; Hopkins PN; Schumacher MC; Hasstedt SJ; Ware J; Chamberlain RM; Weinberg AD; et a;	1992	Clinical Chemistry	3	Does not answer the question
2116	Documented need for more effective diagnosis and treatment of familial hypercholesterolemia according to data from 502 heterozygotes in Utah	Williams RR; Schumacher MC; Barlow GK; Hunt SC; Ware JL; Pratt M; Latham BD;	1993	American Journal of Cardiology	3	Not RCT

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
5289	A World Wide Web site for low-density lipoprotein receptor gene mutations in familial hypercholesterolemia, sequence-based, tabular, and direct submission data handling	Wilson DJ; Gahan M; Haddad L; Heath K; Whittall RA; Williams RR; Humphries SE; Day IN;	1998	American Journal of Cardiology	3	Does not answer the question
5330	Familial hypercholesterolemia, ethical, practical and psychological problems from the perspective of patients	AgÕrd A; Bolmsj÷ IA; HermerÚn G; Wahlst÷m J;	2005	Patient Education and Counseling	6	Outcomes did not answer the question
62	Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia.	Civeira F; International P;	2004	Atherosclerosis	6	Method of review not provided
1138	Quality of life, anxiety and concerns among statin-treated children with familial hypercholesterolaemia and their parents	de Jongh S; Kerckhoffs MC; Grootenhuis MA; Bakker HD; Heymans HSA; Last BF;	2003	Acta Paediatrica	6	Does not answer the question
1741	Ethical issues in molecular screening for heterozygous familial hypercholesterolemia, the complexity of dealing with genetic susceptibility to coronary artery disease	Gaudet D; Gagne C; Perron P; Couture P; Tonstad S;	1999	Community Genetics	6	Narrative review
954	A genetic screening programme for familial hypercholesterolaemia in the RSA, Results and recommendations	Hitzeroth HW; Op TH;	1986	South African Medical Journal	6	Narrative review
1232	Disease knowledge and adherence to treatment in patients with familial hypercholesterolemia	Hollman G; Olsson AG; Ek AC;	2006	Journal of Cardiovascular Nursing	6	

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
369	Effects of a soy-protein beverage on plasma lipoproteins in children with familial hypercholesterolemia	Laurin D; Jacques H; Moorjani S; Steinke FH; GagnÚ C; Brun D; Lupien PJ;	1991	American Journal of Clinical Nutrition	6	In a systematic review on diet in children with FH
144	Getting insurance after genetic screening on familial hypercholesterolaemia, the need to educate both insurers and the public to increase adherence to national guidelines in the Netherlands	Marang-van de Mheen PJ; Van Maarle MC; Stouthard MEA;	2002	Journal of Epidemiology & Community Health	6	Not relevant population - Dutch study
568	Psychological impact of genetic testing for familial hypercholesterolemia within a previously aware population, A randomized controlled trial	Marteau T; Senior V; Humphries SE; Bobrow M; Cranston T; Crook MA; Day L; Fernandez M; Horne R; Iversen A; Jackson Z; Lynas J; Price H; Savine R; Sikorski J; Watson M; Weinman J; Wierzbicki AS; Wray R;	2004	American Journal of Medical Genetics	6	Does not answer the question
438	Familial hypercholesterolemia in children.	Rodenburg J; Vissers MN; Wiegman A; Trip MD; Bakker HD; Kastelein JJ;	2004	Current Opinion in Lipidology	6	Narrative review which included psychological considerations
527	Treatment of familial hypercholesterolaemia in children	Segall MM; Fosbrooke AS; Lloyd JK; Wolff OH;	1970	Lancet	6	Case series 1970
5342	Guidelines for the diagnosis and management of familial hypercholesterolaemia	Sullivan D;	2007	Heart Lung and Circulation	6	Methodology not explained

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
139	Stratification of risk in children with familial hypercholesterolemia with focus on psychosocial issues	Tonstad S;	2001	Nutrition Metabolism and Cardiovascular Diseases	6	Does not answer the question
263	Psychosocial function during treatment for familial hypercholesterolemia	Tonstad S; N°vik TS; Vandvik IH;	1996	Pediatrics	6	Outcomes did not answer the question
125	Long-term compliance with lipid-lowering medication after genetic screening for familial hypercholesterolemia	Umans-Eckenhausen-Marina AW; Defesche JC; van-Dam MJ; Kastelein-John JP;	2003	Archives of Internal Medicine	6	Does not answer the question
5361	Family communication regarding inherited high cholesterol, why and how do patients disclose genetic risk?	van den Nieuwenhoff HW; Mesters I; Gielen C; de Vries NK;	2007	Social Science and Medicine	6	Does not answer the question
32	The importance of written information packages in support of case- finding within families at risk for inherited high cholesterol	van den Nieuwenhoff HWP; Mesters I; Nellissen-Joyce JTM; Stalenhoef AF; de Vries NK;	2006	Journal of Genetic Counseling	6	Does not answer the question
1582	Prenatal diagnosis of familial hypercholesterolemia, importance of DNA analysis in the high-risk South African population	Vergotine J; Thiart R; Langenhoven E; Hillermann R; De J; Kotze MJ;	2001	Genetic Counseling	6	Does not answer the question
137	Baseline lipid values partly determine the response to high-dose simvastatin in patients with familial hypercholesterolemia. The examination of probands and relatives in Statin studies with familial hypercholesterolemia (ExPRESS FH)	de Sauvage Nolting PR; Buirma RJ; Hutten BA; Kastelein JJ; Dutch ExPRESS investigators Group;	2002	Atherosclerosis	7	Not RCT

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
1068	Efficacy and Safety of Once-Daily Vs Twice-Daily Dosing with Fluvastatin, A Synthetic Reductase Inhibitor, in Primary Hypercholesterolemia	Insull W; Black D; DuJovne C; Hosking JD; Hunninghake D; Keilson L; Knopp R; McKenney J; Stein E; Troendle AJ; Wright JT;	1994	Archives of Internal Medicine	7	Does not answer question - not high dose low dose but rather studies dosing schedules
1534	Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study)	Jones P; Kafonek S; Laurora I; Hunninghake D;	1998	American Journal of Cardiology	7	Not FH population
395	Ten-year follow-up of familial hypercholesterolemia patients after intensive cholesterol-lowering therapy	Masaki N; Tatami R; Kumamoto T; Izawa A; Shimada Y; Takamatsu T; Katsushika S; Ishise S; Maruyama Y; Yoshimoto N;	2005	International Heart Journal	7	This is a duplicate report of the study in question
1284	Comparative Pharmacokinetics and Pharmacodynamics of Pravastatin and Lovastatin	Pan HY; Devault AR; Wangiverson D; Ivashkiv E; Swanson BN; Sugerman AA;	1990	Journal of Clinical Pharmacology	7	Primary outcome not LDL level
748	High dose atorvastatin induces regression of carotid atherosclerosis in patients with familial hypercholesterolaemia (FH), The atorvastatin versus simvastatin on atherosclerosis progression (ASAP) study	Smilde TJ; Trip MD; Wissen S; Wollersheim H; Kastelein JJP; Stalenhoef AFH;	2000	Circulation	7	Abstract only
1432	Statins, Within-group comparisons, statin escape and combination therapy	Tikkanen MJ;	1996	Current Opinion in Lipidology	7	Narrative review

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
120	Effect of atorvastatin (80 mg) and simvastatin (40 mg) on plasma fibrinogen levels and on carotid intima media thickness in patients with familial hypercholesterolemia	Trip MD; van W; Smilde TJ; Hutten BA; Stalenhoef AF; Kastelein JJ;	2003	American Journal of Cardiology	7	Not LDL outcome
1448	High dose of simvastatin normalizes postprandial remnant-like particle response in patients with heterozygous familial hypercholesterolemia	Twickler TB; linga-Thie GM; de Valk HW; Schreuder PCNJ; Jansen H; Cabezas MC; Erkelens DW;	2000	Arteriosclerosis, Thrombosis & Vascular Biology	7	Not RCT
807	Pravastatin and lovastatin similarly reduce serum cholesterol and its precursor levels in familial hypercholesterolaemia	Vanhanen H; Miettinen TA;	1992	European Journal of Clinical Pharmacology	7	Not RCT
235	Atorvastatin compared with simvastatin-based therapies in the management of severe familial hyperlipidaemias	Wierzbicki AS; Lumb PJ; Semra Y; Chik G; Christ ER; Crook MA;	1999	Quarterly Journal of Medicine	7	Not RCT
241	High-dose atorvastatin therapy in severe heterozygous familial hypercholesterolaemia	Wierzbicki AS; Lumb PJ; Semra YK; Crook MA;	1998	Quarterly Journal of Medicine	7	Not RCT
637	Statin use benefits children		2004	Clinical Advisor	8	Narrative review
436	Rosuvastatin. Opt for statins with evidence of efficacy on clinical outcome		2004	Prescrire International	8	Narrative review
593	Ezetimibe, new preparation. A cholesterol-lowering drug with no clinical advantage		2004	Prescrire International	8	To be deferred pending ezetimibe TA
340	Bile acid sequestrants.	Ast M; Frishman WH;	1990	Journal of Clinical Pharmacology	8	Narrative review

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
685	Relationship between LDL-C and non-HDL-C levels and clinical outcome in the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study	Athyros VG; Mikhailidis DP; Papageorgiou AA; Symeonidis AN; Daskalopoulou SS; Kakafika AI; Pehlivanidis AN; Bouloukos VI; Langer A;	2004	Current Medical Research & Opinion	8	Not FH population
847	Effect of atorvastatin on high density lipoprotein cholesterol and its relationship with coronary events, a subgroup analysis of the GREek Atorvastatin and Coronary heart-disease Evaluation (GREACE) Study	Athyros VG; Mikhailidis DP; Papageorgiou AA; Symeonidis AN; Mercouris BR; Pehlivanidis AN; Bouloukos VI; Elisaf M;	2004	Current Medical Research and Opinion	8	Not FH patients
397	One-year atorvastatin treatment in hypercholesterolemic patients with or without carotid artery disease	Avellone G; Di Garbo V; Abruzzese G; Campisi D; De Simone R; Raneli G; Licata G;	2006	International Angiology	8	Not RCT
5379	A systematic review and meta-analysis of statin therapy in children with familial hypercholesterolemia	Avis HJ; Vissers MN; Stein EA; Wijburg FA; Trip MD; Kastelein JP; Hutten BA;	2007	Arteriosclerosis, Thrombosis & Vascular Biology	8	This study essentially repeats information in recently published systematic review in the UK by Arambepola et al, 2007
290	Efficacy and safety of fluvastatin, a new HMG CoA reductase inhibitor, in elderly hypercholesterolaemic women	Baggio G; De Candia O; Forte PL; Mello F; Andriolli A; Donazzan S; Valerio G; Milani M; Crepaldi G;	1994	Drugs	8	Not RCT

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
5283	Efficacy and safety of cholesterol-lowering treatment, prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins	Baigent C; Keech A; Kearney PM; Blackwell L; Buck G; Pollicino C; Kirby A; Sourjina T; Peto R; Collins R; Simes R;	2005	Lancet	8	Used for background only
711	Early statin therapy induces complete normalization of endothelial dysfunction in children with familial hypercholesterolemia [abstract]	Bakker HD; de JS; Lilien MR; Stroes ESG; Kastelein JJP;	2002	Journal of Inherited Metabolic Disease	8	Abstract only
135	Familial hypercholesterolaemia, optimum treatment strategies.	Ballantyne CM;	2002	International Journal of Clinical Practice Supplement	8	Narrative review
511	Ezetimibe, Efficacy and safety in clinical trials	Ballantyne CM;	2002	European Heart Journal Supplements	8	Not our population of homozygous or children
858	Apolipoprotein E genotypes and response of plasma lipids and progression-regression of coronary atherosclerosis to lipid-lowering drug therapy	Ballantyne CM; Herd JA; Stein EA; Ferlic LL; Dunn JK; Gotto AM; Marian AJ;	2000	Journal of the American College of Cardiology	8	Not FH patients
97	Pharmacotherapy for dyslipidaemia--current therapies and future agents.	Bays H; Stein EA;	2003	Expert Opinion on Pharmacotherapy	8	Narrative
3320	Long-term treatment of severe familial hypercholesterolemia in children, effect of sitosterol and bezafibrate	Becker M; Staab D; Von B;	1992	Pediatrics	8	Not RCT
45	Comparative efficacy and safety of ciprofibrate and sustained-release bezafibrate in patients with type II hyperlipidaemia	Betteridge DJ; O'Bryan-Tear CG;	1996	Postgraduate Medical Journal	8	No control in this parallel group study

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
382	National Heart, Lung, and Blood Institute type II Coronary Intervention Study, design, methods, and baseline characteristics	Brensike JF; Kelsey SF; Passamani ER; Fisher MR; Richardson JM; Loh IK; Stone NJ; Aldrich RF; Battaglini JW; Moriarty DJ; Myrianthopoulos MB; Detre KM; Epstein SE; Levy RI;	1982	Controlled Clinical Trials	8	Protocol only
1523	Long term treatment of familial hypercholesterolemia with Colestipol, a new anionic exchange resin	Briani G; Fellin R; Balestrieri P; Baggio G; Baiocchi MR; Crepaldi G;	1975	Giornale Italiano di Cardiologia	8	Not RCT
5311	Expert commentary, the safety of fibrates in lipid-lowering therapy	Brown WV;	2007	American Journal of Cardiology	8	Commentary
1524	Homozygous familial hypercholesterolemia, novel therapy with ezetimibe	Bruckert E; Gagne C; Gauder D; Sager P; Ponsonnet D; Lipka L; LeBeaut A; Suresh R; Abreu P; Veltri E;	2002	Atherosclerosis	8	Abstract only
136	Rosuvastatin.	Carswell CI; Plosker GL; Jarvis B;	1986	Drugs	8	Narrative review
877	Rosuvastatin in the management of hyperlipidemia.	Cheng JW;	2004	Clinical Therapeutics	8	Narrative - not systematic review
36	Familial hypercholesterolemia and response to statin therapy according to LDLR genetic background.	Choumerianou DM; Dedoussis GV;	2005	Clinical Chemistry & Laboratory Medicine	8	Narrative
34	Efficacy and safety of lovastatin therapy in adolescent girls with heterozygous familial hypercholesterolemia	Clauss SB; Holmes KW; Hopkins P; Stein E; Cho M; Tate A; Johnson-Levonas AO; Kwiterovich PO;	2005	Pediatrics	8	Included in Simon Broome SR

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
1525	Ezetimibe for primary hypercholesterolemia	Colantonio LD; Cermignani EC; Ciapponi A;	2006		8	Protocol only
3321	Niacin Treatment of Hypercholesterolemia in Children	Colletti RB; Neufeld EJ; Roff NK; Mcauliffe TL; Baker AL; Newburger JW;	1993	Pediatrics	8	Not RCT
437	Familial combined hyperlipidemia in children, clinical expression, metabolic defects, and management.	Cortner JA; Coates PM; Liacouras CA; Jarvik GP;	1993	Journal of Pediatrics	8	Not relevant population
218	Association of specific LDL receptor gene mutations with differential plasma lipoprotein response to simvastatin in young French Canadians with heterozygous familial hypercholesterolemia	Couture P; Brun LD; Szots F; Lelievre M; Gaudet D; Despres JP; Simard J; Lupien PJ; Gagne C;	1998	Arteriosclerosis, Thrombosis & Vascular Biology	8	Did not answer the question. Included in Simon Broome SR
3322	Loss of dental enamel in a patient taking cholestyramine	Curtis DM; Driscoll DJ; Goldman DH; Weidman WH;	1991	Mayo Clinic Proceedings	8	Not RCT
133	Combination treatment with cholestyramine and bezafibrate for heterozygous familial hypercholesterolaemia	Curtis LD; Dickson AC; Ling KL; Betteridge J;	1988	British Medical Journal	8	No control in parallel group study using six treatment sequences with three patients in each sequence.
743	Effect of simvastatin on remnant lipoproteins in heterozygous familial hypercholesterolaemia	Dane-Stewart CA; Watts GF; Mamo JCL; Redgrave TG; Barrett PHR; Dimmitt S;	2000	Atherosclerosis Supplements	8	Abstract only
13	Ezetimibe.	Darkes MJ; Poole RM; Goa KL;	2003	American Journal of Cardiovascular Drugs	8	Narrative review
5312	Safety considerations with fibrate therapy	Davidson MH; Armani A; McKenney JM; Jacobson TA;	2007	American Journal of Cardiology	8	Used for background information only

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
455	European guidelines on cardiovascular disease prevention in clinical practice, Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice	De Backer G; Ambrosioni E; Borch-Johnsen K; Brotons C; Cifkova R; Dallongeville J; Ebrahim S; Faergeman O; Graham I; Mancia G; Cats VM; Orth-Gomer K; Perk J; Pyorala K; Rodicio JL; Sans S; Sansoy V; Sechtem U; Silber S; Thomsen T; Wood D;	2003	European Journal of Cardiovascular Prevention & Rehabilitation	8	General guideline/narrative
300	The effect of simvastatin treatment on the low-density lipoprotein subfraction profile and composition in familial hypercholesterolaemia	de Graaf J; Demacker PN; Stalenhoef AF;	1993	Netherlands Journal of Medicine	8	Not RCT
943	Early statin therapy restores endothelial function in children with familial hypercholesterolemia	de Jongh S; Lilien MR; Roodt JO; Stroes ESG; Bakker HD; Kastelein JJP;	2002	Journal of the American College of Cardiology	8	Included in Simon Broome SR
649	Efficacy and safety of statin therapy in children with familial hypercholesterolemia, a randomized, double-blind, placebo-controlled trial with simvastatin	de Jongh S; Ose L; Szamosi T; Gagne C; Lambert M; Scott R; Perron P; Dobbelaere D; Saborio M; Tuohy MB; Stepanavage M; Sapre A; Gumbiner B; Mercuri M; van-Trotsenburg ASP; Bakker HD; Kastelein JJP;	2002	Circulation	8	Included in Simon Broome SR

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
142	Two-year efficacy and safety of simvastatin 80 mg in familial hypercholesterolemia (the Examination of Probands and Relatives in Statin Studies With Familial Hypercholesterolemia [ExPRESS FH])	de Sauvage Nolting PR; Buirma RJ; Hutten BA; Kastelein JJ; Dutch ExPRESS Investigator Group;	2002	American Journal of Cardiology	8	Not RCT
499	The effect of low-dose simvastatin in children with familial hypercholesterolaemia, A 1-year observation	Dirisamer A; Hachemian N; Bucek RA; Wolf F; Reiter M; Widhalm K;	2003	European Journal of Pediatrics	8	Not RCT. Included in Simon Broome SR
962	Changes in Serum Lipoprotein(A) in Hyperlipidemic Participants Undergoing Long-Term Treatment with Lipid-Lowering Drugs	Dobs AS; Prasad M; Goldberg A; Guccione M; Hoover DR;	1995	Cardiovascular Drugs and Therapy	8	Not specified outcome measure
6	Statins in hypercholesterolaemia, a dose-specific meta-analysis of lipid changes in randomised, double blind trials	Edwards JE; Moore RA;	2003	BMC Family Practice	8	Not FH population
3323	A study of the dose-effect relationship of cholestyramine in children with familial hypercholesterolemia	Farah JR; Kwiterovich PO; Neill CA;	1977	Advances in Experimental Medicine & Biology	8	Not a long term study
417	Rosuvastatin, A risk-benefit assessment for intensive lipid lowering	Ferdinand KC;	2005	Expert Opinion on Pharmacotherapy	8	Not RCT
123	The effect of cholestyramine on serum lipids and platelet aggregation of hypercholesterolemic children (type II A) while on high linoleic acid diet	Fernandes J; jkhuis-Stoffelsma R; Grose WF;	1977	Acta Paediatrica Scandinavica	8	Not a long term study

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
5284	A comprehensive description of muscle symptoms associated with lipid-lowering drugs	Franc S; Dejager S; Bruckert E; Chauvenet M; Giral P; Turpin G;	2003	Cardiovascular Drugs and Therapy	8	Used for background only
288	Pravastatin effectively lowers LDL cholesterol in familial combined hyperlipidemia without changing LDL subclass pattern	Franceschini G; Cassinotti M; Vecchio G; Gianfranceschi G; Pazzucconi F; Murakami T; Sirtori M; D'Acquarica AL; Sirtori CR;	1994	Arteriosclerosis & Thrombosis	8	Not RCT
998	The Affinity of Low-Density Lipoproteins and of Very-Low-Density Lipoprotein Remnants for the Low-Density-Lipoprotein Receptor in Homozygous Familial Defective Apolipoprotein B-100	Gallagher JJ; Myant NB;	1995	Atherosclerosis	8	Does not answer question
1009	Effect of ezetimibe on low-density lipoprotein subtype distribution, results of a placebo-controlled, double-blind trial in patients treated by regular low-density lipoprotein apheresis and statins	Geiss HC; Otto C; Parhofer KG;	2006	Metabolism-Clinical and Experimental	8	Used for background only
3324	Therapy of familial and acquired hyperlipoproteinemia in children and adolescents	Glueck CJ;	1983	Preventive Medicine	8	Narrative review
709	Safety and efficacy of long-term diet and diet plus bile acid-binding resin cholesterol-lowering therapy in 73 children heterozygous for familial hypercholesterolemia	Glueck CJ; Mellies MJ; Dine M; et a;	1986	Pediatrics	8	This is a case series of 33 children with FH who were treated with diet and resins and compared to children treated with resins only and also to normal children. Individual data is presented.

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
66	Therapy of familial hypercholesterolemia in childhood, diet and cholestyramine resin for 24 to 36 months	Glueck CJ; Tsang RC; Fallat RW; Mellies M;	1977	Pediatrics	8	Not RCT
1014	Atorvastatin lowers lipoprotein(a) but not apolipoprotein(a) fragment levels in hypercholesterolemic participants at high cardiovascular risk	Gonbert S; Malinsky S; Sposito AC; Laouenan H; Doucet C; Chapman MJ; Thillet J;	2002	Atherosclerosis	8	No control group
667	Efficacy and safety of statin therapy in children with familial hypercholesterolemia, a randomized controlled trial	Gotto AM;	2005	The Journal of Pediatrics	8	Comment only
3325	Clinical management of children and young adults with heterozygous familial hypercholesterolaemia in the UK	Greene O; Durrington P;	2004	Journal of the Royal Society of Medicine	8	Does not answer the question
143	Dose-dependent action of atorvastatin in type IIB hyperlipidemia, preferential and progressive reduction of atherogenic apoB-containing lipoprotein subclasses (VLDL-2, IDL, small dense LDL) and stimulation of cellular cholesterol efflux	Guerin M; Egger P; Soudant C; Le G; van T; Dupuis R; Chapman MJ;	2002	Atherosclerosis	8	Not FH population
338	The effects of simvastatin on plasma lipoproteins and cholesterol homeostasis in patients with heterozygous familial hypercholesterolaemia	Hagemenas FC; Pappu AS; Illingworth DR;	1990	European Journal of Clinical Investigation	8	Not RCT

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
1041	Pharmacokinetics and response to pravastatin in paediatric patients with familial hypercholesterolaemia and in paediatric cardiac transplant recipients in relation to polymorphisms of the SLCO1B1 and ABCB1 genes	Hedman M; Antikainen M; Holmberg C; Neuvonen M; Eichelbaum M; Kivisto KT; Neuvonen PJ; Niemi M;	2006	British Journal of Clinical Pharmacology	8	Case series, not GDG outcome measures
433	Efficacy and safety of pravastatin in children and adolescents with heterozygous familial hypercholesterolemia, A prospective clinical follow-up study	Hedman M; Matikainen T; Fohr A; Lappi M; Piippo S; Nuutinen M; Antikainen M;	2005	Journal of Clinical Endocrinology & Metabolism	8	Case series, not RCT.
95	Lipid and lipoprotein profiles in children with familial hypercholesterolaemia, Effects of therapy	Hennermann JB; Herwig J; Marz W; Asskali F; Bohles HJ;	1998	European Journal of Pediatrics	8	Not a long term study
210	Effects of atorvastatin on serum lipids of patients with familial hypercholesterolaemia	Hoogerbrugge N;	1998	Journal of Internal Medicine	8	Not RCT
39	Comparative-Evaluation of the Safety and Efficacy of Hmg-Coa Reductase Inhibitor Monotherapy in the Treatment of Primary Hypercholesterolemia	Hsu I; Spinler SA; Johnson NE;	1995	Annals of Pharmacotherapy	8	Narrative report
1060	Effects of One-Year of Treatment with Pravastatin, An Hmg-Coa Reductase Inhibitor, on Lipoprotein-A	Hunninghake DB; Stein EA; Mellies MJ;	1993	Journal of Clinical Pharmacology	8	Not FH population
304	How effective is drug therapy in heterozygous familial hypercholesterolemia?.	Illingworth DR;	1993	American Journal of Cardiology	8	Narrative only

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
323	Hypocholesterolaemic effects of lovastatin in familial defective apolipoprotein B-100.	Illingworth DR; Vakar F; Mahley RW; Weisgraber KH;	1992	Lancet	8	Not RCT
96	Pharmacology and therapeutics of ezetimibe (SCH 58235), a cholesterol-absorption inhibitor.	Jeu L; Cheng JW;	2003	Clinical Therapeutics	8	Not our population of homozygous or children
5	Effects of statin therapy on the progression of carotid atherosclerosis, a systematic review and meta-analysis	Kang S; Wu Y; Li X;	2004	Atherosclerosis	8	Does not answer question
1101	Efficacy, Safety, and Tolerability of Pravastatin for the Long-Term Treatment of Patients with Diverse Types of Hyperlipidemia - A Multicenter Prospective-Study	Katoh K; Mizuno K; Niimura S; Fukuchi S;	1993	Current Therapeutic Research-Clinical and Experimental	8	Not FH patients
1104	3-Year Follow-Up of the Oxford-Cholesterol-Study - Assessment of the Efficacy and Safety of Simvastatin in Preparation for A Large Mortality Study	Keech A; Collins R; Macmahon S; Armitage J; Lawson A; Wallendszus K; Fatemian M; Kearney E; Lyon V; Mindell J; Mount J; Painter R; Parish S; Slavin B; Sleight P; Youngman L; Peto R;	1994	European Heart Journal	8	Not FH population
598	A 4-year trial of simvastatin in the treatment of patients with heterozygous familial hypercholesterolemia	Kitatani M; Koizumi J; Inazu A; Kajinami K; Mabuchi H;	1996	Current Therapeutic Research, Clinical & Experimental	8	Not RCT
250	Short-term efficacy and safety of pravastatin in 72 children with familial hypercholesterolemia.[erratum appears in Pediatr Res 1996 Dec, 40(6):866]	Knipscheer HC; Boelen CC; Kastelein JJ; van D; Groenemeijer BE; van d; Buller HR; Bakker HD;	1996	Pediatric Research	8	Included in Simon Broome SR

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
5384	Evaluation of the efficacy, safety, and tolerability of ezetimibe in primary hypercholesterolaemia, a pooled analysis from two controlled phase III clinical studies	Knopp RH; Dujovne CA; Le BA; Lipka LJ; Suresh R; Veltri EP;	2003	International Journal of Clinical Practice	8	Used for background only
1540	Multiple-dose safety and pharmacokinetics of ezetimibe in adolescent children	Kosoglou T; Kakkar T; Statkevich P; Anderson L; Pai S; Boutros T; Veltri EP; Affrime MB;	2001	Clinical Pharmacology & Therapeutics	8	Abstract only
253	Treatment of familial hypercholesterolemia in children and adolescents, effect of lovastatin. Canadian Lovastatin in Children Study Group	Lambert M; Lupien PJ; Gagne C; Levy E; Blaichman S; Langlois S; Hayden M; Rose V; Clarke JT; Wolfe BM; Clarson C; Parsons H; Stephure DK; Potvin D; Lambert J;	1996	Pediatrics	8	Included in Simon Broome SR
87	The management of familial hypercholesterolaemia in childhood	Lee PJ;	2002	Current Paediatrics	8	Narrative only
1155	Gender-Related Response to Fluvastatin in Patients with Heterozygous Familial Hypercholesterolemia	Leitersdorf E;	1994	Drugs	8	Gender response not a question
317	Beneficial effect of simvastatin in patients with drug resistant familial hypercholesterolaemia	Lewis-Barned NJ; Ball MJ;	1992	New Zealand Medical Journal	8	Case series - no control

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
76	Treatment of Primary Hypercholesterolemia with Simvastatin - New-Zealand Multicenter Evaluation	Lintott CJ; Scott RS; Sharpe DN; Nye ER; Charleson H; French JK; White HD; Reuben S; Maling TJB; Lewis GRB; Sutherland WHF; Robertson MC; Frampton C;	1991	Medical Journal of Australia	8	Not RCT
1203	Ezetimibe for management of hypercholesterolemia	Mauro VF; Tuckerman CE;	2003	Annals of Pharmacotherapy	8	Not our population of homozygous and children
148	A randomized crossover trial of combination pharmacologic therapy in children with familial hyperlipidemia	McCrindle BW; Helden E; Cullen-Dean G; Conner WT;	2002	Pediatric Research	8	Included in Simon Broome SR
116	Acceptability and compliance with two forms of cholestyramine in the treatment of hypercholesterolemia in children, a randomized, crossover trial	McCrindle BW; O'Neill MB; Cullen-Dean G; Helden E;	1997	The Journal of Pediatrics	8	Does not answer the question
107	Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia, a multicenter, randomized, placebo-controlled trial	McCrindle BW; Ose L; Marais AD;	2003	Journal of Pediatrics	8	Included in Simon Broome SR
2	The use of ezetimibe in achieving low density lipoprotein lowering goals in clinical practice, position statement of a United Kingdom consensus panel	Mikhailidis DP; Wierzbicki AS; Daskalopoulou SS; Al-Saady N; Griffiths H; Hamilton G; Monkman D; Patel V; Pittard J; Schachter M;	2005	Current Medical Research and Opinion	8	Not our population - children and homozygous

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
114	A comparative study of colestipol and colestyramine in children and adolescents with familial hypercholesterolaemia	Mordasini R; Twelsick F; Oster P; Schellenberg B; Raetzer H; Heuck CC; Schlierf G;	1978	Monatsschrift fur Kinderheilkunde	8	Non English language study
176	Abnormal low density lipoproteins in children with familial hypercholesterolemia--effect of polyanion exchange resins	Mordasini R; Twelsiek F; Oster P; Schellenberg B; Raetzer H; Heuck CC; Schlierf G;	1978	Klinische Wochenschrift	8	This study is not randomised, blinded and there is no allocation concealment reported. The results described in the text do not correlate with the tables included.
65	Current management of severe homozygous hypercholesterolaemias.	Naoumova RP; Thompson GR; Soutar AK;	2004	Current Opinion in Lipidology	8	Narrative only
606	Long-term treatment with simvastatin in patients with familial combined hyperlipidemia	Napoli C; Lepore S; Condorelli M; Chiariello M;	1995	Current Therapeutic Research, Clinical & Experimental	8	Not FH population
638	Effect of statin treatment for familial hypercholesterolaemia on life assurance, results of consecutive surveys in 1990 and 2002	Neil HAW; Hammond T; Mant D; Humphries SE;	2004	British Medical Journal	8	Not RCT
145	Long-term treatment with pitavastatin (NK-104), a new HMG-CoA reductase inhibitor, of patients with heterozygous familial hypercholesterolemia	Noji Y; Higashikata T; Inazu A; Nohara A; Ueda K; Miyamoto S; Kajinami K; Takegoshi T; Koizumi J; Mabuchi H; Hokuriku NK;	2002	Atherosclerosis	8	Pitavastatin not available in UK
1513	Effect of rosuvastatin on low-density lipoprotein cholesterol in patients with hypercholesterolemia	Olsson AG; Pears J; McKellar J; Mizan J; Raza A;	2001	American Journal of Cardiology	8	Not FH population

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
171	Determinants of variable response to statin treatment in patients with refractory familial hypercholesterolemia	O'Neill FH; Patel DD; Knight BL; Neuwirth CK; Bourbon M; Soutar AK; Taylor GW; Thompson GR; Naoumova RP;	2001	Arteriosclerosis, Thrombosis & Vascular Biology	8	Not RCT
56	Diagnostic, clinical, and therapeutic aspects of familial hypercholesterolemia in children.	Ose L;	2004	Seminars in Vascular Medicine	8	Narrative review
267	Fluvastatin in severe hypercholesterolemia, analysis of a clinical trial database	Peters TK;	1995	American Journal of Cardiology	8	Source of studies included in review not provided
523	Efficacy and safety of atorvastatin 10 mg every other day in hypercholesterolemia	Piamsomboon C; Saguanwong S; Nasawadi C; Pongsiri K; Laothavorn P; Chatlaong B; Tanprasert P;	2002	Journal of the Medical Association of Thailand	8	Not RCT
1311	One Year Experience in the Treatment of Familial Hypercholesterolemia with Simvastatin	Quiney J; Watts GF; Kerrmuir M; Slavin B; Lewis B;	1992	Postgraduate Medical Journal	8	Not RCT
776	Treatment of patients with homozygous familial hypercholesterolemia with expanded doses of simvastatin [abstract]	Raal FJ; Pilcher GJ; Pieterse AC; Stein EA; Laskarzewski P; Illingworth DR; Melino MR; Mitchel YB;	1997	Atherosclerosis Supplements	8	Abstract only
438	Familial hypercholesterolemia in children.	Rodenburg J; Vissers MN; Wiegman A; Trip MD; Bakker HD; Kastelein JJ;	2004	Current Opinion in Lipidology	8	Narrative review

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
334	Therapeutic efficacy of the HMG-CoA-reductase inhibitor pravastatin in hyperlipoproteinaemia type II	Saxenhofer H; Weidmann P; Riesen WF; Beretta-Piccoli C; Fragiacomo C; Wunderlin R; Noseda G;	1990	European Journal of Clinical Pharmacology	8	Not FH population
165	'Low dose' colestipol in children, adolescents and young adults with familial hypercholesterolemia	Schlierf G; Mrozik K; Heuck CC; Middelhoff G; Oster P; Riesen W; Schellenberg B;	1982	Atherosclerosis	8	Poor study quality - not randomised or controlled, high dropout rate
19	A meta-analysis to evaluate the efficacy of statins in children with familial hypercholesterolemia	Shafiq N; Bhasin B; Pattanaik S; Pandhi P; Venkateshan SP; Singh M; Malhotra S;	2007	International Journal of Clinical Pharmacology and Therapeutics	8	An Indian study which repeats information in Arambepola et al, 2007
1374	Simvastatin in Severe Primary Hypercholesterolemia - Efficacy, Safety, and Tolerability in 595 Patients Over 18 Weeks	Simons LA; Abraham R; Beilin L; Masarei J; Beng C; Pannall P; Cain H; Bradfield R; Calvert GD; Cornish G; England J; Craig IH; Heller RF; Smith AJ; Hunt D; Janus ED; Best JD; Lloyd B; Hung J; Newnham H; Barter P; Simons LA; Sullivan D; Thomas DW; Tallis G; Wahlqvist M; Wilcken DE;	1993	Clinical Cardiology	8	Not RCT
187	The effect of cholesterol lowering on carotid and femoral artery wall stiffness and thickness in patients with familial hypercholesterolaemia	Smilde TJ; van d; Wollersheim H; van L; Kastelein JJ; Stalenhoef AF;	2000	European Journal of Clinical Investigation	8	Not LDL outcome

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
566	Diet only and diet plus simvastatin in the treatment of heterozygous familial hypercholesterolemia in childhood	Stefanutti C; Lucani G; Vivenzio A; Di G;	1999	Drugs Under Experimental & Clinical Research	8	Included in Simon Broome review
737	Rosuvastatin (20, 40 and 80 MG) reduces LDL-C, raises HDL-C and achieves treatment goals more effectively than atorvastatin (20, 40 and 80 mg) in patients with heterozygous familial hypercholesterolaemia	Stein E; Strutt KL; Miller E; Southworth H;	2001	Atherosclerosis Supplements	8	Abstract only
159	Statins in children. Why and when.	Stein EA;	2001	Nutrition Metabolism & Cardiovascular Diseases	8	Narrative review
206	Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia, a randomized controlled trial.[see comment]	Stein EA; Illingworth DR; Kwiterovich POJ; Liacouras CA; Siimes MA; Jacobson MS; Brewster TG; Hopkins P; Davidson M; Graham K; Arensman F; Knopp RH; DuJovne C; Williams CL; Isaacsohn JL; Jacobsen CA; Laskarzewski PM; Ames S; Gormley GJ;	1999	JAMA	8	Included in Simon Broome SR
128	More Western Hypercholesterolemic Patients Achieve Japan Atherosclerosis Society LDL-C Goals with Rosuvastatin Therapy Than with Atorvastatin, Pravastatin, or Simvastatin Therapy	Strutt K; Caplan R; Hutchison H; Dane A; Blasetto J;	2004	Circulation Journal	8	We did not review statin versus statin

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
237	Effect of dietary fish supplementation on lipoprotein levels in patients with hyperlipoproteinemia	Sucic M; Katica D; Kovacevic V;	1998	Collegium Antropologicum	8	Not FH population
414	Effects of rosuvastatin on endothelial function in patients with familial combined hyperlipidaemia (FCH)	Ter Avest E; Abbink EJ; Holewijn S; de Graaf J; Tack CJ; Stalenhoef AFH;	2005	Current Medical Research & Opinion	8	Not FH population
3329	A rational approach to treating hypercholesterolaemia in children - Weighing the risks and benefits	Tonstad S;	1997	Drug Safety	8	Narrative review
184	Role of lipid-lowering pharmacotherapy in children.	Tonstad S;	2000	Paediatric Drugs	8	Narrative
3328	Colestipol tablets in adolescents with familial hypercholesterolaemia	Tonstad S; Ose L;	1996	Acta Paediatrica	8	6 month follow up only- require long term follow up
78	Management of hyperlipidemia in the pediatric population	Tonstad S; Thompson GR;	2004	Current Treatment Options in Cardiovascular Medicine	8	Narrative review
111	Long term statin treatment reduces lipoprotein(a) concentrations in heterozygous familial hypercholesterolaemia	van Wissen S; Smilde TJ; Trip MD; de Boo T; Kastelein JJ; Stalenhoef AF;	2003	Heart	8	Not outcome specified
50	Long-term safety and efficacy of high-dose atorvastatin treatment in patients with familial hypercholesterolemia	van Wissen S; Smilde TJ; Trip MD; Stalenhoef AF; Kastelein JJ;	2005	American Journal of Cardiology	8	Not RCT
154	Influence of LDL receptor gene mutation and apo E polymorphism on lipoprotein response to simvastatin treatment among adolescents with heterozygous familial hypercholesterolemia	Vohl MC; Szots F; Lelievre M; Lupien PJ; Bergeron J; Gagne C; Couture P;	2002	Atherosclerosis	8	Not outcome identified by GDG

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
233	Drug therapy of severe hypercholesterolemia.	Weizel A; Richter WO;	1997	European Journal of Medical Research	8	Narrative review
3330	Use of cholestyramine in treatment of children with familial hypercholesterolaemia	West RJ; Lloyd JK;	1973	Archives of disease in childhood	8	Not RCT
1487	Arterial intima-media thickness in children heterozygous for familial hypercholesterolaemia	Wiegman A; de Groot E; Hutten BA; Rodenburg J; Gort J; Bakker HD; Sijbrands EJG; Kastelein JJP;	2004	Lancet	8	Not LDL outcome after treatment
1488	Efficacy and safety of statin therapy in children with familial hypercholesterolemia, a randomized controlled trial.	Wiegman A; Hutten BA; de G; Rodenburg J; Bakker HD; Buller HR; Sijbrands EJ; Kastelein JJ;	2004	JAMA	8	Included in Simon Broome SR
452	Effects of statin therapy in children with familial hypercholesterolemia	Wiegman A; Hutten BA; de G; Roumie CL;	2004	Journal of Clinical Outcomes Management	8	Narrative
48	Efficacy of ezetimibe in patients with statin-resistant and statin-intolerant familial hyperlipidaemias	Wierzbicki AS; Doherty E; Lumb PJ; Chik G; Crook MA;	2005	Current Medical Research & Opinion	8	Not our population - homozygous or children
5385	Comparison of therapy with simvastatin 80 mg and 120 mg in patients with familial hypercholesterolaemia	Wierzbicki AS; Lumb PJ; Chik G;	2001	International Journal of Clinical Practice	8	Not FH population
1496	Dose-response effects of atorvastatin and simvastatin on high-density lipoprotein cholesterol in hypercholesterolaemic patients, a review of five comparative studies	Wierzbicki AS; Mikhailidis DP;	2002	International Journal of Cardiology	8	Non FH patients

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
239	Atorvastatin in the treatment of primary hypercholesterolemia and mixed dyslipidemias. [Review] [99 refs]	Yee HS; Fong NT;	1998	Annals of Pharmacotherapy	8	Narrative, not systematic review
535	Atorvastatin versus four statin-fibrate combinations in patients with familial combined hyperlipidaemia	Athyros VG; Papageorgiou AA; Athyrou VV; Demitriadis DS; Pehlivanidis AN; Kontopoulos AG;	2002	Journal of Cardiovascular Risk	9	Not FH population
595	Pilot study of the effect of the simvastatin-ciprofibrate combination on myocardial infarction risk profile in patients with refractory familial combined hyperlipidaemia	Athyros VG; Papageorgiou AA; Basagiannis EC; Lafaras CT; Kontopoulos AG;	2006	Clinical Drug Investigation	9	Non RCT - no control
536	Atorvastatin plus pravastatin for the treatment of heterozygous familial hypercholesterolaemia - A pilot study	Athyros VG; Papageorgiou AA; Demitriadis DS; Kontopoulos AG;	2001	Current Medical Research & Opinion	9	Not RCT
733	Efficacy and tolerability of four statin-fibrate combinations during long-term (5 years) administration in patients with combined familial hyperlipidemia	Athyros VG; Papageorgiou AA; Demitriadis DS; Pehlivanidis AN; Doukelis PV; Karakasis TD; Kontopoulos AG;	2001	Atherosclerosis Supplements	9	Abstract only
616	Combined treatment with pravastatin and gemfibrozil in patients with refractory familial combined hyperlipidaemia, A clinical study	Athyros VG; Papageorgiou AA; Hagikonstantinou HJ; Papadopoulos GV; Zamboulis CX; Kontopoulos AG;	1994	Drug Investigation	9	Not FH population

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
580	Safety and efficacy of long-term statin-fibrate combinations in patients with refractory familial combined hyperlipidemia	Athyros VG; Papageorgiou AA; Hatzikonstandinou HA; Didangelos TP; Carina MV; Kranitsas DF; Kontopoulos AG;	1997	American Journal of Cardiology	9	Not FH population
252	Fish oil supplementation in patients with heterozygous familial hypercholesterolemia	Balestrieri GP; Maffi V; Sleiman I; Spandrio S; Di S; Salvi A; Scalvini T	1996	Recenti Progressi in Medicina	9	This is not a placebo controlled trial but compared fish oil and statins to olive oil and statins
861	Efficacy and safety of rosuvastatin alone and in combination with cholestyramine in patients with severe hypercholesterolemia, A randomized, open-label, multicenter trial	Ballantyne CM; Miller E; Chitra R;	2004	Clinical Therapeutics	9	Not FH population. This study included adults with severe hypercholesterolemia but excluded homozygous FH and familial dysbetalipoproteinemia. There is no specific inclusion diagnosis for heterozygous FH and the patient clinical characteristics indicate
865	A Multicenter Comparison of the Effects of Simvastatin and Fenofibrate Therapy in Severe Primary Hypercholesterolemia, with Particular Emphasis on Lipoproteins Defined by Their Apolipoprotein Composition	Bard JM; Parra HJ; Camare R; Luc G; Ziegler O; Dachet C; Bruckert E; Dousteblazy P; Drouin P; Jacotot B; Degennes JL; Keller U; Fruchart JC;	1992	Metabolism-Clinical and Experimental	9	Does not answer question
875	Effect of ezetimibe and/or simvastatin on coenzyme Q10 levels in plasma - A randomised trial	Berthold HK; Naini A; Di Mauro S; Hallikainen M; Gylling H; Krone W; Gouni-Berthold I;	2006	Drug Safety	9	Not our population of homozygous and children

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
605	Comparison of gemfibrozil versus simvastatin in familial combined hyperlipidemia and effects on apolipoprotein-B-containing lipoproteins, low- density lipoprotein subfraction profile, and low-density lipoprotein oxidizability	Bredie SJH; De B; Demacker PNM; Kastelein JJP; Stalenhoef AFH;	1995	American Journal of Cardiology	9	Not FH population
876	Effects of gemfibrozil or simvastatin on apolipoprotein-B-containing lipoproteins, apolipoprotein-CIII and lipoprotein(a) in familial combined hyperlipidaemia	Bredie SJH; Westerveld HT; Knipscheer HC; De B; Kastelein JJP; Stalenhoef AFH;	1996	Netherlands Journal of Medicine	9	Not FH population. Not primary outcome measure of LDL cholesterol.
256	Comparison of the efficacy of simvastatin and standard fibrate therapy in the treatment of primary hypercholesterolemia and combined hyperlipidemia	Bruckert E; De Gennes JL; Malbecq W; Baigts F;	1995	Clinical Cardiology	9	Not a question asked
597	Pravastatin, cholestyramine, and bezafibrate in patients with heterozygous familial hypercholesterolemia, The Spanish Multicenter Pravastatin Study	Carmena R; De Oya M; Gomez-Gerique J; Mata P; Serrano S; Franco M; Martinez-Triguero ML; varez-Sala L; Matesanz J; Rubio MJ; Gras X; Olivan J;	1996	Cardiovascular Risk Factors	9	Not randomised in follow up study
37	Lipid altering-efficacy of ezetimibe co-administered with simvastatin compared with rosuvastatin, a meta-analysis of pooled data from 14 clinical trials	Catapano A; Brady WE; King TR; Palmisano J;	2005	Current Medical Research & Opinion	9	Not our population of homozygous and children

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
1538	Treatment of familial hypercholesterolemia with ezetimibe/simvastatin in a child less than 10 years of age	Cathey V; Beck J; Bond A; Placket P;	2006	Journal of Pediatric Nursing	9	This is an abstract of a case study of one patient
5383	Efficacy and safety of ezetimibe coadministered with statins, randomised, placebo-controlled, blinded experience in 2382 patients with primary hypercholesterolemia	Davidson MH; Ballantyne CM; Kerzner B; Melani L; Sager PT; Lipka L; Strony J; Suresh R; Veltri E;	2004	International Journal of Clinical Practice	9	Used for background only
758	Effects of equal doses of pravastatin, simvastatin and atorvastatin in heterozygous patients with familial hypercholesterolemia	De Mattei S; Masturzo P; Fascetti P; Elicio N; Bertolini S;	1999	Atherosclerosis Supplements	9	Abstract only
956	Effects of bezafibrate and simvastatin on endothelial activation and lipid peroxidation in hypercholesterolemia, evidence of different vascular protection by different lipid-lowering treatments	Desideri G; Croce G; Tucci M; Passacquale G; Broccoletti S; Valeri L; Santucci A; Ferri C;	2003	Journal of Clinical Endocrinology and Metabolism	9	Not FH population
81	Comparison between lovastatin and cholestyramine in the treatment of moderate to severe primary hypercholesterolaemia	Ebeling T; Turtola H; Voutilainen E; Uusitupa M; Py÷rõlõ K; Reijonen T;	1992	Annals of Medicine	9	Not question asked
341	Efficacy and safety of simvastatin (alone or in association with cholestyramine). A 1-year study in 66 patients with type II hyperlipoproteinaemia	Emmerich J; Aubert I; Bauduceau B; Dachet C; Chanu B; Erlich D; Gautier D; Jacotot B; Rouffy J;	1990	European Heart Journal	9	Not an RCT
346	Plasma lipoprotein changes after treatment with pravastatin and gemfibrozil in patients with familial hypercholesterolemia	Franceschini G; Sirtori M; Vaccarino V; Gianfranceschi G; Chiesa G; Sirtori CR;	1989	Journal of Laboratory & Clinical Medicine	9	There is no control in this parallel group study. The study does not answer question 9.

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
1017	Treatment of Primary Hypercholesterolemia - Fluvastatin Versus Bezafibrate	Greten H; Beil FU; Schneider J; Weisweiler P; Armstrong VW; Keller C; Klor HU; Vonhodenberg E; Weidinger G; Eskotter H; Farber L; Assmann G;	1994	American Journal of Medicine	9	Not a question
215	Combination therapy with statins. [Review] [51 refs]	Gylling H; Miettinen TA;	2002	Current Opinion in Investigational Drugs	9	Narrative only
1539	Homozygous hypercholesterolaemia and ezetimibe, a case report	Hendriksz CJ; Norbury G; Tabrah S; Taylor A; Humphries SE;	2004	Acta Paediatrica	9	This is a single case study
75	Treatment of dyslipidemia in children and adolescents	Holmes KW; Kwiterovich J;	2005	Current Cardiology Reports	9	Narrative review
333	Influence of lovastatin plus gemfibrozil on plasma lipids and lipoproteins in patients with heterozygous familial hypercholesterolemia	Illingworth DR; Bacon S;	1989	Circulation	9	RCT
1070	Short-Term and Long-Term Effects of Lovastatin and Pravastatin Alone and in Combination with Cholestyramine on Serum-Lipids, Lipoproteins and Apolipoproteins in Primary Hypercholesterolemia	Jacob BG; Mohrle W; Richter WO; Schwandt P;	1992	European Journal of Clinical Pharmacology	9	Not RCT

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
1071	Long-Term Treatment (2 Years) with the Hmg Coa Reductase Inhibitors Lovastatin Or Pravastatin in Combination with Cholestyramine in Patients with Severe Primary Hypercholesterolemia	Jacob BG; Richter WO; Schwandt P;	1993	Journal of Cardiovascular Pharmacology	9	Not RCT
43	Low-Dose Combination Therapy with Colestipol and Simvastatin in Patients with Moderate to Severe Hypercholesterolemia	Johansson J;	1995	Nutrition Metabolism and Cardiovascular Diseases	9	Non FH population
46	Comparison of ezetimibe plus simvastatin versus simvastatin monotherapy on atherosclerosis progression in familial hypercholesterolemia. Design and rationale of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENH	Kastelein JJ; Sager PT; de G; Veltri E;	2005	American Heart Journal	9	Used for background only
1529	Efficacy of colestimide coadministered with atorvastatin in japanese patients with heterozygous familial hypercholesterolemia (FH)	Kawashiri MA; Higashikata T; Nohara A; Kobayashi J; Inazu A; Koizumi J; Mabuchi H;	2005	Circulation Journal	9	Not RCT
587	Effects of simvastatin and ciprofibrate alone and in combination on lipid profile, plasma fibrinogen and low density lipoprotein particle structure and distribution in patients with familial combined hyperlipidaemia and coronary artery disease	Kontopoulos AG; Athyros VG; Papageorgiou AA; Hatzikonstandinou HA; Mayroudi MC; Boudoulas H;	1996	Coronary Artery Disease	9	Not FH population

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
71	The Use of Pravastatin Alone and in Combination with Colestipol Or Probucol in the Treatment of Primary Hypercholesterolemia	Kostis JB; Wilson AC; Pan HY; Kuo PT; Tannenbaum AK;	1992	Current Therapeutic Research-Clinical and Experimental	9	Not RCT
265	Efficacy and safety of triple therapy (fluvastatin-bezafibrate-cholestyramine) for severe familial hypercholesterolemia	Leitersdorf E; Muratti EN; Eliav O; Peters TK;	1995	American Journal of Cardiology	9	Not RCT
1530	Effects of lovastatin alone and in combination with cholestyramine on serum lipids and apolipoproteins in heterozygotes for familial hypercholesterolemia	Leren TP; Hjermann I; Berg K; Leren P; Foss OP; Viksmoen L;	1988	Atherosclerosis	9	Not RCT
660	Long-term effect of lovastatin alone and in combination with cholestyramine on lipoprotein (a) level in familial hypercholesterolemic participants	Leren TP; Hjermann I; Foss OP; Leren P; Berg K;	1992	Clinical Investigator	9	Not RCT
659	Long term treatment with pravastatin, simvastatin and gemfibrozil in patients with primary hypercholesterolaemia, A controlled study	Muggeo M; Travia D; Querena M; Zenti MG; Bagnani M; Branzi P; Cigolini M;	1992	Drug Investigation	9	Does not answer the question
291	Fluvastatin in familial hypercholesterolemia, a cohort analysis of the response to combination treatment	Muratti EN; Peters TK; Leitersdorf E;	1994	American Journal of Cardiology	9	Not RCT
190	Ezetimibe/Simvastatin, a review of its use in the management of hypercholesterolemia. [Review] [60 refs]	Murdoch D; Scott LJ;	2004	American Journal of Cardiovascular Drugs	9	Not our population of homozygous and children

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
1239	Effects of Simvastatin, Bezafibrate and Gemfibrozil on the Quantity and Composition of Plasma-Lipoproteins	Nakandakare E; Garcia RC; Rocha JC; Sperotto G; Oliveira HCF; Quintao ECR;	1990	Atherosclerosis	9	Does not answer question
584	Long-term treatment with pravastatin alone and in combination with gemfibrozil in familial type IIB hyperlipoproteinemia or combined hyperlipidemia	Napoli C; Lepore S; Chiariello P; Condorelli M; Chiariello M;	1997	Journal of Cardiovascular Pharmacology & Therapeutics	9	Not FH population
1248	Meeting national cholesterol education goals in clinical practice - A comparison of lovastatin and fluvastatin in primary prevention	Nash DT;	1996	American Journal of Cardiology	9	Not FH population
676	Comparison of raloxifene and atorvastatin effects on serum lipids composition of healthy post-menopausal women	Piperi C; Kalofoutis C; Lagogianni I; Troupis G; Kalofoutis A;	2004	Molecular & Cellular Biochemistry	9	Not FH patients
675	Beneficial effects of raloxifene and atorvastatin on serum lipids and HDL phospholipids levels of postmenopausal women	Piperi C; Kalofoutis C; Skenderi K; Economidou O; Kalofoutis A;	2004	Journal of Obstetrics and Gynaecology , the journal of the Institute of Obstetrics and Gynaecology	9	Not FH
1327	Comparative Effects of 2 Hmg-Coa Reductase Inhibitors (Lovastatin and Pravastatin) on Serum-Lipids and Lipoproteins	Richter WO; Jacob BG; Schwandt P;	1991	International Journal of Tissue Reactions-Experimental and Clinical Aspects	9	Not RCT
617	Effects of fish oil on serum lipids and lipoprotein(A) levels in heterozygous familial hypercholesterolemia	Salvi A; Di S; Sleiman I; Spandrio S; Balestrieri GP; Scalvini T;	1993	Current Therapeutic Research, Clinical & Experimental	9	Not RCT

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
83	Efficacy, safety and tolerability of lovastatin and bezafibrate retard in patients with hypercholesterolemia	Schumacher M; Eber B; Silberbauer K; Breier C; St³hlinger W; Schmidt P; Gaul G; Klein W;	1992	Acta medica Austriaca	9	Not question asked
721	Fluvastatin and fish oil are more effective on cardiovascular risk factors than fluvastatin alone	Singer P; sal	2002	Medizinische Welt	9	Non English article (German)
1381	Rationale, design and baseline characteristics of a clinical trial comparing the effects of robust vs conventional cholesterol lowering and intima media thickness in patients with familial hypercholesterolaemia	Smilde TJ; Trip MD; Wollersheim H; van Wissen S; Kastelein JJP; Stalenhoef AFH;	2000	Clinical Drug Investigation	9	Protocol only
1531	Low-Dose Combined Therapy with Fluvastatin and Cholestyramine in Hyperlipidemic Patients	Sprecher DL; Abrams J; Allen JW; Keane WF; Chrysant SG; Ginsberg H; Fischer JJ; Johnson BF; Theroux P; Jokubaitis L;	1994	Annals of Internal Medicine	9	Not FH population
1532	Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia, efficacy and safety of ezetimibe co-administered with atorvastatin	Stein E; Stender S; Mata P; Sager P; Ponsonnet D; Melani L; Lipka L; Suresh R; Maccubbin D; Veltri E;	2004	American Heart Journal	9	Not our population of homozygous and children
740	ZD4522 is superior to atorvastatin in the treatment of patients with heterozygous familial hypercholesterolemia [abstract]	Stein E; Strutt KL; Miller E;	2001	Atherosclerosis Supplements	9	Abstract only

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
1541	Treatment of dyslipidemia with lovastatin and ezetimibe in an adolescent with cholesterol ester storage disease	Tadiboyina VT; Liu DM; Miskie BA; Wang J; Hegele RA;	2005	Lipids in Health & Disease	9	This is a single case study
77	Familial hypercholesterolemia in a paediatric patient	Ullah M; Ahmad SA;	2005	Journal of the College of Physicians & Surgeons Pakistan	9	Case study
274	Comparison of lovastatin (20 mg) and nicotinic acid (1.2 g) with either drug alone for type II hyperlipoproteinemia	Vacek JL; Dittmeier G; Chiarelli T; White J; Bell HH;	1995	American Journal of Cardiology	9	No control in this parallel group study which utilized four treatment sequences.
723	Heterozygous familial hypercholesterolemia, coadministration of ezetimibe plus atorvastatin	Vermaak W; Pinto X; Ponsonnet D; Sager P; Lipka L; Suresh R; Veltri E;	2002	Atherosclerosis Supplements	9	Abstract only
1482	Simvastatin Plus Low-Dose Colestipol in the Treatment of Severe Familial Hypercholesterolemia	Weisweiler P;	1988	Current Therapeutic Research-Clinical and Experimental	9	No control group
351	Simvastatin and bezafibrate, effects on serum lipoproteins and lecithin, cholesterol acyltransferase activity in familial hypercholesterolaemia	Weisweiler P;	1988	European Journal of Clinical Pharmacology	9	Does not answer question
771	Fenofibrate-simvastatin therapy compared to simvastatin-resin therapy and atorvastatin for familial hypercholesterolaemia	Wierzbicki AS; Lumb PJ; Cheung J; Crook MA;	1997	Atherosclerosis Supplements	9	Abstract only
651	Treatment of severe, resistant familial combined hyperlipidemia with a bezafibrate-lovastatin combination	Yeshurun D; Abukarshin R; Elias N; Lanir A; Naschitz JE;	1993	Clinical Therapeutics	9	Not FH population

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
5231	Effectiveness of association of plasma exchange and cholestyramine in treatment of homozygous familial hypercholesterolaemia	Alfano G; Salera P; Rossi PL; et a;	1986	Acta Medica Romana	10	Case report
86	Impact of the characteristics of patients and their clinical management on outcomes in children with homozygous familial hypercholesterolemia	Al-Shaikh AM; Abdullah MH; Barclay A; Cullen-Dean G; McCrindle BW;	2002	Cardiology in the Young	10	Not the question
91	Low-density lipoprotein apheresis, clinical results with different methods	Bambauer R;	2002	Artificial Organs	10	Does not answer the question - comparison of different systems
5236	Is lipoprotein (a)-apheresis useful?	Bambauer R;	2005	Therapeutic Apheresis & Dialysis, Official Peer-Reviewed Journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy	10	Narrative review
5232	Low-density lipoprotein apheresis for prevention and regression of atherosclerosis, clinical results	Bambauer R; Olbricht CJ; Schoeppe E;	1997	Therapeutic Apheresis	10	Population not all FH, no absolute numbers reported, use of concomitant drugs unclear
5235	Low-density lipoprotein apheresis, an overview.	Bambauer R; Schiel R; Latza R;	2003	Therapeutic Apheresis & Dialysis, Official Peer-Reviewed Journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy	10	Narrative
5233	Apheresis technologies for prevention and regression of atherosclerosis, clinical results	Bambauer R; Schneidewind JM; Latza R;	1999	ASAIO Journal	10	Repeat of 1997 report

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
98	Atorvastatin improves blood rheology in patients with familial hypercholesterolemia (FH) on long-term LDL apheresis treatment	Banyai S; Banyai M; Falger J; Jansen M; Alt E; Derfler K; Koppensteiner R;	2001	Atherosclerosis	10	Does not answer the question
5237	Therapeutic efficiency of lipoprotein(a) reduction by low-density lipoprotein immunoapheresis	Banyai S; Streicher J; Strobl W; Gabriel H; Gottsauner-Wolf M; Rohac M; Weidinger F; Horl WH; Derfler K;	1998	Metabolism, Clinical & Experimental	10	16 patients
166	Pregnancy outcome in familial homozygous hypercholesterolemic females treated with long-term plasma exchange	Beigel Y; Bar J; Cohen M; Hod M;	1998	Acta Obstetricia et Gynecologica Scandinavica	10	2 FH patients - 5 pregnancies
398	Regression of atherosclerosis in patients with familial hypercholesterolaemia under LDL-apheresis	Borberg H; Gaczkowski A; Hombach V; Oette K; Stoffel W;	1988	Progress in Clinical & Biological Research	10	10 patients only
5239	Direct adsorption of low-density lipoprotein by DALI-LDL-apheresis, results of a prospective long-term multicenter follow-up covering 12,291 sessions	Bosch T; Gahr S; Belschner U; Schaefer C; Lennertz A; Rammo J; for t;	2006	Therapeutic Apheresis & Dialysis, Official Peer-Reviewed Journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy	10	FH sub population report not provided
5240	Plasma exchange versus an affinity column for cholesterol reduction	Burgstaler EA; Pineda AA;	1992	Journal of Clinical Apheresis	10	Case study

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
390	Selective and semiselective low-density lipoprotein apheresis in familial hypercholesterolemia	Busnach G; Cappelleri A; Vaccarino V; Franceschini G; Dal C; Perrino ML; Brando B; Sirtori C; Minetti L;	1988	Blood Purification	10	7 patients
365	Double-filtration plasmapheresis in heterozygous familial hypercholesterolemia, our experience over 25 treatments	Candrina R; Spandrio S; Di S; Scalvini T; Cotelli M; Tosoni M; Giustina G;	1988	Beitrage zur Infusionstherapie	10	6 patients - study of technique only
5264	Comparison between treatments of severe forms of familial hypercholesterolemia by total plasma exchange and selective removal of low density lipoproteins (LDLapheresis)].	Dairou F; Rottembourg J; De G; Assogba U; Bruckert E; Jacobs C; Truffert J;	1988	Presse Medicale	10	10 patients
538	Combined LDL-apheresis and statin treatment in homozygous and heterozygous familial hyperlipoproteinaemia	Derfler K; Goldammer A;	2001	Journal of Clinical & Basic Cardiology	10	14 patients
5241	One year experience with a low density lipoprotein apheresis system	Durst R; Rund D; Schurr D; Eliav O; Ben-Yehuda D; Shpizen S; Ben-Avi L; Schaap T; Pelz I; Leitersdorf E;	2002	Israel Medical Association Journal	10	13 patients only
5242	Long-term clinical experience with HELP-LDL-apheresis in combination with HMG-CoA-reductase inhibitors for maximum treatment of coronary heart disease associated with severe hypercholesterolemia	Eisenhauer T; Armstrong VW; Schuff-Werner P; Schutz E; Thiery J; Scheler F; Seidel D;	1989	ASAIO Transactions	10	10 patients

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
407	Long-term experience with the HELP system for treatment of severe familial hypercholesterolemia	Eisenhauer T; Schuff-Werner P; Armstrong VW; Talartschik J; Scheler F; Seidel D;	1987	ASAIO Transactions	10	10 patients
630	Lipoprotein particles in homozygous familial hypercholesterolemic patients treated with portacaval shunt and LDL apheresis	Gairin D; Monard F; Cachera C; Bard JM; Amouyel P; Duriez P; Tacquet A; Fruchart JC;	2003	Clinica Chimica Acta	10	2 patients
5243	Composition and immunoreactivity of serum low density lipoproteins (LDL) before and after LDL-apheresis on dextran sulfate-cellulose columns	Gandjini H; Gambert P; Athias A; Mousson C; Rifle G; Lallemant C;	1994	Transfusion Science	10	4 patients only
38	In vivo metabolism of LDL subfractions in patients with heterozygous FH on statin therapy, rebound analysis of LDL subfractions after LDL apheresis	Geiss HC; Bremer S; Barrett PH; Otto C; Parhofer KG;	2004	Journal of Lipid Research	10	Does not answer the question
1009	Effect of ezetimibe on low-density lipoprotein subtype distribution, results of a placebo-controlled, double-blind trial in patients treated by regular low-density lipoprotein apheresis and statins	Geiss HC; Otto C; Parhofer KG;	2006	Metabolism-Clinical and Experimental	10	Not our population of homozygous and children
784	Atorvastatin compared with simvastatin in patients with severe LDL hypercholesterolaemia treated by regular LDL apheresis	Geiss HC; Parhofer KG; Schwandt P;	1999	Journal of Internal Medicine	10	Does not answer the question
80	Atorvastatin in low-density lipoprotein apheresis-treated patients with homozygous and heterozygous familial hypercholesterolemia	Goldammer A; Wiltschnig S; Heinz G; Jansen M; Stulnig T; Horl WH; Derfler K;	2002	Metabolism, Clinical & Experimental	10	14 patients

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
801	Effect of different LDL-apheresis methods on parameters involved in atherosclerosis	Hershcovici T; Schechner V; Orlin J; Harell D; Beigel Y;	2004	Journal of Clinical Apheresis	10	6 patients only, does not answer the question
61	Long-term effect of low-density lipoprotein apheresis in patients with heterozygous familial hypercholesterolemia.	Higashikata T; Mabuchi H;	2003	Therapeutic Apheresis & Dialysis, Official Peer-Reviewed Journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy	10	Narrative review
70	Effects of combined low-density lipoprotein apheresis and aggressive statin therapy on coronary calcified plaque as measured by computed tomography	Hoffmann U; Derfler K; Haas M; Stadler A; Brady TJ; Kostner K;	2003	American Journal of Cardiology	10	8 patients only
423	Comparison of selectivity of LDL removal by double filtration and dextran-sulfate cellulose column plasmapheresis	Homma Y; Mikami Y; Tamachi H; Nakaya N; Nakamura H; Araki G; Goto Y;	1986	Atherosclerosis	10	4 patients only
5244	Clinical outcome of patients with familial hypercholesterolemia and coronary artery disease undergoing partial ileal bypass surgery	Issa JS; Garrido AJ; Giannini SD; Forti N; Diament J; Pinotti HW;	2000	Arquivos Brasileiros de Cardiologia	10	Case study
271	Therapy of severe familial heterozygous hypercholesterolemia by low-density lipoprotein apheresis with immunoadsorption, effects of the addition of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors to therapy	Jacob BG; Richter WO; Schwandt P;	1993	Clinical Investigator	10	8 patients only

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
822	Lipid reductions by low-density lipoprotein apheresis, A comparison of three systems	Jovin IS; Taborski U; Stehr A; Muller-Berghaus G;	2000	Metabolism-Clinical and Experimental	10	Case study
5245	Therapeutic effects of LDL apheresis in the prevention of atherosclerosis.	Kajinami K; Mabuchi H;	1999	Current Opinion in Lipidology	10	Narrative review
315	LDL-apheresis, results of longterm treatment and vascular outcome.	Keller C;	1991	Atherosclerosis	10	Narrative review
5246	Indication of low-density lipoprotein apheresis in severe hypercholesterolemia and its atherosclerotic vascular complications, dextran sulfate cellulose low-density lipoprotein apheresis.	Keller C;	2003	Therapeutic Apheresis & Dialysis	10	Narrative review
392	Changes of atherosclerosis of the carotid arteries due to severe familial hypercholesterolemia following long-term plasmapheresis, assessed by duplex scan	Keller C; Spengel FA;	1988	Klinische Wochenschrift	10	3 patients only
5247	Nonpharmacologic approaches for the treatment of hyperlipidemia.	Kermani T; Frishman WH;	2005	Cardiology in Review	10	Narrative report
254	Coronary atherosclerosis reduced in patients with familial hypercholesterolemia after intensive cholesterol lowering with low-density lipoprotein-apheresis, 1-year follow-up study. The Osaka LDL-Apheresis Multicenter Trial Group	Kitabatake A; Sato H; Hori M; Kamada T; Kubori S; Hoki N; Minamino T; Yamada M; Kato T;	1994	Clinical Therapeutics	10	13 patients

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
174	The familial hypercholesterolemia regression study, a randomized comparison of therapeutic reduction of both low-density lipoprotein and lipoprotein(a) versus low-density lipoprotein alone	Kitano Y; Thompson GR;	1997	Therapeutic Apheresis	10	Repeat of Thomson et al study
55	Differential indication of lipoprotein apheresis during pregnancy.	Klingel R; Gohlen B; Schwarting A; Himmelsbach F; Straube R;	2003	Therapeutic Apheresis & Dialysis, Official Peer-Reviewed Journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy	10	Narrative review
175	The retardation of progression, stabilization, and regression of coronary and carotid atherosclerosis by low-density lipoprotein apheresis in patients with familial hypercholesterolemia.	Koga N;	1997	Therapeutic Apheresis	10	Narrative review
5249	Efficacy and safety measures for low density lipoprotein apheresis treatment using dextran sulfate cellulose columns.	Koga N;	1999	Therapeutic Apheresis	10	Narrative review
283	Reduction of lipoprotein(a) by LDL-apheresis using a dextran sulfate cellulose column in patients with familial hypercholesterolemia	Koizumi J; Koizumi I; Uno Y; Inazu A; Kajinami K; Haraki T; Yagi K; Kamon N; Miyamoto S; Takegoshi T; et a;	1993	Atherosclerosis	10	13 patients

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
5250	Retrospective comparison of 5 different methods for long-term LDL-apheresis in 20 patients between 1986 and 2001	Krebs A; Krebs K; Keller F;	2004	International Journal of Artificial Organs	10	Not the question - a comparison of methods
871	Effect of apheresis of low-density lipoprotein on peripheral vascular disease in hypercholesterolemic patients with coronary artery disease	Kroon AA; vanAsten WNJC; Stalenhoef AFH;	1996	Annals of Internal Medicine	10	Repeat of article published elsewhere
202	Treatment of hypercholesterolemia with heparin-induced extracorporeal low-density lipoprotein precipitation (HELP).	Lees RS; Holmes NN; Stadler RW; Ibrahim SF; Lees AM;	1996	Journal of Clinical Apheresis	10	Narrative review
44	Clinical applications of long-term LDL-apheresis on and beyond refractory hypercholesterolemia.	Mabuchi H; Higashikata T; Kawashiri MA;	2004	Transfusion & Apheresis Science	10	Narrative review
5252	Long-term effect of low-density lipoprotein apheresis in patients with homozygous familial hypercholesterolemia.	Makino H; Harada-Shiba M;	2003	Therapeutic Apheresis & Dialysis	10	Narrative review
5253	Changes in lipoprotein profile after selective LDL apheresis	Matsunaga T; Takasaki S; Masakane I; Okazaki M; Tomoike H;	2004	Internal Medicine	10	Case study
17	Hypercholesterolemia and LDL apheresis.	Morelli F; Carlier P; Giannini G; De L; Dejana AM; Ruzzenenti MR;	2005	International Journal of Artificial Organs	10	Narrative
65	Current management of severe homozygous hypercholesterolaemias.	Naoumova RP; Thompson GR; Soutar AK;	2004	Current Opinion in Lipidology	10	Narrative review

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
311	LDL cholesterol apheresis by dextran sulfate cellulose adsorption. Long-term experience in patients with familial hypercholesterolemia	Olbricht CJ; Schulzeck P;	1991	ASAIO Transactions	10	5 patients
932	Effect of HELP-LDL-apheresis on outcomes in patients with advanced coronary-atherosclerosis and severe hypercholesterolemia	Park JW; Merz M; Braun P;	1998	Atherosclerosis	10	Not clear is this is an FH population
167	Long-term effect of low-density lipoprotein apheresis on plasma lipoproteins and coronary heart disease in native vessels and coronary bypass in severe heterozygous familial hypercholesterolemia	Richter WO; Donner MG; Hofling B; Schwandt P;	1998	Metabolism, Clinical & Experimental	10	Repeat of Donner study
680	Short- and long-term effects on serum lipoproteins by three different techniques of apheresis	Richter WO; Donner MG; Schwandt P;	1996	Artificial Organs	10	Comparison of three types of systems in 19 patients - not the question
141	Three low density lipoprotein apheresis techniques in treatment of patients with familial hypercholesterolemia, a long-term evaluation	Richter WO; Donner MG; Schwandt P;	1999	Therapeutic Apheresis	10	Does not answer the question - we did not review apheresis techniques
619	Treatment of severe hypercholesterolemia with heparin-induced LDL apheresis	Richter WO; Jacob B; Ritter MM; Suhler K; Vierneisel K; Schwandt P;	1992	Current Therapeutic Research, Clinical & Experimental	10	5 patients

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
280	Three-year treatment of familial heterozygous hypercholesterolemia by extracorporeal low-density lipoprotein immunoadsorption with polyclonal apolipoprotein B antibodies	Richter WO; Jacob BG; Ritter MM; Suhler K; Vierneisel K; Schwandt P;	1993	Metabolism, Clinical & Experimental	10	8 patients
375	Lipoprotein changes in familial hypercholesterolemia after extracorporeal immunoadsorption of low density lipoproteins	Riesen WF; Jaross W; Descoeudres C; Mordasini R; Koban F; Thulin H; Fisher S; Bergmann S;	1988	Annales de Biologie Clinique	10	2 patients
307	Treatment of severe hypercholesterolaemia by LDL-apheresis	Scarpato N; Gnasso A; Nappi G; Falco C; Postiglione A; Formisano S; Mancini M;	2001	Biomaterials, Artificial Cells, & Immobilization Biotechnology	10	14 patients
5257	Impact of chronic LDL-apheresis treatment on Achilles tendon affection in patients with severe familial hypercholesterolemia, a clinical and ultrasonographic 3-year follow-up study	Scheel AK; Schettler V; Koziolek M; Koelling S; Werner C; Muller GA; Strutz F;	2004	Atherosclerosis	10	Does not answer the question
211	H.E.L.P. apheresis therapy in the treatment of severe hypercholesterolemia, 10 years of clinical experience.	Seidel D;	1996	Artificial Organs	10	Review
5259	A review of randomized controlled trials using therapeutic apheresis	Shehata N; Kouroukis C; Kelton JG;	2002	Transfusion Medicine Reviews	10	Narrative review
547	Plasmapheresis by using secondary membrane filters, Twelve years of experience	Siami FS; Siami GA;	2000	ASAIO Journal	10	Does not answer the question - type of system only
5265	LDL-apheresis, current status.	Stefanutti C; Vivenzio A; Lucani G; Di G;	2001	Clinica Terapeutica	10	11 children in study

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
5313	Guidelines on the use of therapeutic apheresis in clinical practice-Evidence-based approach from the apheresis applications committee of the American society for apheresis	Szczepiorkowski ZM; Bandarenko N; Kim HC; Linenberger ML; Marques MB; Sarode R; Schwartz J; Shaz BH; Weinstein R; Wirk A; Winters JL;	2007	Journal of Clinical Apheresis	10	Guidelines on apheresis technique not appropriate for this question
5314	The new approach to assignment of ASFA categories-Introduction to the fourth special issue, Clinical applications of therapeutic apheresis	Szczepiorkowski ZM; Shaz BH; Bandarenko N; Winters JL;	2007	Journal of Clinical Apheresis	10	Does not answer the question - new model for grading clients
297	Regression of coronary atherosclerosis by combined LDL-apheresis and lipid-lowering drug therapy in patients with familial hypercholesterolemia, a multicenter study. The LARS Investigators	Tatami R; Inoue N; Itoh H; Kishino B; Koga N; Nakashima Y; Nishide T; Okamura K; Saito Y; Teramoto T; et a;	1992	Atherosclerosis	10	Repeat of Koga study
266	LDL-apheresis, clinical experience and indications in the treatment of severe hypercholesterolemia.	Thiery J; Seidel D;	1993	Transfusion Science	10	Narrative review
5260	A systematic review of LDL apheresis in the treatment of cardiovascular disease.	Thompsen J; Thompson PD;	2006	Atherosclerosis	10	Not specific to FH. Review for FH not complete
5262	LDL apheresis.	Thompson GR;	2003	Atherosclerosis	10	Narrative review
430	Improved survival of patients with homozygous familial hypercholesterolaemia treated with plasma exchange	Thompson GR; Miller JP; Breslow JL;	1985	British Medical Journal	10	5 homozygous atients only

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
301	Treatment of children with homozygous familial hypercholesterolemia, safety and efficacy of low-density lipoprotein apheresis	Uauy R; Zwiener RJ; Phillips MJ; Petruska ML; Bilheimer DW;	1992	Journal of Pediatrics	10	3 children
374	The treatment of familial hypercholesterolaemia by partial ileal bypass surgery. A review of the literature. [Review] [40 refs]	Van Niekerk JL; Hendriks T; De Boer HH;	1984	Netherlands Journal of Medicine	10	Narrative review
101	Low-density lipoprotein apheresis for the treatment of refractory hyperlipidemia.	Vella A; Pineda AA; O'Brien T;	2001	Mayo Clinic Proceedings	10	Narrative review
243	The effect of LDL apheresis on progression of coronary artery disease in patients with familial hypercholesterolemia. Results of a multicenter LDL apheresis study	Waidner T; Franzen D; Voelker W; Ritter M; Borberg H; Hombach V; Hopp HW;	1994	Clinical Investigator	10	Repeat of study by Borberg
100	Apheresis technology for prevention and regression of atherosclerosis.	Yamamoto A; Harada-Shiba M; Kawaguchi A; Tsushima M;	2001	Therapeutic Apheresis	10	Narrative review
179	Apheresis technology for prevention and regression of atherosclerosis, an overview.	Yamamoto A; Kawaguchi A; Harada-Shiba M; Tsushima M; Kojima S;	1997	Therapeutic Apheresis	10	Narrative review
402	LDL-apheresis, potential procedure for prevention and regression of atheromatous vascular lesion	Yokoyama S; Yamamoto A; Hayashi R; Satani M;	1987	Japanese Circulation Journal	10	9 patients

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
492	Screening for hypercholesterolaemia in 10,000 neonates in a multi-ethnic population	Beeso J; Wong N; Ayling R; Eldridge P; Marshall W; Sherwood R; Peters T;	1999	European Journal of Pediatrics	11	Does not answer the question
9	[Pathogenetic bases and surgical alternatives in the treatment of familial hypercholesterolemia]. [Review] [104 refs] [Spanish]	Benito Fernandez C; Cienfuegos Suarez JA; Voltas Baro J;	1991	Medicina Clinica	11	Narrative review
35	Metabolic effects of portacaval shunt surgery and liver transplantation in familial hypercholesterolemia. [Review] [48 refs]	Bilheimer DW;	1988	Beitrage zur Infusionstherapie	11	Narrative review
40	Portacaval shunt surgery and liver transplantation in the treatment of homozygous familial hypercholesterolemia. [Review] [24 refs]	Bilheimer DW;	1988	Progress in Clinical & Biological Research	11	Narrative review
5270	Liver transplantation to provide low-density-lipoprotein receptors and lower plasma cholesterol in a child with homozygous familial hypercholesterolemia	Bilheimer DW; Goldstein JL; Grundy SM; Starzl TE; Brown MS;	1984	New England Journal of Medicine	11	Case study
3287	The validity of screening for hypercholesterolaemia at different ages from 2 to 17 years	Boulton TJC;	1979	Australian & New Zealand Journal of Medicine	11	Does not answer the question
1118	Cholesterol in Childhood - How High Is Ok - Recommendations for Screening, Case-Finding and Intervention	Boulton TJC; Seal JA; Magarey AM;	1991	Medical Journal of Australia	11	Recommendations only

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
5272	Orthotopic liver transplantation as a successful treatment for familial hypercholesterolemia	Cienfuegos JA; Turrion V; Pardo F; Ardaiz J; Mora NP; Escartin P; Barrios C; Cuervas-Mons V; Garrido A;	1988	Transplantation Proceedings	11	Transplantation technique not our question
62	Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia.	Civeira F; International P;	2004	Atherosclerosis	11	Methodology not described
1465	Prevalence and significance of cardiovascular risk factors in a large cohort of patients with familial hypercholesterolaemia	de Sauvage Nolting PR; Defesche JC; Buirma RJ; Hutten BA; Lansberg PJ; Kastelein JJ;	2003	Journal of Internal Medicine	11	Does not answer the question
2736	Genetic tests may have additional predictive power over and above the accepted risk factors in patients with severe hypercholesterolemia	Descamps OS;	2005	Louvain Medical	11	Does not answer the question
1516	Heterozygous familial hypercholesterolemia. Relationship between plasma lipids, lipoproteins, clinical manifestations and ischaemic heart disease in men and women	Gagne C; Moorjani S; Brun D; Toussaint M; Lupien PJ;	1979	Atherosclerosis	11	Does not answer the question
1741	Ethical issues in molecular screening for heterozygous familial hypercholesterolemia, the complexity of dealing with genetic susceptibility to coronary artery disease	Gaudet D; Gagne C; Perron P; Couture P; Tonstad S;	1999	Community Genetics	11	Does not answer the question
5275	Pharmacologic and surgical treatment of dyslipidemic children and adolescents. [Review] [55 refs]	Hoeg JM;	1991	Annals of the New York Academy of Sciences	11	Narrative review

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
1232	Disease knowledge and adherence to treatment in patients with familial hypercholesterolemia	Hollman G; Olsson AG; Ek AC;	2006	Journal of Cardiovascular Nursing	11	Does not answer the question
75	Treatment of dyslipidemia in children and adolescents	Holmes KW; Kwiterovich J;	2005	Current Cardiology Reports	11	Does not answer the question
5244	Clinical outcome of patients with familial hypercholesterolemia and coronary artery disease undergoing partial ileal bypass surgery	Issa JS; Garrido AJ; Giannini SD; Forti N; Diament J; Pinotti HW;	2000	Arquivos Brasileiros de Cardiologia	11	Case review of three patients
2526	Apolipoprotein B measurement in blood spotted on paper (a screening test for familial type II A hyperlipoproteinemia)	Koffigan M; Fruchart JC; Dhondt JL; Moschetto Y; Farriaux JP;	1982	Ricerca in Clinica e in Laboratorio	11	Does not answer the question
2531	Assessment of plasma total cholesterol as a test to detect elevated low density (beta) lipoprotein cholesterol levels (type IIa hyperlipoproteinemia) in young participants from a population-based sample	Kwiterovich POJ; Heiss G; Johnson N; Chase GA; Tamir I; Rifkind B;	1982	American Journal of Epidemiology	11	Does not answer the question
87	The management of familial hypercholesterolaemia in childhood	Lee PJ;	2002	Current Paediatrics	11	
1294	Lipid profile of children with a family history of coronary heart disease or hyperlipidemia, 9-year experience of an outpatient clinic for the prevention of cardiovascular diseases	Makedou A; Kourti M; Makedou K; Lazaridou S; Varlamis G;	2005	Angiology	11	Not our population
5277	Homozygous familial hypercholesterolemia and its management. [Review] [64 refs]	Marais AD; Firth JC; Blom DJ;	2004	Seminars in Vascular Medicine	11	Narrative review

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
1508	A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia	Marks D; Thorogood M; Neil HA; Humphries SE;	2003	Atherosclerosis	11	A narrative review
1335	Exercise testing in asymptomatic patients with heterozygous familial hypercholesterolaemia	Michaelides AP; Fourlas CA; Pitsavos C; Andrikopoulos GK; Skoumas I; Kartalis A; Katsaros A; Stougiannos P; Stefanadis CI;	2004	Coronary Artery Disease	11	Does not answer the question
65	Current management of severe homozygous hypercholesterolaemias.	Naoumova RP; Thompson GR; Soutar AK;	2004	Current Opinion in Lipidology	11	Narrative review
56	Diagnostic, clinical, and therapeutic aspects of familial hypercholesterolemia in children.	Ose L;	2004	Seminars in Vascular Medicine	11	Narrative review
1112	Screening for Familial Hypercholesterolemia by Measurement of Apolipoproteins in Capillary Blood	Skovby F; Micic S; Jepsen B; Larsen SO; Hansen B; Tegllund L; Pedersen BN;	1991	Archives of Disease in Childhood	11	Does not answer the question
1675	Hereditary dyslipidemias and combined risk factors in children with a family history of premature coronary artery disease	Sveger T; Flodmark CE; Nordborg K; Nilsson-Ehle P; Borgfors N;	2000	Archives of disease in childhood	11	Does not answer the question
301	Treatment of Children with Homozygous Familial Hypercholesterolemia - Safety and Efficacy of Low-Density-Lipoprotein Apheresis	Uauy R; Zwiener RJ; Phillips MJ; Petruska ML; Bilheimer DW;	1992	Journal of Pediatrics	11	Case reports of three children
58	Clinical, diagnostic, and therapeutic aspects of familial hypercholesterolemia.	van Aalst Cohen ES; Jansen AC; de Jongh S; de Sauvage Nolting P.R.; Kastelein JJ;	2004	Seminars in Vascular Medicine	11	Narrative review

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
5292	Noninvasive assessment of arterial stiffness and risk of atherosclerotic events in children. [Review] [50 refs]	Aggoun Y; Szezepanski I; Bonnet D;	2005	Pediatric Research	12	Narrative review
543	Sustained long-term improvement of arterial endothelial function in heterozygous familial hypercholesterolemia patients treated with simvastatin	Alonso R; Mata P; De A; Villacastin BP; Martinez-Gonzalez J; Badimon L;	2001	Atherosclerosis	12	Not an RCT
5293	Familial homozygous hypercholesterolemia, clinical and cardiovascular features in 18 patients	Brook GJ; Keidar S; Boulos M; Grenadier E; Wiener A; Shehada N; Markiewicz W; Benderli A; Aviram M;	1989	Clinical Cardiology	12	Not heterozygous population
391	Vascular stiffness in familial hypercholesterolaemia is associated with C-reactive protein and cholesterol burden	Cheng HM; Ye ZX; Chiou KR; Lin SJ; Charng MJ;	2007	European Journal of Clinical Investigation	12	Does not answer the question
208	Familial hypercholesterolaemia with supravalvular aortic stenosis	Chidambaram N; Prasad PV;	1997	Journal of the Indian Medical Association	12	Case Study

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
455	European guidelines on cardiovascular disease prevention in clinical practice, Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice	De Backer G; Ambrosioni E; Borch-Johnsen K; Brotons C; Cifkova R; Dallongeville J; Ebrahim S; Faergeman O; Graham I; Mancia G; Cats VM; Orth-Gomer K; Perk J; Pyorala K; Rodicio JL; Sans S; Sansoy V; Sechtem U; Silber S; Thomsen T; Wood D;	2003	European Journal of Cardiovascular Prevention & Rehabilitation	12	General guidelines
294	Impact of genetic defects on atherosclerosis in patients suspected of familial hypercholesterolaemia	Descamps OS; Gilbeau JP; Leysen X; Van L; Heller FR;	2001	European Journal of Clinical Investigation	12	Does not answer the question - looks at risk by genotype but not ongoing evaluation
5294	Secondary prevention with lipid lowering therapy in familial hypercholesterolemia, a correlation between new evolution of stenotic lesion and achieved cholesterol levels after revascularization procedures	Fukuzawa S; Ozawa S; Inagaki M; Morooka S; Inoue T;	1999	Internal Medicine	12	Does not answer the question
5296	Atherosclerotic plaque evolution in the descending thoracic aorta in familial hypercholesterolemic patients. A transesophageal echo study	Herrera CJ; Frazin LJ; Dau PC; DeFrino P; Stone NJ; Mehlman DJ; Vonesh MJ; Talano JV; McPherson DD;	1994	Arteriosclerosis & Thrombosis	12	Not a study of CAD

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
5297	Detection and quantitation of calcify atherosclerosis by ultra fast computed tomography in children and young adults with homozygous familial hypercholesterolemia	Hoeg JM; Feuerstein IM; Tucker EE;	1994	Arteriosclerosis & Thrombosis	12	Not heterozygous population
168	Linking genotype to aorta-coronary atherosclerosis, a model using familial hypercholesterolemia and aorta-coronary calcification	Jensen JM; Kruse TA; Brorholt-Petersen JU; Christiansen TM; Jensen HK; Kolvraa S; Faergeman O;	1999	Annals of Human Genetics	12	Does not answer the question
5300	Cardiovascular risk reduction in high-risk pediatric patients, A scientific statement from the American Heart Association expert panel on population and prevention science, the councils on cardiovascular disease in the young, epidemiology and prevention,	Kavey RE; Allada V; Daniels SR; Hayman LL; McCrindle BW; Newburger JW; Parekh RS; Steinberger J;	2006	Circulation	12	This is a study about risk and does not answer the question
164	Characteristic cardiovascular manifestation in homozygous and heterozygous familial hypercholesterolemia	Kawaguchi A; Miyatake K; Yutani C; Beppu S; Tsushima M; Yamamura T; Yamamoto A;	1999	American Heart Journal	12	Not heterozygous population
343	Results of serial coronary angiography in patients with homozygous familial hypercholesterolaemia	Klein JM; Drobinski G; Bruckert E; Dairou F; Thomas D; De G; Grosgogeat Y;	1988	European Heart Journal	12	Not heterozygous population
5301	Aortic root involvement in homozygous familial hypercholesterolemia--transesophageal echocardiography appearances of supravalvular aortic stenosis	Koh TW;	2005	Echocardiography	12	Not heterozygous population

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
231	Development of coronary atherosclerosis in asymptomatic heterozygous patients with familial hypercholesterolemia	Miida T; Nakamura Y; Okada M;	1996	Journal of Cardiology	12	Does not answer the question
533	Homodynamic and angiographic evaluation of cardiovascular involvement in patients with homozygous familial hypercholesterolemia	Piscione F; Cappelli-Bigazzi M; Postiglione A; Gnasso A; Focaccio A; Chiariello M;	1990	Coronary Artery Disease	12	Not heterozygous population
313	Relative protection from cerebral atherosclerosis of young patients with homozygous familial hypercholesterolemia	Postiglione A; Nappi A; Brunetti A; Soricelli A; Rubba P; Gnasso A; Cammisa M; Frusciante V; Cortese C; Salvatore M; et a;	1991	Atherosclerosis	12	Wrong population and wrong question
5303	Extent and severity of atherosclerotic involvement of the aortic valve and root in familial hypercholesterolaemia	Rallidis L; Naoumova RP; Thompson GR; Nihoyannopoulos P;	1998	Heart	12	Wrong for question - not ongoing assessment or evaluation of test
234	Aortic stenosis in homozygous familial hypercholesterolaemia	Rallidis L; Nihoyannopoulos P; Thompson GR;	1996	Heart	12	Wrong population
347	Extra coronary atherosclerosis in familial hypercholesterolemia	Rubba P; De S; Postiglione A; Cortese C; Gnasso A; Mancini M;	1988	Atherosclerosis	12	Did not answer the question
1081	Coronary Risk-Factors and the Severity of Angiographic Coronary-Artery Disease in Members of High-Risk Pedigrees	Sharp SD; Williams RR; Hunt SC; Schumacher MC;	1992	American Heart Journal	12	Study wrong for the question. This study refers to coronary risk.

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
5304	Clinical review 168, What vascular ultrasound testing has revealed about pediatric parthenogenesis, and a potential clinical role for ultrasound in pediatric risk assessment. [Review] [77 refs]	Slyper AH;	2004	Journal of Clinical Endocrinology & Metabolism	12	Narrative review
5305	Cardiovascular features of homozygous familial hypercholesterolemia, analysis of 16 patients	Sprecher DL; Schaefer EJ; Kent KM; Gregg RE; Zech LA; Hoeg JM; McManus B; Roberts WC; Brewer HBJ;	1984	American Journal of Cardiology	12	Wrong population
188	Evaluation of the aortic root by MRI, insights from patients with homozygous familial hypercholesterolemia	Summers RM; ndrasko-Bourgeois J; Feuerstein IM; Hill SC; Jones EC; Busse MK; Wise B; Bove KE; Rishforth BA; Tucker E; Spray TL; Hoeg JM;	1998	Circulation	12	Not heterozygous population
5266	Carotid intima-media thickness and plaque in patients with familial hypercholesterolaemia mutations and control participants.[see comment]	Tonstad S; Joakimsen O; Stensland-Bugge E; Ose L; Bonaa KH; Leren TP;	1998	European Journal of Clinical Investigation	12	CMT not our outcome measure
1487	Arterial intima-media thickness in children heterozygous for familial hypercholesterolaemia	Wiegman A; de Groot E; Hutten BA; Rodenburg J; Gort J; Bakker HD; Sijbrands EJG; Kastelein JJP;	2004	Lancet	12	Does not address ongoing assessment or an evaluation of testing

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
5331	Long-term compliance and changes in plasma lipids, plant sterols and arytenoids in children and parents with FH consuming plant sterol ester-enriched spread	Amundsen AL; Ntanios F; Put Nv; Ose L;	2004	European Journal of Clinical Nutrition	13	This is an open label follow up of the 2002 study in the Cochrane systematic review
5332	Plant sterol ester-enriched spread lowers plasma total and LDL cholesterol in children with familial hypercholesterolemia	Amundsen AL; Ose L; Nenseter MS; Ntanios FY;	2002	American Journal of Clinical Nutrition	13	This study is included in a systematic review
2611	Tracing and treatment of children with essential familial hypercholesterolemia	Andersen GE; Clausen J;	1972	Zeitschrift fur Ernahrungswissenschaft	13	Poorly designed and reported study
252	Fish oil supplementation in patients with heterozygous familial hypercholesterolemia	Balestrieri GP; Maffi V; Sleiman I; Spandrio S; Di SO; Salvi A; Scalvini T;	1996	Recenti Progressi in Medicina	13	This paper is included in a systematic review.
878	Treatment of severe familial hypercholesterolemia in childhood with sitosterol and sitosterol	Becker M; Staab D; Von BK;	1993	Journal of Pediatrics	13	This study in included in both systematic reviews.
880	Dietary management of patients with familial hypercholesterolaemia treated with simvastatin	Chisholm A; Mann J; Sutherland W; Williams S; Ball M;	1992	Quarterly Journal of Medicine	13	This study is included in a systematic review.
5333	The effect of dietary fat content on plasma no cholesterol sterol concentrations in patients with familial hypercholesterolemia treated with simvastatin	Chisholm A; Sutherland W; Ball M;	1994	Metabolism, Clinical and Experimental	13	This study is included in a systematic review.
925	Dietary treatment of familial hypercholesterolemia	Connor WE; Connor SL;	1989	Arteriosclerosis	13	This is a narrative paper.
860	Importance of diet in the treatment of familial hypercholesterolemia	Connor WE; Connor SL;	1993	American Journal of Cardiology	13	This is a narrative review.

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
5334	Plant sterols lower LDL cholesterol without improving endothelial function in prepubertal children with familial hypercholesterolaemia	de Jongh S; Vissers MN; Rol P; Bakker HD; Kastelein JJP; Stroes ESG;	2003	Journal of Inherited Metabolic Disease	13	This study is included in a systematic review.
377	Effects of n-3 and n-6 fatty acid-enriched diets on plasma lipoproteins and apolipoproteins in heterozygous familial hypercholesterolemia	Friday KE; Failor RA; Childs MT; Bierman EL;	1991	Arteriosclerosis & Thrombosis	13	This is a case series
373	Dietary treatment for familial hypercholesterolemia--differential effects of dietary soy protein according to the apolipoprotein E phenotypes	Gaddi A; Ciarrocchi A; Matteucci A; Rimondi S; Ravaglia G; Descovich GC; Sirtori CR;	1991	American Journal of Clinical Nutrition	13	Not RCT
517	Pediatric familial type II hyperlipoproteinemia, therapy with diet and colestipol resin	Glueck CJ; Fallat RW; Mellies M; Tsang RC;	1976	Pediatrics	13	Not RCT
709	Safety and efficacy of long-term diet and diet plus bile acid-binding resin cholesterol-lowering therapy in 73 children heterozygous for familial hypercholesterolemia	Glueck CJ; Mellies MJ; Dine M; et a;	1986	Pediatrics	13	Not RCT
364	Relationships of serum plant sterols (phytosterols) and cholesterol in 595 hypercholesterolemic participants, and familial aggregation of phytosterols, cholesterol, and premature coronary heart disease in hyperphytosterolemic probands and their first-degree r	Glueck CJ; Speirs J; Tracy T; Streicher P; Illig E; Vandegrift J;	1991	Metabolism, Clinical and Experimental	13	Population not all FH, does not answer the question.

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
66	Therapy of familial hypercholesterolemia in childhood, diet and cholestyramine resin for 24 to 36 months	Glueck CJ; Tsang RC; Fallat RW; Mellies M;	1977	Pediatrics	13	Not RCT
516	Diet in children heterozygous for familial hypercholesterolemia	Glueck CJ; Tsang RC; Fallat RW; Mellies MJ;	1977	American Journal of Diseases of Children	13	This study is in a systematic review.
478	Soybean protein independently lowers plasma cholesterol levels in primary hypercholesterolemia	Goldberg AP; Lim A; Kolar JB; Grundhauser JJ; Steinke FH; Schonfeld G;	1982	Atherosclerosis	13	Not RCT, not defined FH population.
5335	Effect of a rapeseed oil substituting diet on serum lipids and lipoproteins in children and adolescents with familial hypercholesterolemia	Gulesserian T; Widhalm K;	2002	Journal of the American College of Nutrition	13	Not RCT
813	Sitostanol ester margarine in dietary treatment of children with familial hypercholesterolemia	Gylling H; Siimes MA; Miettinen TA;	1995	Journal of Lipid Research	13	This study is included in a systematic review.
1205	Comparison of the effects of plant sterol ester and plant stanol ester-enriched margarines in lowering serum cholesterol concentrations in hypercholesterolaemic participants on a low-fat diet	Hallikainen MA; Sarkkinen ES; Gylling H; Erkkila AT; Uusitupa MIJ;	2000	European Journal of Clinical Nutrition	13	Not FH population
5336	Influence of diets containing cow's milk or soy protein beverage on plasma lipids in children with familial hypercholesterolemia	Jacques H; Laurin D; Moorjani S; Steinke FH; GagnÚ C; Brun D; Lupien PJ;	1992	Journal of the American College of Nutrition	13	Not RCT

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
5338	Squalene and noncholesterol sterols in serum and lipoproteins of children with and without familial hypercholesterolemia	Ketomõki A; Gylling H; Siimes MA; Vuorio A; Miettinen TA;	2003	Pediatric Research	13	Does not answer the question
532	The treatment of familial hypercholesterolemia with a plant sterol	KNODE KT; LEVKOFF AH;	1957	Pediatrics	13	Not RCT. This is a case study
3326	Treatment of hypercholesterolemia in children and adolescents	Koletzko B; Kupke I; Wendel U;	1992	Acta Paediatrica	13	Not RCT
140	Safety and efficacy of treatment of children and adolescents with elevated low density lipoprotein levels with a step two diet or with lovastatin	Kwiterovich PO;	2001	Nutrition Metabolism and Cardiovascular Diseases	13	This is a narrative paper.
5340	Cholesterol-free diet with a high ratio of polyunsaturated to saturated fatty acids in heterozygous familial hypercholesterolemia, significant lowering effect on plasma cholesterol	Mokuno H; Yamada N; Sugimoto T; Kobayashi T; Ishibashi S; Shimano H; Takizawa M; Kawakami M; Takaku F; Murase T;	1990	Hormone and Metabolic Research	13	Poorly designed study of 11 days duration
5344	Randomised controlled trial of use by hypercholesterolaemic patients of a vegetable oil sterol-enriched fat spread	Neil HA; Meijer GW; Roe LS;	2001	Atherosclerosis	13	This study is included in a systematic review.
54	Plant stanol and sterol esters in the control of blood cholesterol levels, mechanism and safety aspects	Plat J; Mensink RP;	2005	American Journal of Cardiology	13	This is a narrative paper.
5348	Sitosterol in juvenile type II hyperlipoproteinemia	Schlierf G; Oster P; Heuck CC; Raetzer H; Schellenberg B;	1978	Atherosclerosis	13	This study is included in a systematic review.

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
566	Diet only and diet plus simvastatin in the treatment of heterozygous familial hypercholesterolemia in childhood	Stefanutti C; Lucani G; Vivenzio A; Di G;	1999	Drugs Under Experimental & Clinical Research	13	Not RCT
5343	Stanol ester margarine alone and with simvastatin lowers serum cholesterol in families with familial hypercholesterolemia caused by the FH-North Karelia mutation	Vuorio AF; Gylling H; Turtola H; Kontula K; Ketonen P; Miettinen TA;	2000	Arteriosclerosis, Thrombosis & Vascular Biology	13	This study is in a systematic review.
328	Effect of soy protein diet versus standard low fat, low cholesterol diet on lipid and lipoprotein levels in children with familial or polygenic hypercholesterolemia	Widhalm K; Brazda G; Schneider B; Kohl S;	1993	Journal of Pediatrics	13	Not RCT, not defined FH population.
5347	Potential role of raising dietary protein intake for reducing risk of atherosclerosis	Wolfe BM;	1995	Canadian Journal of Cardiology	13	This study is in a systematic review.
5345	High protein diet complements resin therapy of familial hypercholesterolemia	Wolfe BM; Giovannetti PM;	1992	Clinical and Investigative Medicine	13	Not RCT
5320	The use of a large-scale surveillance system in Planned Parenthood Federation of America clinics to monitor cardiovascular events in users of combination oral contraceptives	Burnhill MS;	1999	International Journal of Fertility & Womens Medicine	14	Not FH population
424	Estrogen and progestin components of oral contraceptives, Relationship to vascular disease	Carr BR; Ory H;	1997	Contraception	14	Narrative review only

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
160	Hormones and cardiovascular health in women	Crosignani PG; Farley T; Fauser B; Glasier A; Greer I; Hanson MA; La V; Mishell D; Rosano G; Simon T; Baird DT; Benagiano G; Collins J; Dicfalusy E; Lanzone A; Negri E; Schmidt-Gollwitzer K; Skouby SO; Volpe A;	2006	Human Reproduction Update	14	Narrative review only
5321	Safety of implantable contraceptives for women, data from observational studies	Curtis KM;	2002	Contraception	14	Not FH population. No discussion of women with cardiovascular disease
5322	Contraception for women in selected circumstances	Curtis MK; Chrisman CE; Peterson HB;	2002	Obstetrics and Gynecology	14	Not FH population or women at high risk for CV disease
5323	Oral contraceptive-induced changes in plasma lipids, do they have any clinical relevance?.	Hoppe G;	1987	Clinical Reproduction & Fertility	14	Narrative review. No systematic strategy provided
412	Estimates of the risk of cardiovascular death attributable to low-dose oral contraceptives in the United States	Schwingl PJ; Ory HW; Visness CM;	1999	American Journal of Obstetrics and Gynecology	14	Not FH population
5325	Myocardial infarction and use of low-dose oral contraceptives, A pooled analysis of 2 US studies	Sidney S; Siscovick DS; Petitti DB; Schwartz SM; Quesenberry CP; Psaty BM; Raghunathan TE; Kelaghan J; Koepsell TD;	1998	Circulation	14	Not FH population
284	Metabolic changes in Singapore women using NORPLANT(TM) implants, A four year review	Singh K; Viegas OAC; Ratnam SS;	1991	Advances in Contraceptive Delivery Systems	14	Not FH or women on statins or with high CV risk

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
204	The risk of myocardial infarction is lower with third-,compared to second-, generation OC - Meta-analysis	Spitzer WO; Faith JM; MacRae KD; Dunn N;	2003	Evidence-Based Obstetrics & Gynecology	14	Commentary only
132	Past use of oral contraceptives and cardiovascular disease, a meta-analysis in the context of the Nurses' Health Study	Stampfer MJ; Willett WC; Colditz GA; Speizer FE; Hennekens CH;	1990	American Journal of Obstetrics & Gynecology	14	Not FH population - a study of women free from CV disease
166	Pregnancy outcome in familial homozygous hypercholesterolemic females treated with long-term plasma exchange	Beigel Y; Bar J; Cohen M; Hod M;	1998	Acta Obstetricia et Gynecologica Scandinavica	15	Case study only
5381	Risks of statin use during pregnancy, a systematic review	Kazmin A; Garcia BF; Koren G;	2007	Journal of Obstetrics and Gynaecology Canada	15	Study does not add anything to the review
55	Differential indication of lipoprotein apheresis during pregnancy.	Klingel R; Gohlen B; Schwarting A; Himmelsbach F; Straube R;	2003	Therapeutic Apheresis & Dialysis, Official Peer-Reviewed Journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy	15	Narrative review only
105	Pregnancy in a patient with homozygous familial hypercholesterolemia treated with long-term low-density lipoprotein apheresis	Kroon AA; Swinkels DW; van D; Stalenhoef AF;	1994	Metabolism, Clinical & Experimental	15	Case study only
230	Maternal hyperlipidemia in pregnancy	Salameh WA; Mastrogiannis DS;	1994	Clinical Obstetrics & Gynecology	15	Narrative review only
102	Pregnancy in a patient with homozygous familial hypercholesterolemia undergoing low-density lipoprotein apheresis by dextran sulfate adsorption	Teruel JL; Lasuncion MA; Navarro JF; Carrero P; Ortuno J;	1995	Metabolism, Clinical & Experimental	15	Case study only

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
5369	Systematic review on the risk and benefit of different cholesterol-lowering interventions	Bucher HC; Griffith LE; Guyatt GH;	1999	Arteriosclerosis, Thrombosis & Vascular Biology	17	No quality assessment
5368	N-3 polyunsaturated fatty acids in coronary heart disease, A meta-analysis of randomized controlled trials	Bucher HC; Hengstler P; Schindler C; Meier G;	2002	American Journal of Medicine	17	Cholesterol not an outcome
272	How effective are dietary interventions in lowering lipids in adults with dyslipedemia?	Buckley D; Muench J; Hamilton A;	2007	Journal of Family Practice	17	No methodology
5365	Dietary lipids and blood cholesterol, quantitative meta-analysis of metabolic ward studies	Clarke R; Frost C; Collins R; Appleby P; Peto R;	1997	British Medical Journal	17	No quality assessment
158	Long-term safety and efficacy of low-fat diets in children and adolescents	Clauss SB; Kwiterovich PO;	2002	Minerva Paediatrica	17	No methodology
275	What is the dietary treatment for low HDL cholesterol?	Crawford P; Paden SL;	2006	Journal of Family Practice	17	No methodology
5370	Systematic review of randomised controlled trials of multiple risk factor interventions for preventing coronary heart disease	Ebrahim S; Smith GD;	1997	British Medical Journal	17	Multiple risk factor intervention
5371	Secondary prevention of coronary heart disease in primary care	Enriquez PA; Khunti K;	2001	Journal of Clinical Governance	17	This is a guideline not a meta analysis
85	Monounsaturated versus polyunsaturated dietary fat and serum lipids, a meta-analysis	Gardner CD; Kraemer HC;	1995	Arteriosclerosis, Thrombosis & Vascular Biology	17	Only Medline was searched

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
5373	Dietary fat intake and prevention of cardiovascular disease, systematic review	Hooper L; Summerbell CD; Higgins JP; Thompson RL; Capps NE; Smith GD; Riemersma RA; Ebrahim S;	2001	British Medical Journal	17	Cholesterol not an outcome
544	Omega 3 fatty acids for prevention and treatment of cardiovascular disease	Hooper L; Thompson RL; Harrison RA; Summerbell CD; Moore H; Worthington HV; Durrington PN; Ness AR; Capps NE; Davey SG; Riemersma RA; Ebrahim SBJ;	2004		17	Not relevant to guideline question - Omega 3
5376	Effectiveness of individual lifestyle interventions in reducing cardiovascular disease and risk factors	Ketola E; Sipila R; Makela M;	2000	Annals of Medicine	17	Not our population
445	Meta-analysis, clinical trials, and transferability of research results into practice, The case of cholesterol-lowering interventions in the secondary prevention of coronary heart disease	Marchioli R; Marfisi RM; Carinci F; Tognoni G;	1996	Archives of Internal Medicine	17	Wrong population - study looked at secondary prevention of coronary health disease

RM ID	Title	Author(s)	Year	Journal	Question	Reason(s) for exclusion
117	Dietetic guidelines on food and nutrition in the secondary prevention of cardiovascular disease - evidence from systematic reviews of randomized controlled trials (second update, January 2006)	Mead A; Atkinson G; Albin D; Alphey D; Baic S; Boyd O; Cadigan L; Clutton L; Craig L; Flanagan C; Greene P; Griffiths E; Lee NJ; Li M; McKechnie L; Ottaway J; Paterson K; Perrin L; Rigby P; Stone D; Vine R; Whitehead J; Wray L; Hooper L;	2006	Journal of human nutrition and dietetics	17	Wrong population - study looked at secondary prevention of cardiovascular disease
240	Effect of dietary fatty acids on serum lipids and lipoproteins. A meta-analysis of 27 trials	Mensink RP; Katan MB;	1992	Arteriosclerosis & Thrombosis	17	No clear methodology or quality assessment
5366	Randomised trial of lipid lowering dietary advice in general practice, the effects on serum lipids, lipoproteins, and antioxidants	Neil HA; Roe L; Godlee RJ; Moore JW; Clark GM; Brown J; Thorogood M; Stratton IM; Lancaster T; Mant D; .;	1995	British Medical Journal	17	This trial was included in the Cochrane review "Reduced or modified dietary fat for preventing cardiovascular disease (Review)" Hooper et al 2000. This is an RCT, only meta analyses are to be included
5377	Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors, a meta-analysis of randomized controlled trials	Nordmann AJ; Nordmann A; Briel M; Keller U; Yancy WS; Brehm BJ; Bucher HC;	2006	Archives of Internal Medicine	17	Wrong population - study only looked at over-weight population.
5364	Systematic review of dietary intervention trials to lower blood total cholesterol in free-living participants	Tang JL; Armitage JM; Lancaster T; Silagy CA; Fowler GH; Neil HA;	1998	British Medical Journal	17	This paper is reasonably old (1998) and a Cochrane review has been included which is more up to date
5378	Review of dietary intervention studies, effect on coronary events and on total mortality	Truswell AS;	1994	Australian and New Zealand Journal of Medicine	17	No methodology