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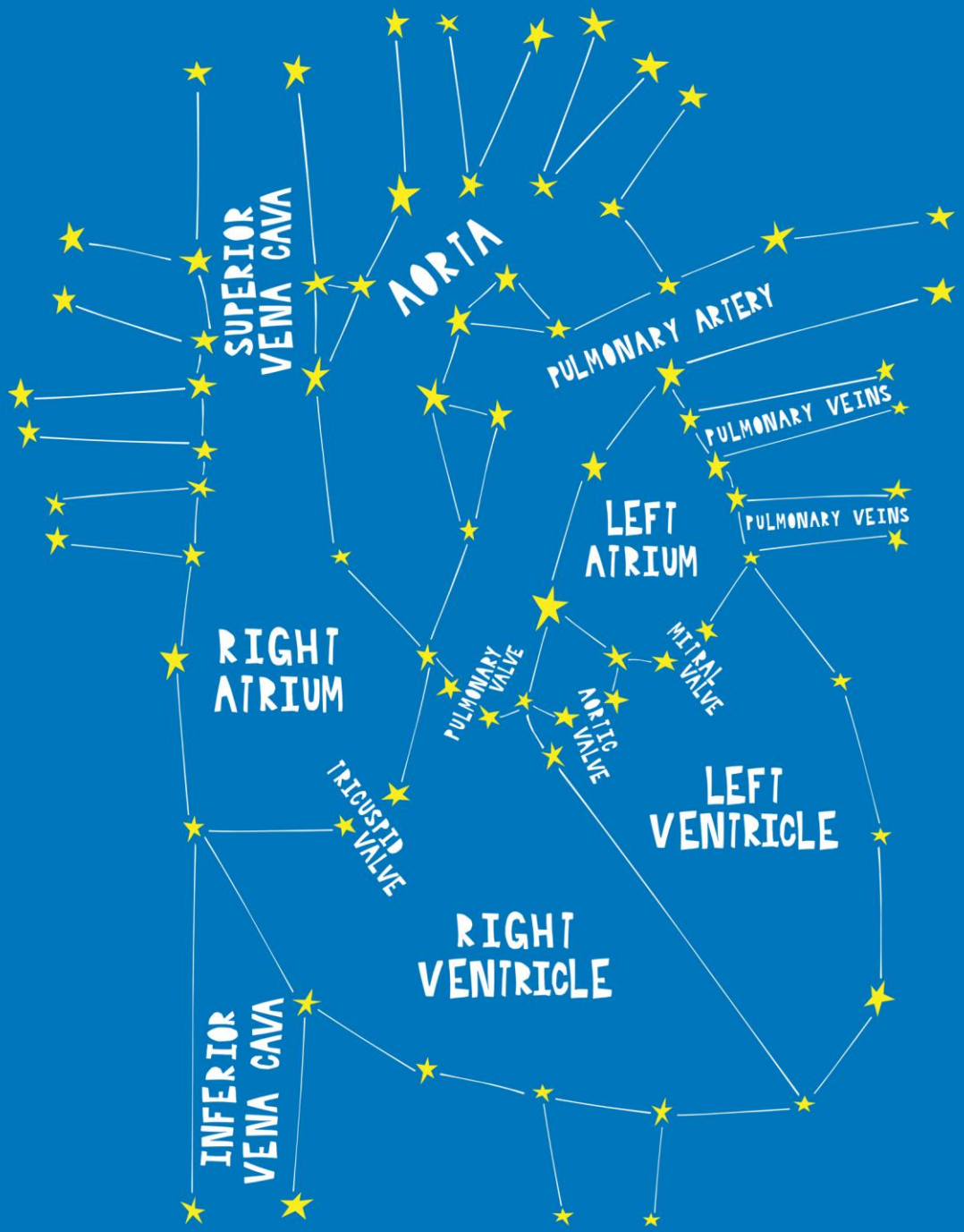
Screening and Treatment of Hyperlipidemia in Children



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6/30/2025

Disclosures

- I have no relevant financial interests/relationships to disclose

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Learning Objectives

- Understand rationale and evidence for screening for hyperlipidemia in children
- Describe recommendations for when to screen for hyperlipidemia in children
- Recognize the primary indication for statin treatment in children, familial hypercholesterolemia (FH), and its basic pathophysiology, genetic basis, and natural history
- Describe the evidence for the effectiveness of statin therapy initiated in childhood for familial hypercholesterolemia (FH)
- Discuss the safety profile of statin therapy in children

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Screening for Lipid Disorders

Table 1. Reasons provided by 262 respondents for declining to check cholesterol in pediatric patients.

	All Respondents	Respondents Treating Patients < 18 Years	Respondents Only Treating Patients ≥ 18 Years	*p*-Value
n	262	49	213	
Not familiar with pediatric guidelines (%)	75.6	57.1	79.8	<0.001
Feel there is insufficient evidence that screening children prevents ASCVD (%)	19.5	42.9	14.1	<0.001
Their children are not my patients (%)	25.2	22.5	25.8	0.62
Feel there are "no safe treatment options" for high cholesterol in childhood (%)	8.4	22.5	5.2	<0.001

ASCVD, atherosclerotic cardiovascular disease.

Petersen et al. *J Clin Med*.2021;10:3090.

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Screening rates are decreasing

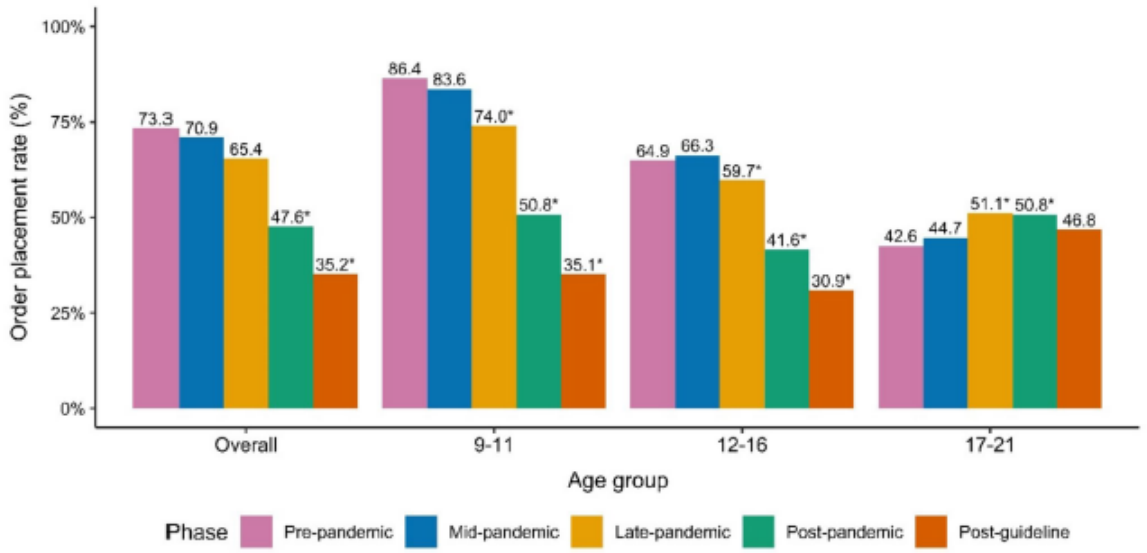

Fig. 1 Order placement rate for youth cholesterol screening by age and time period. * indicates OPR that is statistically significantly different compared to pre-pandemic rate ($p < 0.05$)

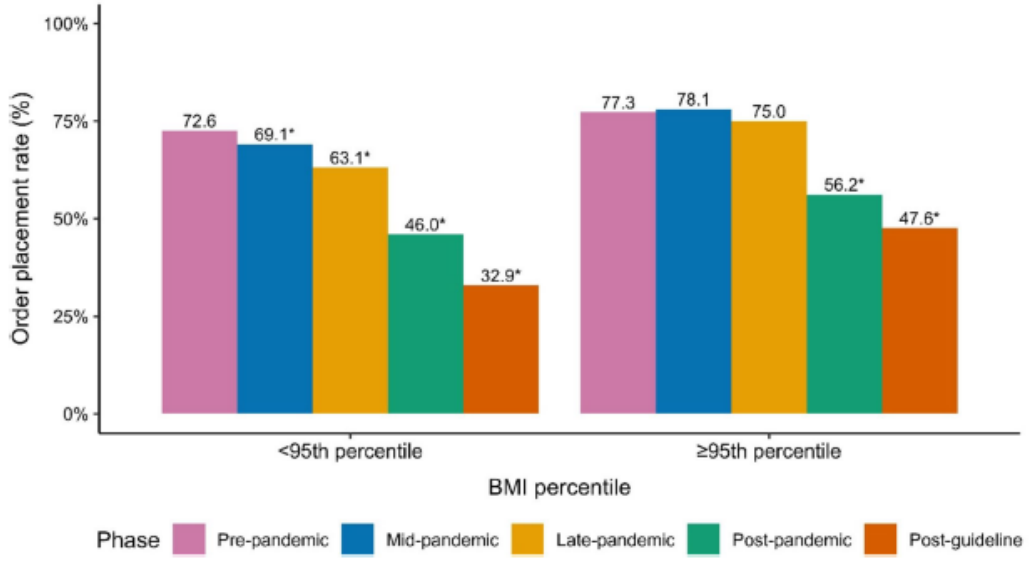

Fig. 3 Order placement rate for youth cholesterol screening by youth's BMI percentile. * indicates OPR that is statistically significantly different compared to pre-pandemic rate ($p < 0.05$)

Pediatric Cardiology
https://doi.org/10.1007/s00246-025-03831-7

RESEARCH

Changes in Youth Cholesterol Screening Rates in an Academic Center During the COVID-19 Pandemic

Jessica K. Schwartz[1] · Xiao Zhang[2] · Amy L. Peterson[2]

Received: 22 January 2025 / Accepted: 12 March 2025

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Screening for Lipid Disorders

USPSTF Recommendation: Screening for Lipid Disorders in Youth

US Preventive Services Task Force Clinical Review & Education

Figure 2. Screening for Lipid Disorders in Children and Adolescents: Clinical Summary

Population	Asymptomatic children and adolescents 20 years or younger
Recommendation	No recommendation. Grade: I (insufficient evidence)

Risk Assessment	Multifactorial dyslipidemia is associated with risk factors such as environmental factors (eg, obesity) and currently unidentified genetic factors. Familial hypercholesterolemia is an autosomal dominant disorder caused by a genetic mutation.
Screening Tests	Total cholesterol may be measured with fasting or nonfasting serum testing. Serum LDL-C levels may be calculated using the Friedewald formula. Direct LDL-C measurement does not require fasting. Other recent guidelines on screening for dyslipidemia in children have recommended measuring either LDL-C or non-HDL-C levels.
Treatment and Interventions	Interventions for dyslipidemia include lifestyle modification (eg, changes in diet and physical activity) and pharmacotherapy (eg, statins, bile acid-sequestering agents, or cholesterol absorption inhibitors). The appropriate age at which to start statin use is subject to debate. The long-term benefits and harms of statin use in children and adolescents are unknown.
Balance of Benefits and Harms	The USPSTF concludes that the current evidence is insufficient and that the balance of benefits and harms of screening for lipid disorders in asymptomatic children and adolescents 20 years or younger cannot be determined.
Other Relevant USPSTF Recommendations	The USPSTF recommends that clinicians screen for obesity in children 6 years or older and offer them or refer them to a comprehensive, intensive behavioral intervention (B recommendation). The USPSTF found insufficient evidence on screening for primary hypertension in asymptomatic children and adolescents to prevent subsequent cardiovascular disease in childhood or adulthood (I statement). These recommendations are available on the USPSTF website (http://www.uspreventiveservicestaskforce.org).

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to (http://www.uspreventiveservicestaskforce.org).

U.S. Preventive Services TASK FORCE

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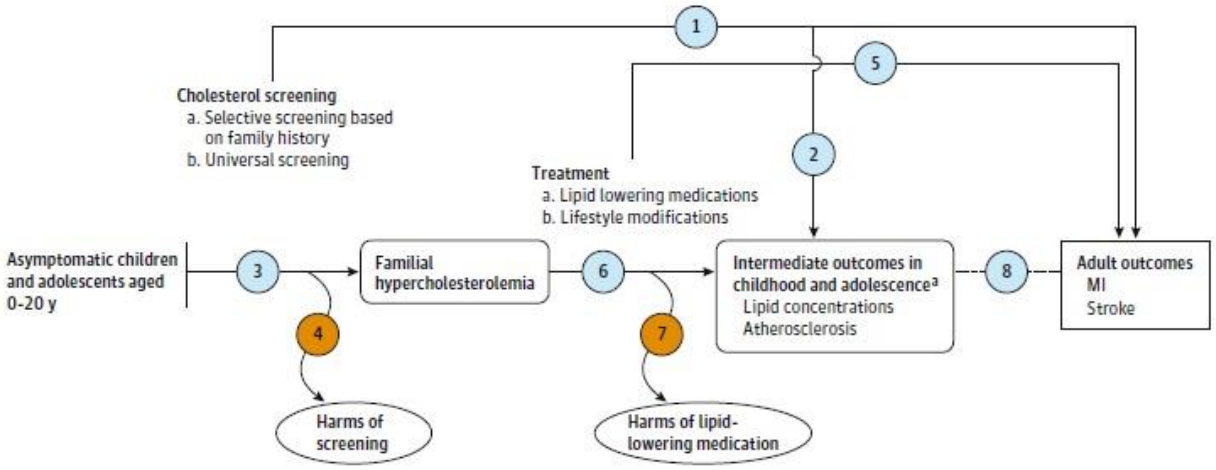
USPSTF Framework

Figure 1. Analytic Framework and Key Questions



Screening key questions

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

Treatment key questions

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

Outcomes key question

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

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Lozano et al. *JAMA*.2016;316(6):645-666.

Childhood Risk Factors and Adult CVD

- There are 5 major lines of evidence:

1. There is evidence of atherosclerosis in children and young adults
2. This atherosclerosis is related to identifiable risk factors
    1. More risk factors result in more atherosclerosis
    2. Children and young adults with no risk factors have little/no atherosclerosis
3. There is also evidence of end-organ damage in children with identifiable CVD risk factors
    1. Including children with FH
4. Risk factors track into adulthood
5. Untreated patients with FH have marked increase in CVD early in life & treatment with statins in childhood appears to lower risk of adult CVD

1. There is evidence of atherosclerosis in children and young adults

- Studies dating back to the 1950s in Korean War casualties have demonstrated atherosclerotic changes in young adults and children
- These findings have been repeated in:
  - Vietnam War casualties
  - Accidental death
    - Bogalusa study
    - Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study

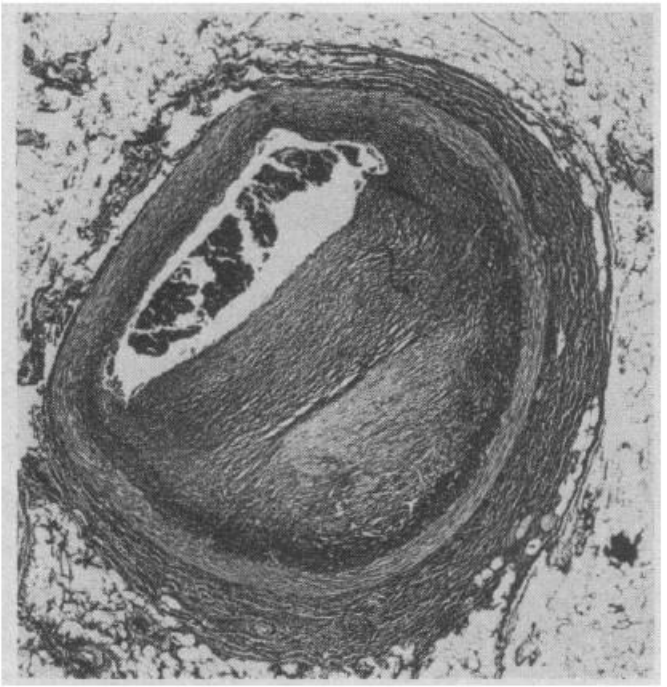

Figure 3.

Enos, W.F. and Beyer, J.C. Coronary Artery Disease in Younger Men. JAMA, 1971; 218(9):1434.

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2. Atherosclerosis is related to identifiable risk factors

- Both the Bogalusa and PDAY studies linked CVD risk factors with extent of atherosclerosis

TABLE 1. CORRELATION BETWEEN THE EXTENT OF LESIONS IN THE AORTA AND CORONARY ARTERIES AND ANTEMORTEM RISK-FACTOR VARIABLES.*

RISK-FACTOR VARIABLE	AORTA		CORONARY ARTERIES	
	FATTY STREAKS	FIBROUS PLAQUES	FATTY STREAKS	FIBROUS PLAQUES
Body-mass index	0.33†	0.24‡	0.41§	0.29†
Systolic blood pressure	0.31†	0.17	0.47§	0.41§
Diastolic blood pressure	0.14	0.10	0.18	0.24‡
Total cholesterol	0.54§	0.15	0.26‡	0.23
LDL cholesterol	0.54§	0.16	0.29‡	0.32†
HDL cholesterol	−0.03	0.05	−0.14	−0.12
Triglycerides	0.23	0.26‡	0.32†	0.37†

*Values shown are Spearman correlation coefficients. In this analysis, we used average z scores for risk factors in subgroups, defined by age, race, and sex, of all participants in the cross-sectional surveys. Although there was a total of 93 participants, because of missing data, the numbers used varied from 65 to 86, depending on the variables.

†P<0.01.
‡P<0.05.
§P<0.001.

The New England Journal of Medicine

ASSOCIATION BETWEEN MULTIPLE CARDIOVASCULAR RISK FACTORS AND ATHEROSCLEROSIS IN CHILDREN AND YOUNG ADULTS

GERALD S. BERENSON, M.D., SATHANUR R. SRINIVASAN, PH.D., WEIHANG BAO, PH.D., WILLIAM P. NEWMAN III, M.D., RICHARD E. TRACY, M.D., PH.D., AND WENDY A. WATTIGNEY, M.S., FOR THE BOGALUSA HEART STUDY

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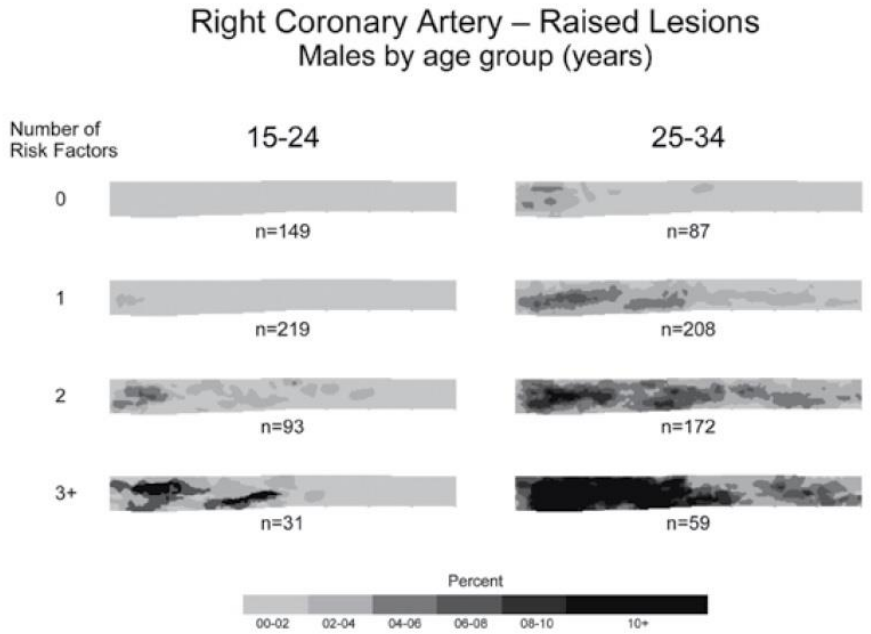
2. Atherosclerosis is related to identifiable risk factors

- The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study showed similar findings, and also implicated low HDL, tobacco use, and DM as risk factors
- Importantly it also showed that increased number of risk factors correlated with more significant atherosclerotic lesions
- Just as important- those with no risk factors had little to no atherosclerotic lesions



These computerized images from the Pathobiological Determinants of Atherosclerosis in Youth study are prevalence maps of fatty streaks and raised lesions, with color intensity reflecting the density and grade of the lesions for the two age groups and the number of risk factors. SOURCE: Edward E. Herderick and C. Alex McMahan for the Pathobiological Determinants of Atherosclerosis in Youth Study Group, unpublished observation.

Full Report of the Expert Panel on Integrated Guidelines for Pediatric Cardiovascular Health and Risk Reduction, National Heart, Lung, and Blood Institute (NHLBI). 2012.

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3. There is also evidence of end-organ damage in children with identifiable CVD risk factors

- Non-invasive measures of end-organ damage have been seen in several studies in children/young adults with CVD risk factors
  - Coronary calcium CT scores
  - Increased carotid intima-media thickness (cIMT) on ultrasound (US)
  - Reduced flow-mediated dilation (FMD) of brachial artery on US
  - Increased left ventricular mass (LVM) on echocardiography

Table 4. Risk of Coronary Artery Calcification From Stepwise Multiple Logistic Regression Analysis of Coronary Risk Factors*

	Odds Ratio (95% CI)
Childhood	
Weight	3.0 (1.3–6.7)
Young adult	
DBP	4.2 (1.9–9.6)
BMI	5.3 (2.2–13.0)
Total chol/HDL ratio	4.3 (1.7–10.7)
Most recent	
SBP	6.5 (2.6–16.5)
BMI	6.1 (2.4–15.1)
LDL	3.1 (1.3–7.6)
HDL	5.5 (2.0–15.2)

*Adjusted for age group and gender; highest decile (lowest for high density lipoprotein [HDL]) versus other nine deciles. CI = confidence interval; other abbreviations as in Table 1.

Mahoney, L.T. et al. Coronary Risk Factors Measured in Childhood and Young Adult Life Are Associated With Coronary Artery Calcification in Young Adults: The Muscatine Study. JACC. 27(2):277-284.

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3. There is also evidence of end-organ damage in children with identifiable CVD risk factors

- Study comparing 198 children with heterozygous FH to 64 unaffected siblings

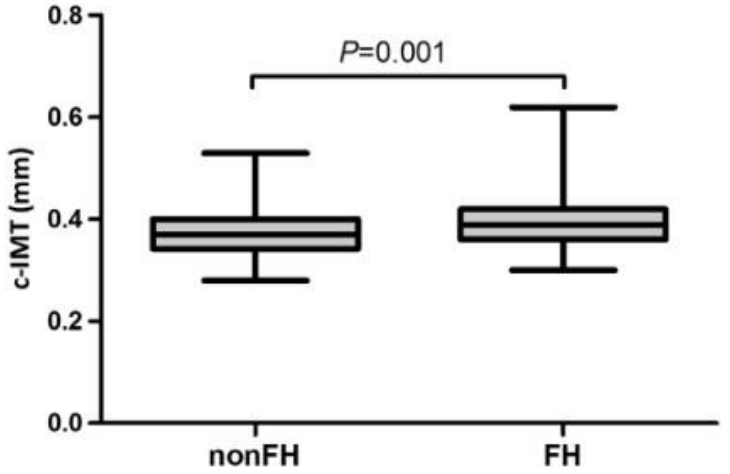

Figure 2 Mean for patients with FH and siblings without FH at baseline. c-IMT, carotid intima-media thickness; FH, familial hypercholesterolemia.

Usefulness of Electron Beam Tomography in Adolescents and Young Adults With Heterozygous Familial Hypercholesterolemia

Samuel S. Gidding, MD; Lisa C. Bookstein, MS, RD; Eva V. Chomka, MD

- 29 patients age 11-23 years underwent calcium coronary CT scans
- 7/29 (24%) had significant coronary calcium and 19/29 (66%) had some coronary calcium

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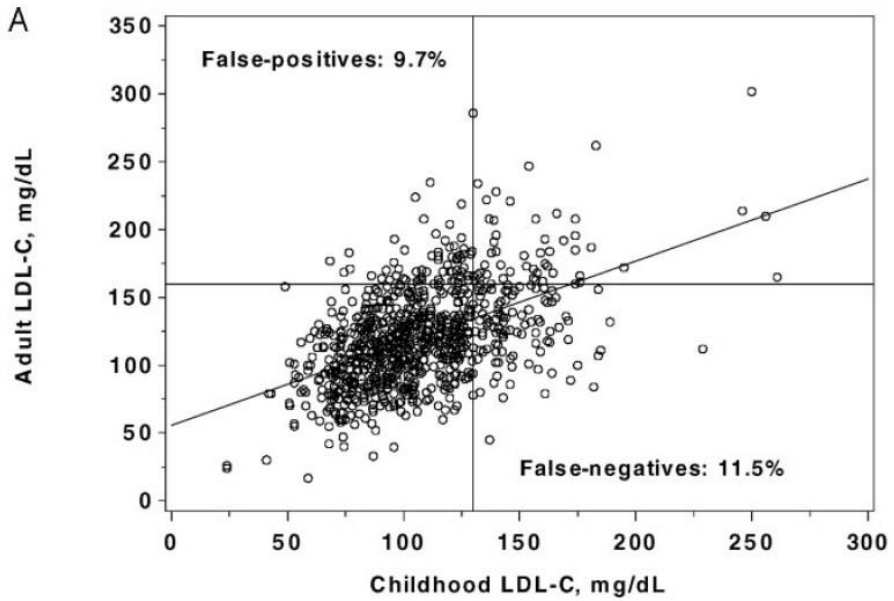
Kusters et al. J Clin Lipidol. 2013;7:408-413.

4. Risk factors track into adulthood

- Several studies have shown that childhood risk factors track into adulthood
  - Cholesterol tracks modestly
    - Obesity tracks very strongly
    - BP tracks modestly
    - Physical activity levels do not track well



Friedman, L.A. et al. Sensitivity and specificity of pediatric lipid determinations for adult lipid status: findings from the Princeton Lipid Research Clinics Prevalence Program Follow-up Study. Pediatrics. 2006;188(1):165-172.

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TABLE IV—*Mortality analysis: coronary heart disease (ICD (ninth revision) codes 410-414)*

Age (years)	Person years of observation	Observed deaths	Expected deaths	Standardised mortality ratio	95% Confidence interval
			Men		
20-39	439	5	0·06	8975**	2710 to 19400
40-59	653	4	1·28	312	85 to 800
60-74	133	1	1·34	75	2 to 416
20-74	1226	10	2·67	374***	180 to 689
			Women		
20-39	335	1	0·01	16039*	253 to 55700
40-59	447	4	0·26	1538***	419 to 3940
60-74	225	0	0·94		
20-74	1008	5	1·21	413*	134 to 964
			Men and women		
20-39	774	6	0·06	9686***	3670 to 21800
40-59	1110	8	1·54	519***	224 to 1020
60-74	358	1	2·28	44	1 to 244
20-74	2234	15	3·88	386***	210 to 639

*p<0·05. **-<0·01. ***p<0·001.

TABLE V—*Mortality analysis: all causes*

Age (years)	Person years of observation	Observed deaths	Expected deaths	Standardised mortality ratio	95% Confidence interval
			Men		
20-39	439	5	0·47	1065***	345 to 2480
40-59	653	6	3·36	179	65 to 389
60-74	133	4	3.61	111	30 to 284
20-74	1226	15	7·44	202*	113 to 333
			Women		
20-39	335	1	0·20	511*	127 to 279
40-59	447	7	1·79	391**	157 to 806
60-74	225	1	3·67	27	1 to 152
20-74	1008	9	5·66	159	73 to 302
			Men and women		
20-39	774	6	0·67	902***	329 to 1950
40-59	1110	13	5·15	253**	134 to 432
60-74	358	5	7·28	69	22 to 160
20-74	2234	24	13.10	183**	117 to 273

*p<0·05. **p<0·01. ***p<0·001.

5. FH and CVD Risk

Risk of fatal coronary heart disease in familial hypercholesterolaemia

Scientific Steering Committee on behalf of the Simon Broome Register Group

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5. FH and CVD Risk

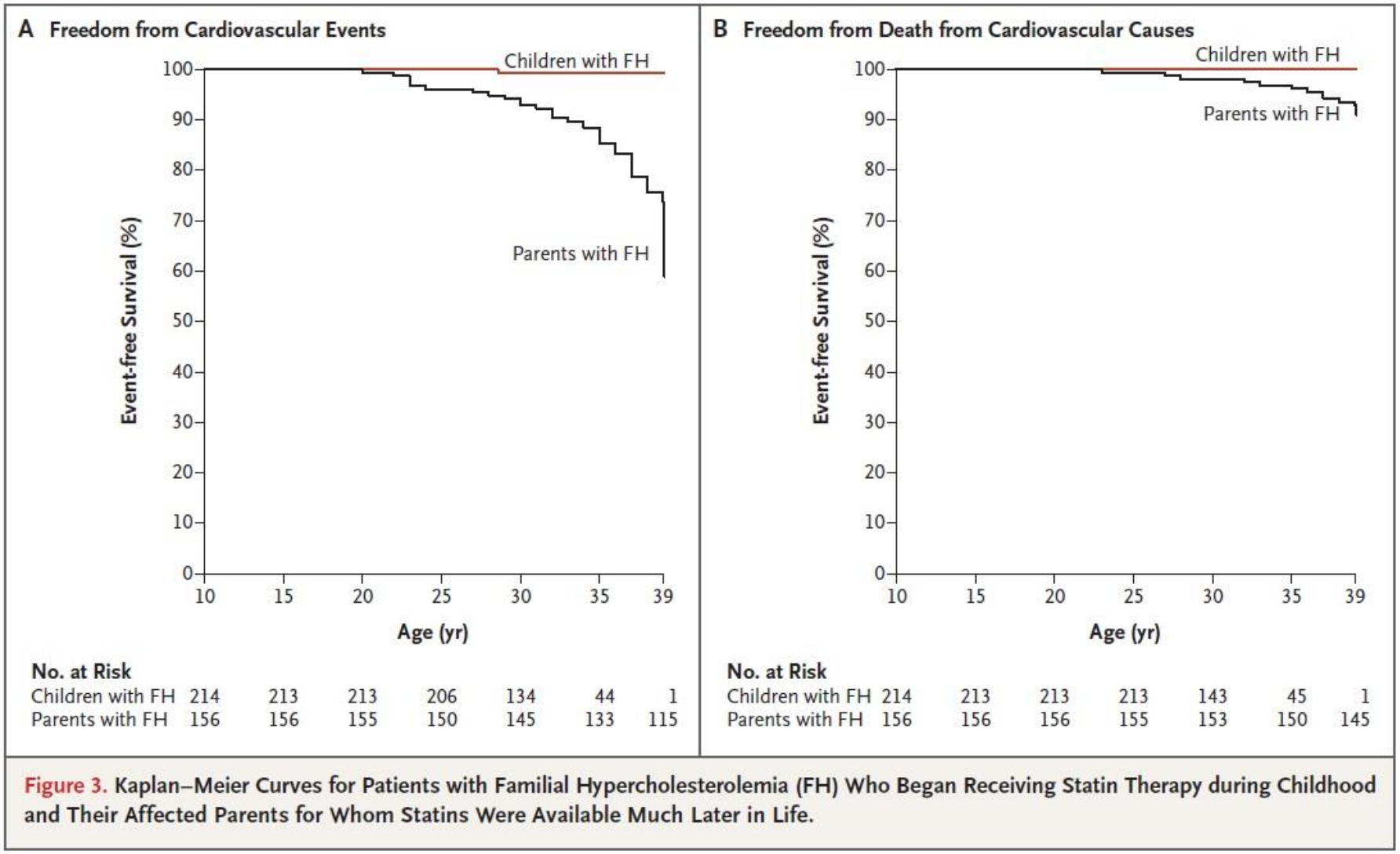

Figure 3. Kaplan–Meier Curves for Patients with Familial Hypercholesterolemia (FH) Who Began Receiving Statin Therapy during Childhood and Their Affected Parents for Whom Statins Were Available Much Later in Life.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

20-Year Follow-up of Statins in Children with Familial Hypercholesterolemia

Ilse K. Luirink, M.D., Albert Wiegman, M.D., Ph.D., D. Meeike Kusters, M.D., Ph.D., Michel H. Hof, Ph.D., Jaap W. Groothoff, M.D., Ph.D., Eric de Groot, M.D., Ph.D., John J.P. Kastelein, M.D., Ph.D., and Barbara A. Hutten, Ph.D.

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Screening and Long Term Outcomes

- There is good evidence that atherosclerosis begins in childhood and is associated with risk factors (including elevated cholesterol)
- Risk factors are also associated with end organ damage in childhood
- Children with very high LDL (i.e. those with FH) have increased risk for early CVD
  - Early treatment with statins appears to decrease risk of CVE

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History of Screening Recommendations

Evolution of United States pediatric lipid screening recommendations.

Guideline	Recommendation for pediatric lipid screening	Recommendation against pediatric lipid screening
1989 AAP Committee on Nutrition	Selective screening of children 2 years and older.[25]	
1992 NIH National Cholesterol Education Panel	Selective screening of children 2 years and older.[26]	
2007 USPSTF	Sparse information regarding the epidemiology and pathophysiology of "familial dyslipidemia."[16]	Insufficient evidence to screen individuals 20 years and younger.[16]
2011 NHLBI / AAP	Universal screening of children aged 9–11 and 17–21.[18] Targeted screening of children aged 2–8 or 12–16.[18]	
2011 NLA	Universal screening of children aged 9–11 with all patients screened by age 20.[27] Selective screening beginning at age 2.[27]	
2014 AAP Bright Futures	Endorses 2011 NHLBI / AAP recommendations.[28]	
2015 NLA	Selective screening of children 2 years and older.[29]	
2016 USPSTF	Universal screening of children aged 9–11 and at 20 years old.[29] First mention of expanded details on the two most common forms of dyslipidemia in children: FH and "multi-factorial dyslipidemia."[1,16,17]	Insufficient evidence to screen individuals 20 years and younger.[17]
2017 AACE / ACE	Selective screening of children at ages under 3, between 9 and 11, and at 18. Patients older than 16 should be screened every 5 years.	Endorses previous NLA, AAP, and NHLBI guidelines but states "universal screening may be reasonable."[30]
2018 AHA / ACC multi-society	Selective screening of children 2 years and older.[19]	Universal screening in children ages 9- to 11- years old and again at 17- to 21- years old *"may be reasonable* given the substantial benefits of identifying severe hypercholesterolemia … including FH, and possible benefits of lifestyle counseling for multi-factorial dyslipidemias."[19]
2023 USPSTF	Includes details of "FH prevalence, polygenic variants, and health outcomes."[1]	Insufficient evidence to screen individuals 20 years and younger.[1]

Abbreviations: American Academy of Pediatrics (AAP); National Institutes of Health (NIH); United States Preventive Services Task Force (USPSTF); National Heart, Lung, and Blood Institute (NHLBI); National Lipid Association (NLA); American Association of Clinical Endocrinologists (AACE); American College of Endocrinology (ACE); American Heart Association (AHA); American College of Cardiology (ACC).

J Clin Lipidol. 2024 ; 18(3): e297–e307. doi:10.1016/j.jacl.2024.02.008.

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Screening for Lipid Disorders

CHOLESTEROL CLINICAL PRACTICE GUIDELINES

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

4.4.4.3. Children and Adolescents

Recommendations for Children and Adolescents

IIa	C-LD	6. In children and adolescents with obesity or other metabolic risk factors, it is reasonable to measure a fasting lipid profile to detect lipid disorders as components of the metabolic syndrome.[S4.4.4.3-25–S4.4.4.3-27]
IIb	B-NR	7. In children and adolescents without cardiovascular risk factors or family history of early CVD, it may be reasonable to measure a fasting lipid profile or nonfasting non HDL-C once between the ages of 9 and 11 years, and again between the ages of 17 and 21 years, to detect moderate to severe lipid abnormalities.[S4.4.4.3-19,S4.4.4.3-21,S4.4.4.3-27–S4.4.4.3-29]

*Family history of early CVD is defined here as MI, documented angina, or atherosclerosis by angiography in parents, siblings, grandparents, aunts, or uncles (<55 years of age for men, <65 years of age for women).

†TC ≥240 mg/dL (≥6.2 mmol/L), LDL-C ≥190 mg/dL (≥4.9 mmol/L), non–HDL-C ≥220 mg/dL (≥5.7 mmol/L), or known primary hypercholesterolemia.

IIa	B-NR	4. In children and adolescents with a family history of either early CVD* or significant hypercholesterolemia,† it is reasonable to measure a fasting or nonfasting lipoprotein profile as early as age 2 years to detect FH or rare forms of hypercholesterolemia.[S4.4.4.3-17–S4.4.4.3-21]

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AAP Bright Futures

Bright Futures Medical Screening Reference Table
Adolescence Visits (11 Through 21 Years)

Universal Screening	Action
Cervical Dysplasia (all young women at the 21 Year Visit)	Pap smear
Depression: Adolescent (beginning at the 12 Year Visit)	Depression screen[a]
Dyslipidemia (once between 9 and 11 Year and 17 and 21 Year Visits)	Lipid profile
Hearing (once between 11 and 14 Year, 15 and 17 Year, and 18 and 21 Year Visits)	Audiometry, recommended to include 6,000 and 8,000 Hz frequencies
Hepatitis C Virus (HCV) Infection (once between 18 and 79 years)	HCV antibody (anti-HCV) test
HIV (once between 15 and 18 Year Visits)	HIV test[b]
Tobacco, Alcohol, or Drug Use	Tobacco, alcohol, or drug use assessment
Vision (12 and 15 Year Visits)	Objective measure with age-appropriate visual acuity measurement using HOTV or LEA symbols, Sloan letters, or Snellen letters

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Screening for dyslipidemia in obese children

CLINICAL PRACTICE GUIDELINE Guidance for the Clinician in Rendering Pediatric Care

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents With Obesity

KAS 5. Pediatricians and other PHCPs should evaluate for dyslipidemia by obtaining a fasting lipid panel in children 10 y and older with overweight (BMI ≥ 85th percentile to <95th percentile) and obesity (BMI ≥ 95th percentile) and may evaluate for dyslipidemia in children 2 through 9 y of age with obesity.

Aggregate Evidence Quality	Grade B: Children ≥10 y of Age With Obesity. Grade C: Children 2 Through 9 y of Age

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Screening for Lipid Disorders

Table 9–1. **ACCEPTABLE, BORDERLINE HIGH, AND HIGH PLASMA LIPID, LIPOPROTEIN, AND APOLIPOPROTEIN CONCENTRATIONS (MG/DL) FOR CHILDREN AND ADOLESCENTS***

Note: Values given are in mg/dL. To convert to SI units, divide the results for total cholesterol (TC), low-density lipoprotein cholesterol (LDL–C), high-density lipoprotein cholesterol (HDL–C), and non-HDL–C by 38.6; for triglycerides (TG), divide by 88.6.

Category	Acceptable	Borderline High	High†
TC	< 170	170–199	≥ 200
LDL-C	< 110	110–129	≥ 130
Non-HDL-C	< 120	120–144	≥ 145
Apolipoprotein B (ApoB)	< 90	90–109	≥ 110
TG			
0-9 years	< 75	75–99	≥ 100
10-19 years	< 90	90–129	≥ 130

Category	Acceptable	Borderline Low	Low†
HDL-C	> 45	40–45	< 40
Apolipoprotein A–1 (ApoA-1)	>120	115–120	<115

In adults, better predictor of CVD than LDL. In children equal to better predictor of adult dyslipidemia and fatty streaks. Measures cholesterol content of atherogenic apoB lipoproteins (chylomicrons, VLDL, IDL, LDL and remnants)

Full Report of the Expert Panel on Integrated Guidelines for Pediatric Cardiovascular Health and Risk Reduction, National Heart, Lung, and Blood Institute (NHLBI). 2012.

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Screening for Lipid Disorders

- Changes in lipid levels during childhood

	Males	Females
Birth- 2 years	Initially very low and slowly increase	
2 years - puberty	Stable	
Puberty	↓ TC and LDL	↓ TC and LDL
	↓ HDL	No Δ HDL
Young adult	↑ TC and LDL	↑ TC and LDL

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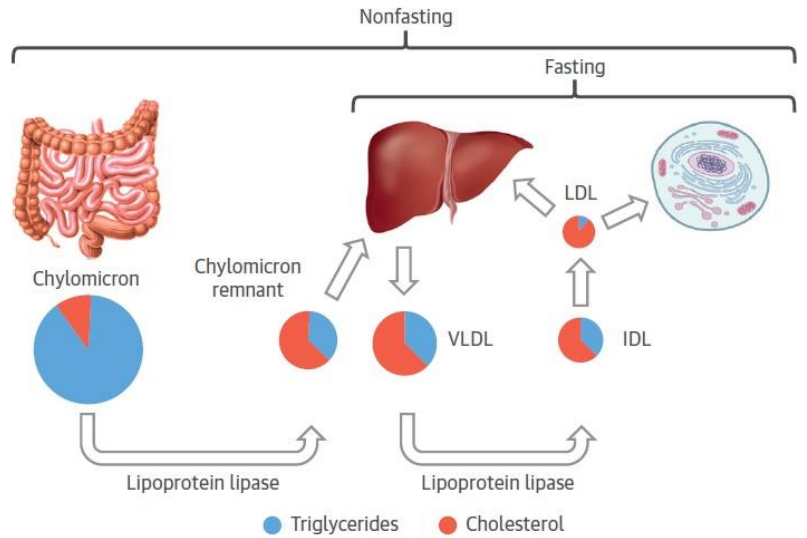
Screening for Lipid Disorders

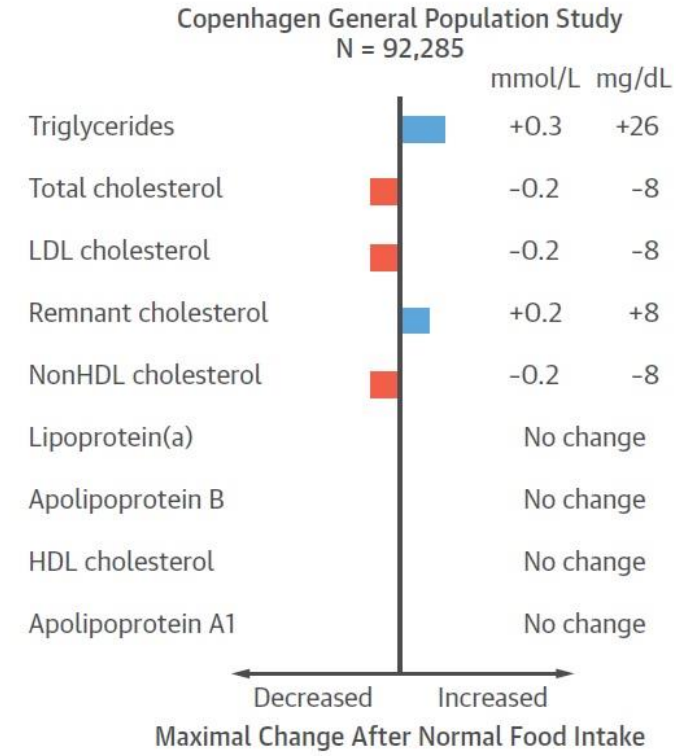
- Fasting vs Nonfasting lipid panels

FIGURE 2 Atherogenic Lipoproteins Present in the Blood During Periods of Fasting and Nonfasting



During fasting, only liver-derived lipoproteins are present in plasma, whereas in the nonfasting state, intestinal-derived lipoproteins are likewise found in plasma. IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein.

FIGURE 6 Mean Maximal Change in Lipids, Lipoproteins, and Apolipoproteins in Random, Nonfasting Compared With Fasting Lipid Profiles in Individuals in the General Population



These changes all are clinically insignificant. Adapted with permission from Nordestgaard et al. (5). Abbreviations as in Figures 2 and 3.

Nordestgaard, B.G. A Test in Context: Lipid Profile, Fasting Versus Nonfasting. JACC.2017;70(13):1637-46.

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Familial Hypercholesterolemia (FH)

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Types of dyslipidemia

- Primary inherited
  - Familial hypercholesterolemia (FH)
  - Other rare monogenic dyslipidemias
    - Sitosterolemia
    - Familial chylomicronemia syndrome (FCS)

- Multifactorial dyslipidemia
  - Polygenic
  - Lifestyle
  - Co-morbidities

- Secondary dyslipidemias
  - Hypothyroidism
  - Nephrotic Syndrome
  - Medications

Based on classification proposed by: Civeria et al. *J Clin Lipidol*. 2022;16:813-821.

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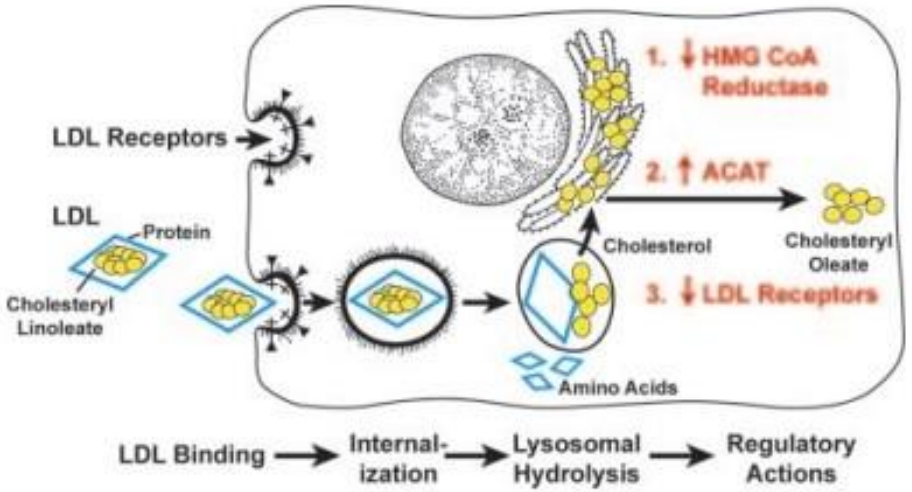
Familial Hypercholesterolemia (FH)



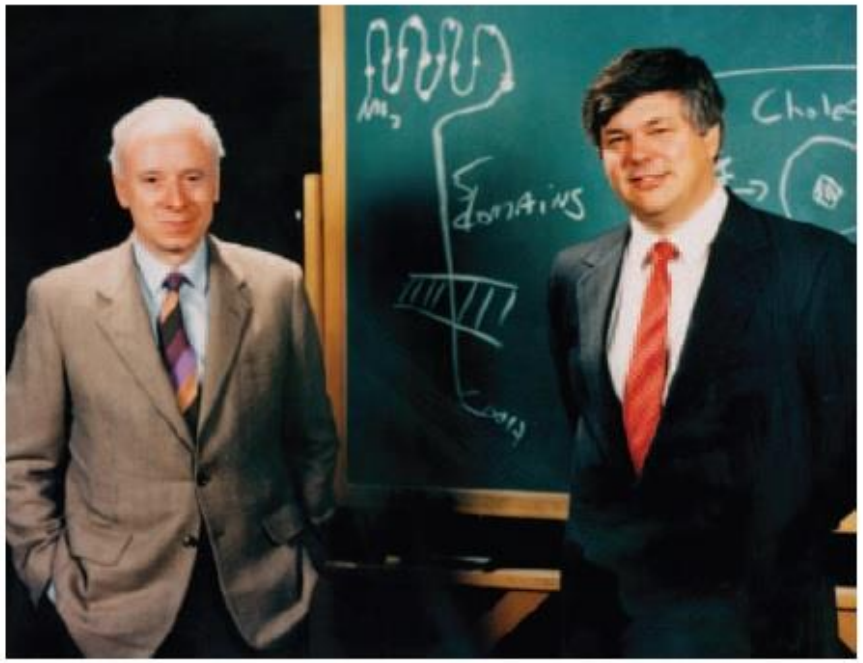


Figure 6. Joseph L. Goldstein (left) and Michael S. Brown on the day of announcement of their Nobel Prize in Physiology or Medicine on October 15, 1985.

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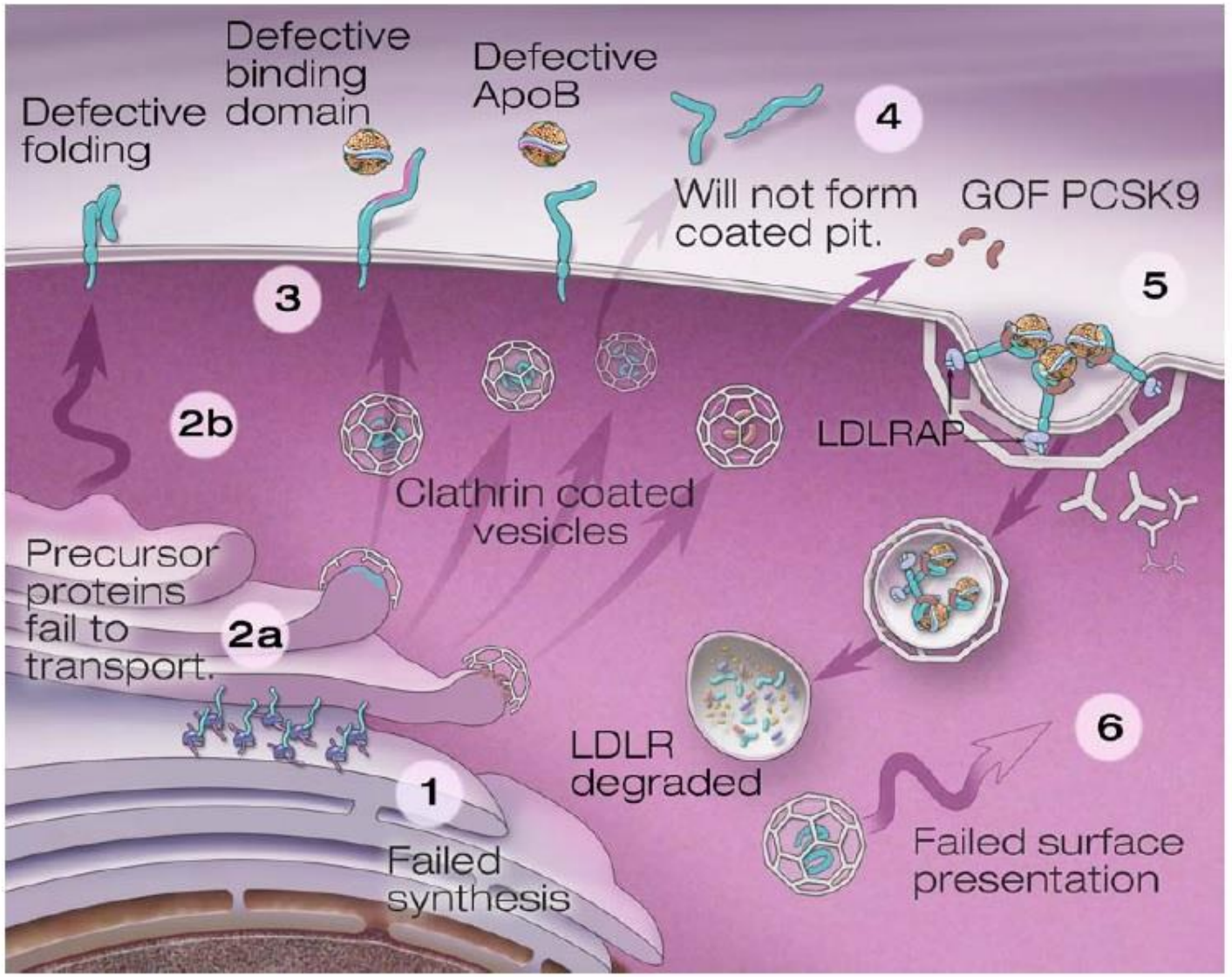
Goldstein and Brown. *Arterioscler Thromb Vasc Biol*.2009;29:431-438

FH



Gidding, S.S. et al. The Agenda for Familial Hypercholesterolemia A Scientific Statement From the American Heart Association. Circulation. 2015;132:2167-2192.

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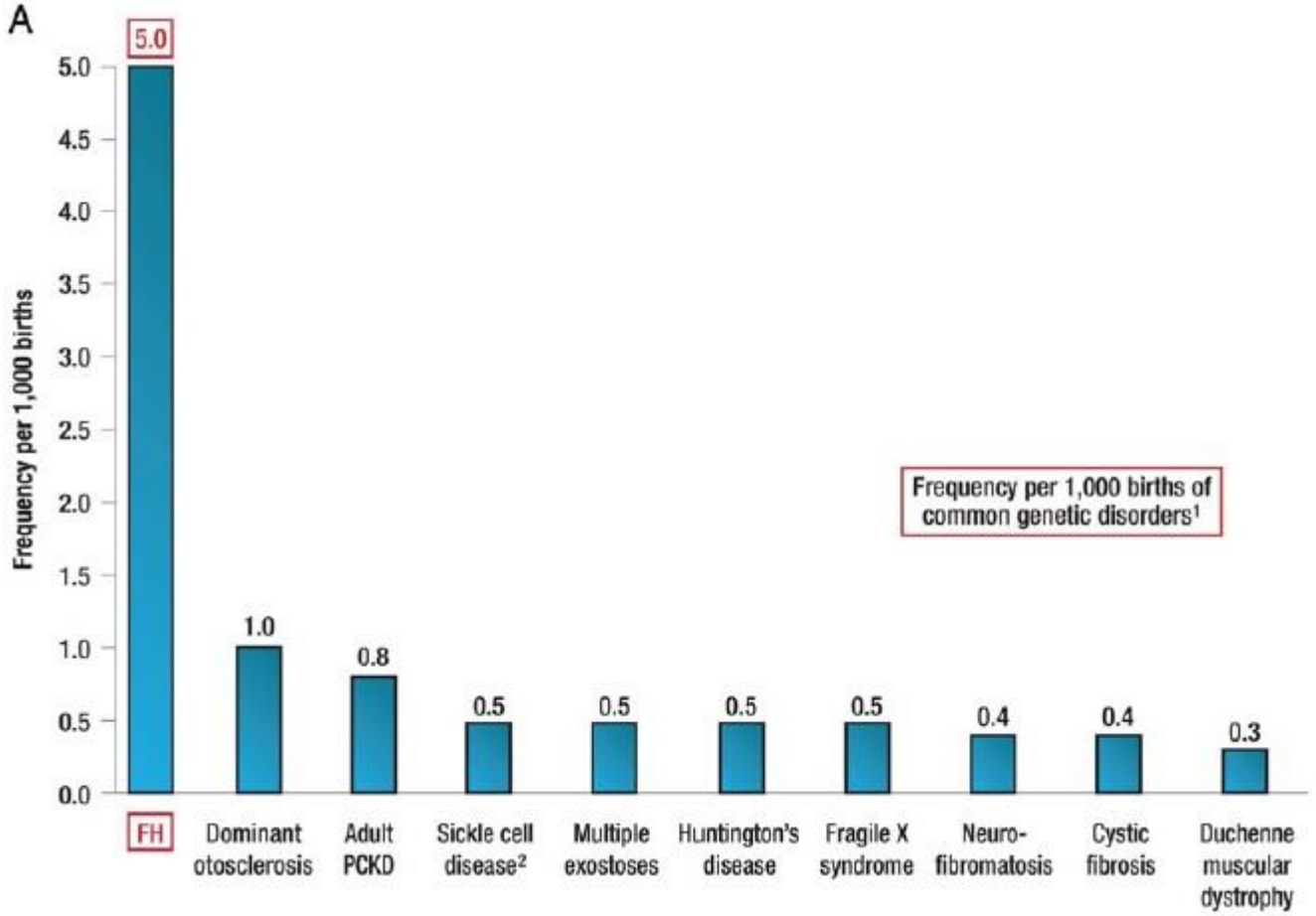
Prevalence of FH

- Heterozygous FH: estimated 1:200-500
- Homozygous FH: estimated 1:160,00-1,000,000



Wiegman et al. Eur Heart J. 2015;36:2425-2437.

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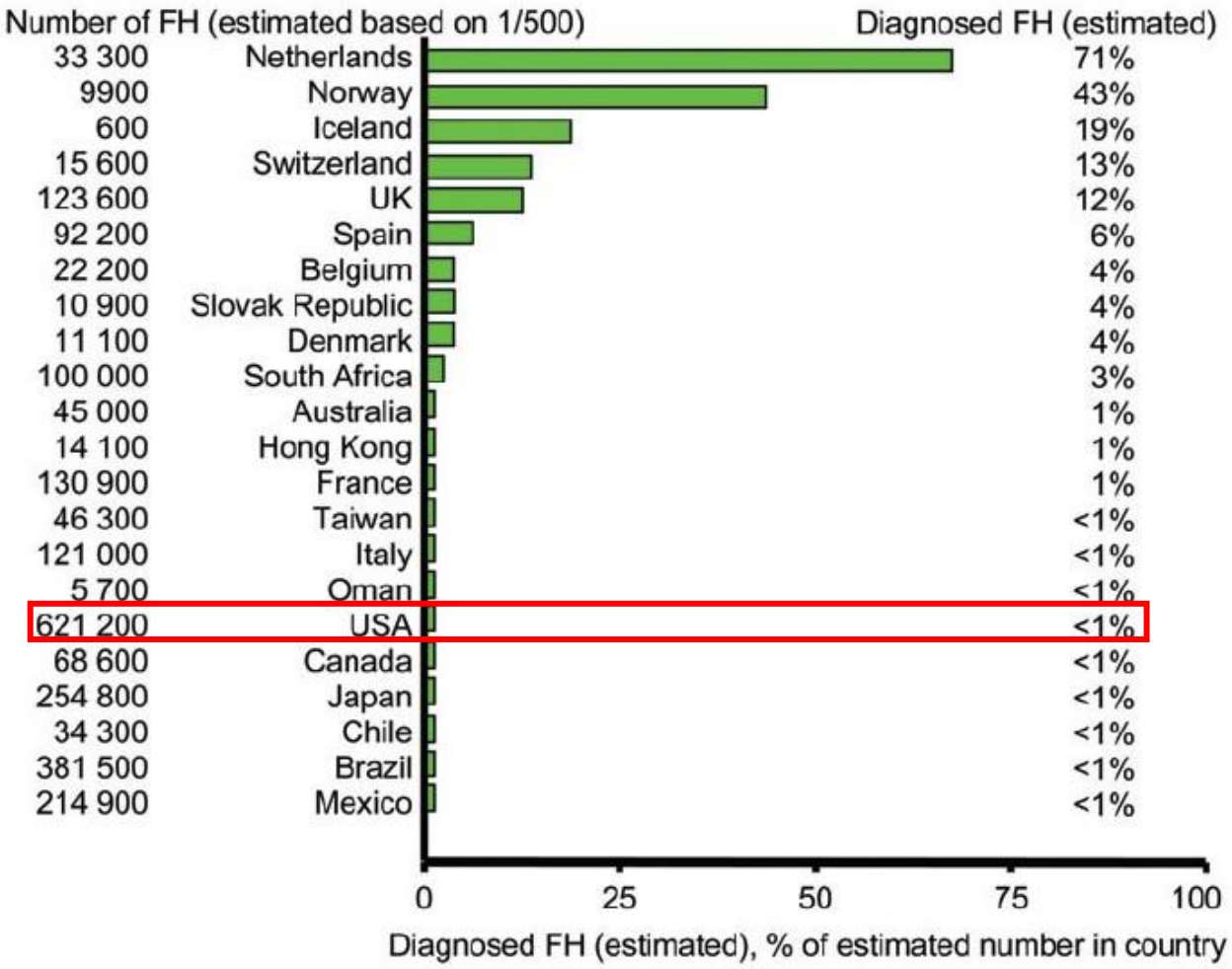
Underdiagnosis of FH



Nordestgaard et al. Eur Heart J. 2013;34:3478-3490.

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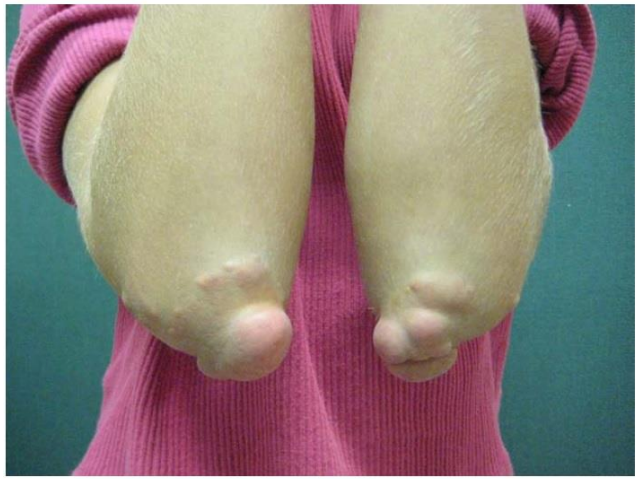
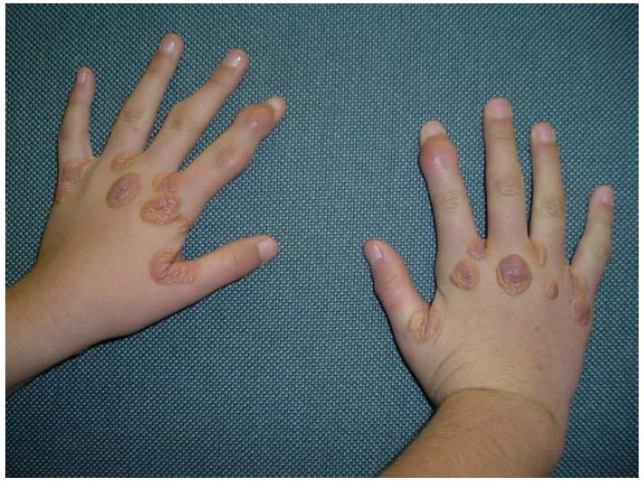
Clinical Presentation

- Heterozygous FH: Asymptomatic in childhood
- Homozygous FH: CV events as early as age 4 years





Gidding, S.S. et al. The Agenda for Familial Hypercholesterolemia A Scientific Statement From the American Heart Association. Circulation. 2015;132:2167-2192.

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Diagnosis of FH

- Clinical diagnosis of heterozygous FH= elevated LDL + FMHx

LDL level	Family History
≥ 160 mg/dL in children	1st degree relative with similar LDL cholesterol levels OR
≥ 190 mg/dL in adults	Premature coronary artery disease [usually defined as < 55 years in males; < 65 years in females] OR
	Positive genetic testing for LDL raising gene defect (LDL-R, apoB, or PCSK9)

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Treatment of FH

CHOLESTEROL CLINICAL PRACTICE GUIDELINES

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

IIa	B-R	3. In children and adolescents 10 years of age or older with an LDL-C level persistently 190 mg/dL or higher (≥4.9 mmol/L) or 160 mg/dL or higher (4.1 mmol/L) with a clinical presentation consistent with FH (see Section 4.2.) and who do not respond adequately with 3 to 6 months of lifestyle therapy, it is reasonable to initiate statin therapy.[S4.4.4.3-13–S4.4.4.3-16]

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Society	Guideline (year published)	Threshold for initiation	Age to initiate statins	Goal
NLHBI	Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction (2011)	LDL ≥ 190 mg/dL; or as low as ≥ 130 mg/dL if multiple risk factors	≥ 10 years	LDL < 130 mg/dL
International FH Foundation	Integrated guidance on the care of FH (2014)	Dx of FH	≥ 8 years Consider earlier if risk factors	< 155 mg/dL if ≤ 10 years < 135 mg/dL if > 10 years
AHA	Agenda for FH (2015)	Dx of FH	≥ 8 years	Not identified
AHA/ACC multisociety	Guidelines on Management of Blood Cholesterol (2018)	LDL ≥ 160 mg/dL + clinical presentation of FH or LDL ≥ 190 mg/dL	≥ 10 years	Not identified
ESC/EAS	Guidelines for the management of dyslipidaemias (2019)	Dx of FH	Considered at ≥ 6 years Definitely start at 8 years	≥ 50% reduction if ≤ 10 years < 135 mg/dL if > 10 years
IAS	Guidance for implementing best practice in the care of FH (2023)	Dx of FH	≥ 8 years Consider at < 8 years if LDL persistently ≥ 190 mg/dL	LDL ≤ 135 mg/dL or 50% reduction LDL ≤ 100 mg/dL if risk factors

Article #1

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

20-Year Follow-up of Statins in Children with Familial Hypercholesterolemia

Ilse K. Luirink, M.D., Albert Wiegman, M.D., Ph.D.,
D. Meeike Kusters, M.D., Ph.D., Michel H. Hof, Ph.D.,
Jaap W. Groothoff, M.D., Ph.D., Eric de Groot, M.D., Ph.D.,
John J.P. Kastelein, M.D., Ph.D., and Barbara A. Hutten, Ph.D.

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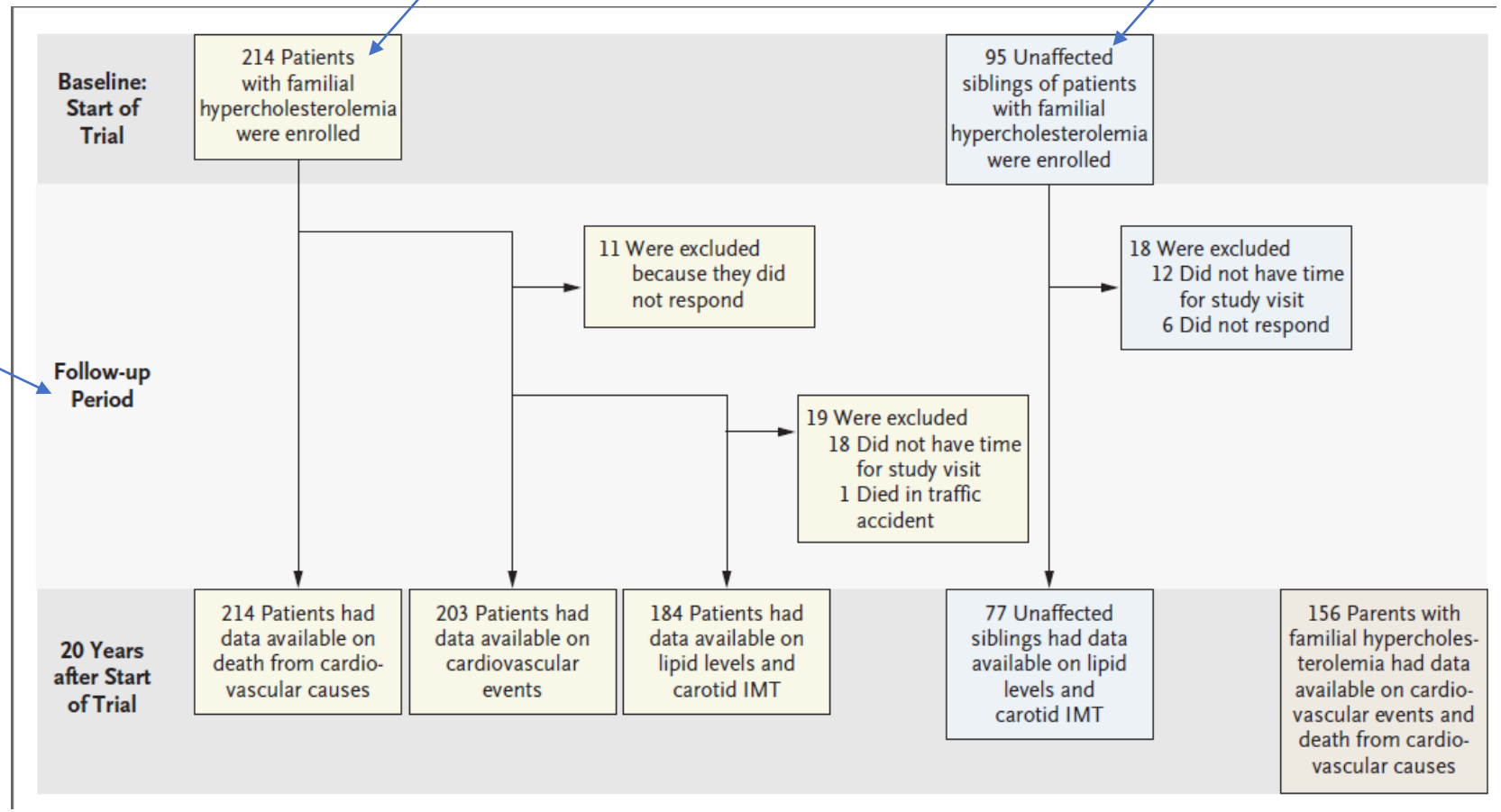
Cohort

Mean age at baseline= 13 yr
Mean age at f/u= 31.7 yr

Mean age at baseline= 12.9 yr
Mean age at f/u= 31.6 yr

20 years



All patients and sibs underwent genetic testing. 98% of patients were positive for P variant; all sibs were negative

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Demographics and Clinical Characteristics

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline and at 20-Year Follow-up.*

Characteristic	At Baseline			At Follow-up		
	Patients with FH (N=214)	Unaffected Siblings (N=95)	Difference (95% CI)†	Patients with FH (N=184)	Unaffected Siblings (N=77)	Difference (95% CI)†
Age — yr	13.0±2.9	12.9±2.9	0.1 (−0.8 to 0.6)	31.7±3.2	31.6±3.0	0.1 (−0.9 to 0.6)
Male sex — no. (%)	100 (47)	50 (53)	−6 (−18 to 6)	88 (48)	43 (56)	−8 (−21 to 5)
Height — m	1.57±0.15	1.57±0.15	0.00 (−0.05 to 0.03)	1.75±0.10	1.76±0.09	−0.01 (−0.04 to 0.01)
Weight — kg	49.4±15.1	48.7±16.6	0.7 (−3.3 to 4.6)	77.6±14.6	79.4±14.2	−1.7 (−5.5 to 2.1)
Body-mass index‡	19.6±3.6	19.1±3.7	0.5 (−0.4 to 1.4)	25.3±4.2	25.5±3.9	−0.2 (−1.2 to 0.9)
Blood pressure — mm Hg						
Systolic	110.2±12.4	110.1±12.0	0.1 (−2.8 to 3.0)	121.0±12.3	121.5±12.5	−0.5 (−3.8 to 2.8)
Diastolic	61.5±8.6	62.2±8.5	−0.8 (−2.8 to 1.3)	74.2±8.1	75.1±9.0	−0.9 (−3.2 to 1.4)
Risk factors — no. (%)						
Diabetes	0	0	—	1 (1)	2 (3)	−2 (−6 to 2)
Hypertension	0	0	—	16 (9)	10 (13)	−4 (−13 to 4)
Current smoking	24 (11)	6 (6)	5 (−2 to 11)	41 (22)	26 (34)	−11 (−24 to 1)
Statin use — no. (%)	0	0	—	146 (79)	1 (1)	78 (70 to 83)
Cholesterol — mg/dl						
Total	300.6±51.3	166.9±24.9	133.7 (125.1 to 147.0)	232.6±75.6	201.5±38.6	31.1 (125.1 to 147.0)
LDL	237.3±50.0	98.5±22.1	138.8 (130.7 to 147.0)	160.7±72.6	121.9±37.0	38.8 (25.5 to 52.1)
HDL	47.8±10.7	54.8±13.8	−7.0 (−10.2 to −3.7)	53.3±13.9	56.3±16.1	−3.0 (−7.1 to 1.1)
Apolipoprotein — mg/dl						
B-100	141.2±30.7	82.7±18.4	58.5 (52.8 to 64.2)	117.7±41.5	95.1±28.6	22.6 (13.9 to 31.4)
A-I	124.7±19.3	137.8±24.6	−13.1 (−19.1 to −7.1)	151.7±38.5	161.5±38.5	−9.9 (−20.1 to 0.4)
Lipoprotein(a) — mg/liter§						
Median	121	79	20 (−43 to 83)	141	96	31 (−47 to 108)
Interquartile range	46 to 265	37 to 248		64 to 299	48 to 326	

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Follow-up

- At follow-up patients with FH:
  - 79% taking statins
  - Initiated at mean age 14 years (+/- 13.1 years)

- Parents (with FH)
  - Based on when statin introduced (1988) earliest could have started therapy= mean age 32 years (+/- 3 years; range 20-51 years old))

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Lipid Levels at Follow-up

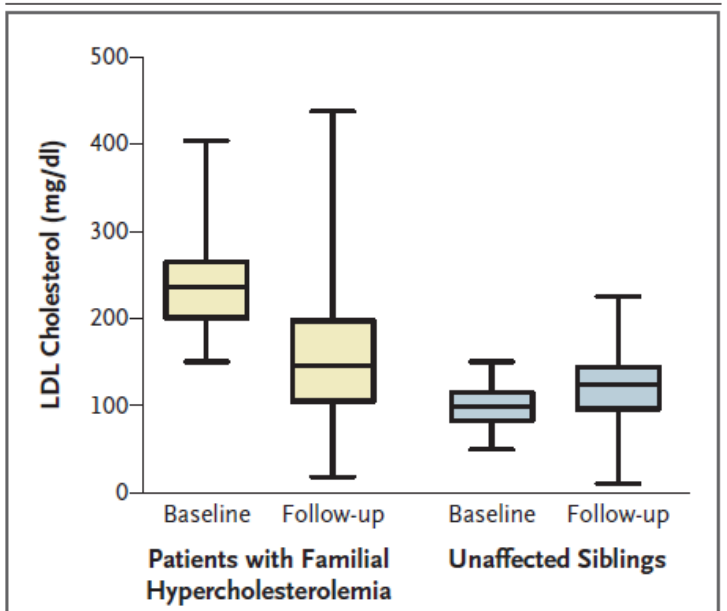

Figure 2. Low-Density Lipoprotein (LDL) Cholesterol Levels of Patients with Familial Hypercholesterolemia and Their Unaffected Siblings at Baseline and at Follow-up.

The top and bottom borders of each box indicate the interquartile range, the horizontal bar within each box indicates the median, and the I bars indicate the range of observations. To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

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Benefits of Earlier Treatment

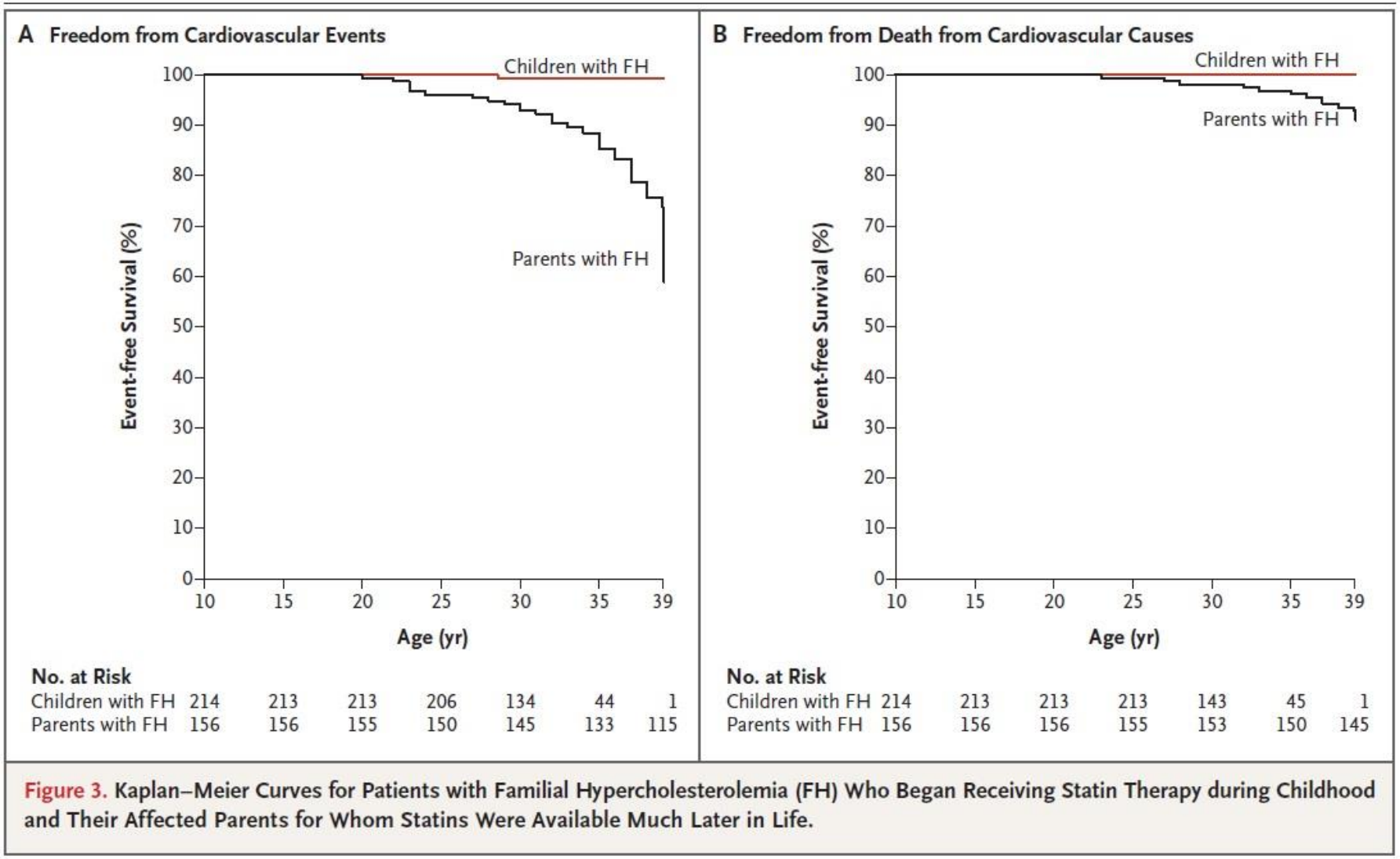

Figure 3. Kaplan–Meier Curves for Patients with Familial Hypercholesterolemia (FH) Who Began Receiving Statin Therapy during Childhood and Their Affected Parents for Whom Statins Were Available Much Later in Life.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

20-Year Follow-up of Statins in Children with Familial Hypercholesterolemia

Ilse K. Luirink, M.D., Albert Wiegman, M.D., Ph.D., D. Meeike Kusters, M.D., Ph.D., Michel H. Hof, Ph.D., Jaap W. Groothoff, M.D., Ph.D., Eric de Groot, M.D., Ph.D., John J.P. Kastelein, M.D., Ph.D., and Barbara A. Hutten, Ph.D.

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Statins

Article #2

Cochrane Library

Cochrane Database of Systematic Reviews

Statins for children with familial hypercholesterolemia (Review)

Vuorio A, Kuoppala J, Kovanen PT, Humphries SE, Tonstad S, Wiegman A, Drogari E, Ramaswami U

Vuorio A, Kuoppala J, Kovanen PT, Humphries SE, Tonstad S, Wiegman A, Drogari E, Ramaswami U.
Statins for children with familial hypercholesterolemia.
Cochrane Database of Systematic Reviews 2019, Issue 11. Art. No.: CD006401.
DOI: 10.1002/14651858.CD006401.pub5.

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Treatment for Dyslipidemias

Preventive Cardiology: Companion to Braunwald's Heart Disease. Roger S. Blumenthal, JoAnne M. Foody, Nathan D. Wong Eds. 2011. Elsevier, Philadelphia.

HMG-CoA reductase inhibitors: statins

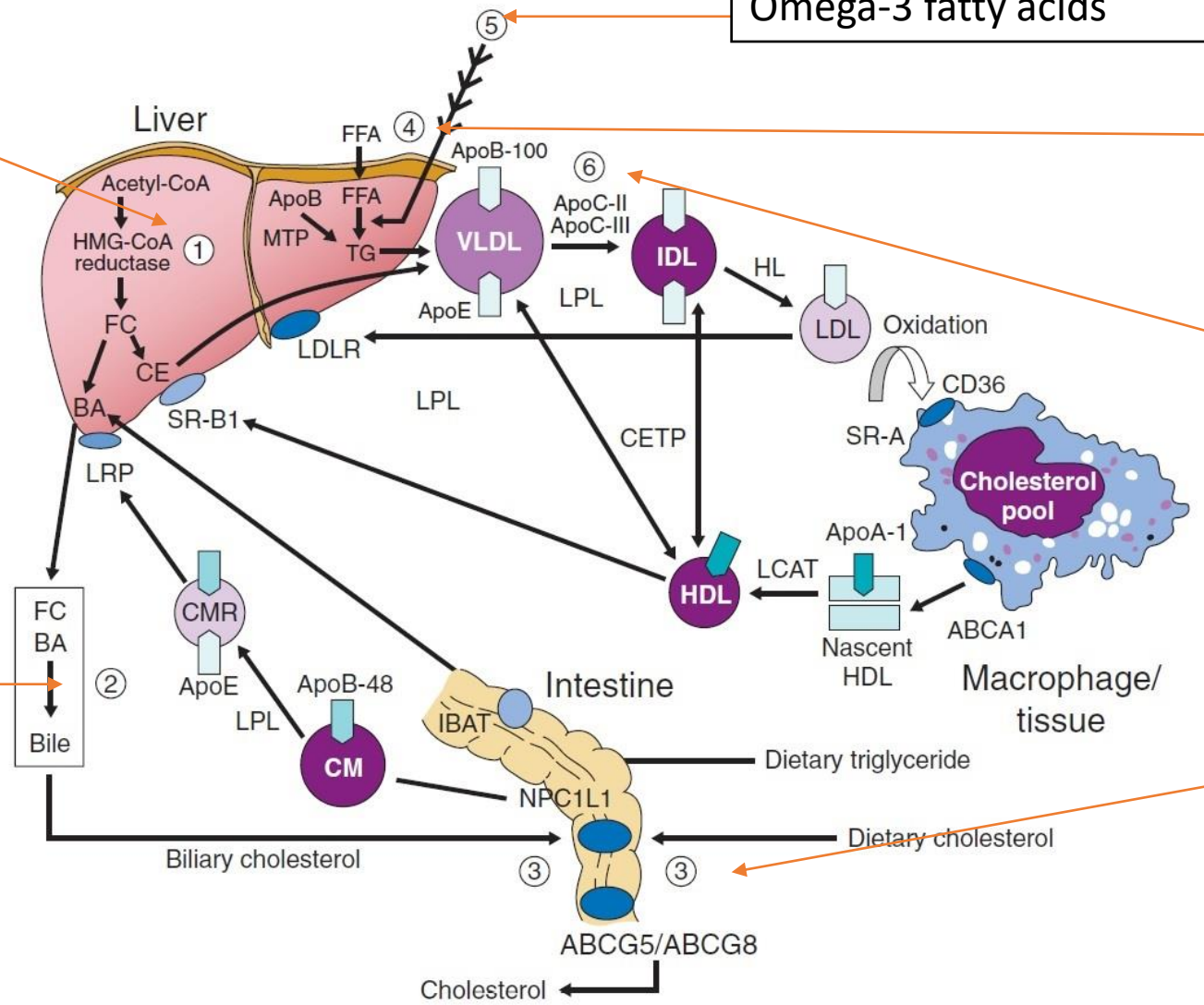
Omega-3 fatty acids

Nicotinic acid derivative (niacin)

Fibrates: fenofibrate, gemfibrozil

Bile acid sequestrants: cholestyramine, colestipol, colsevelam

Cholesterol absorption inhibitor: ezetimibe



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Statins

- Lower LDL via 3 mechanisms:
  - Decreased intrahepatic cholesterol → ↑ LDL-R→ ↑ uptake of circulating LDL
  - ↑ uptake of circulating VLDL by LDL-R
  - Decreased intrahepatic VLDL synthesis
- Also appear to improve endothelial function, promote plaque stability, decrease lipoprotein oxidation, and decrease inflammation

Statins

- Side effects
  - AST/ALT elevation
    - Usually asymptomatic and not associated with liver disease
    - Reversed with medication change
  - Myopathy/CK elevations
    - Severe myopathy (CK > 10x normal) relatively rare in adults (1 in 10,000)
    - More common if Atorvastatin/Lovastatin/Simvastatin + drugs that inhibit 3A4 isoform of cytochrome P450
  - Teratogenic (all pregnancy category X)
  - Drug-drug interactions
    - Cytochrome P-450
    - Potential interactions
      - Fibrates
      - Azol antifungals
      - Macrolide antibiotics
      - HIV protease inhibitors
      - Some antiarrhythmics- amiodarone, verapamil, diltiazem

Goals

- Controlled clinical studies assessing:
  - Primary outcomes:

1. Change in carotid intima-media thickness
2. Change in serum LDL cholesterol level
3. Change in measures of growth and maturation, e.g. age of onset of puberty

  - Secondary outcomes:

1. Liver dysfunction: change in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels
2. Myopathy: change in serum creatine kinase (CK) levels
3. Rhabdomyolysis (degeneration of skeletal muscle tissue) or death due to rhabdomyolysis

Change in endothelial function (measured by flow-mediated dilation of the brachial artery)

5. Change in serum total and high-density lipoprotein (HDL) cholesterol and triglyceride (TG) level
6. Quality of life
7. Compliance to study medication
8. Other adverse events which may be associated with statins

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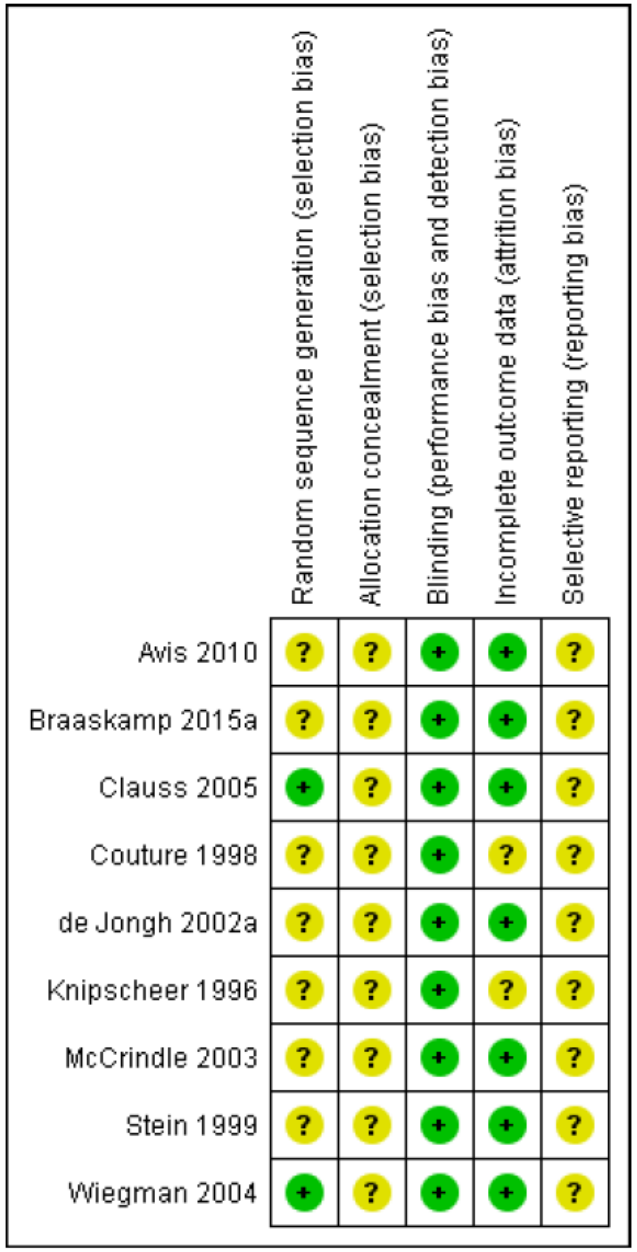
Included studies

- 26 identified



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Outcomes

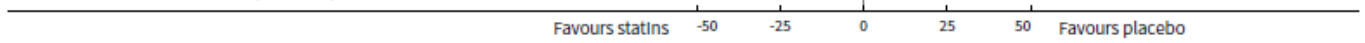
1. cIMT- only one study reported (small, but significant improvement). Considered low quality evidence

Outcomes

2. LDL lowering

Analysis 1.2. Comparison 1 Statins versus control, Outcome 2 Change in serum LDL cholesterol level (%).

Study or subgroup	Statins N	Statins Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.2.1 At 1 month							
Braaskamp 2015a	76	-31 (0)	27	1 (0)			Not estimable
Clauss 2005	35	-23 (20)	19	3 (17)		29.74%	-26[-36.12,-15.88]
Knipscheer 1996	53	-27 (10)	18	-3 (13)		70.26%	-24[-30.58,-17.42]
Subtotal ***	**164**		**64**			**100%**	**-24.59[-30.11,-19.08]**
Heterogeneity: Tau^2=0; Chi^2=0.11, df=1(P=0.75); I^2=0%							
Test for overall effect: Z=8.74(P<0.0001)							
1.2.2 At 6 months							
Clauss 2005	35	-27 (20)	19	5 (17)		6.27%	-32[-42.12,-21.88]
de Jongh 2002a	101	-38 (16)	64	-1 (11)		37.75%	-37[-41.12,-32.88]
McCrindle 2003	140	-40 (13)	47	0 (13)		34.78%	-40[-44.3,-35.7]
Stein 1999	63	-27 (16)	59	-3 (15)		21.21%	-24[-29.5,-18.5]
Subtotal ***	**339**		**189**			**100%**	**-34.97[-37.51,-32.44]**
Heterogeneity: Tau^2=0; Chi^2=21.81, df=3(P<0.0001); I^2=86.24%							
Test for overall effect: Z=27.06(P<0.0001)							
1.2.3 At 1 year							
de Jongh 2002a	86	-41 (39)	58	0 (10)		29.69%	-41[-49.64,-32.36]
Stein 1999	61	-25 (16)	49	-4 (14)		70.31%	-21[-26.61,-15.39]
Subtotal ***	**147**		**107**			**100%**	**-26.94[-31.64,-22.23]**
Heterogeneity: Tau^2=0; Chi^2=14.49, df=1(P=0); I^2=93.1%							
Test for overall effect: Z=11.22(P<0.0001)							
1.2.4 At end of follow-up							
Braaskamp 2015a	76	-31 (0)	27	1 (0)			Not estimable
Clauss 2005	35	-27 (20)	19	5 (17)		7.39%	-32[-42.12,-21.88]
de Jongh 2002a	86	-41 (39)	58	0 (10)		10.14%	-41[-49.64,-32.36]
Knipscheer 1996	53	-27 (10)	18	-3 (13)		17.46%	-24[-30.58,-17.42]
McCrindle 2003	140	-40 (13)	47	0 (13)		40.99%	-40[-44.3,-35.7]
Stein 1999	61	-25 (16)	49	-4 (14)		24.02%	-21[-26.61,-15.39]
Subtotal ***	**451**		**218**			**100%**	**-32.15[-34.9,-29.4]**
Heterogeneity: Tau^2=0; Chi^2=37.92, df=4(P<0.0001); I^2=89.45%							
Test for overall effect: Z=22.92(P<0.0001)							

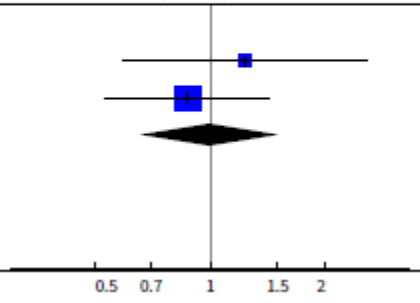


Outcomes

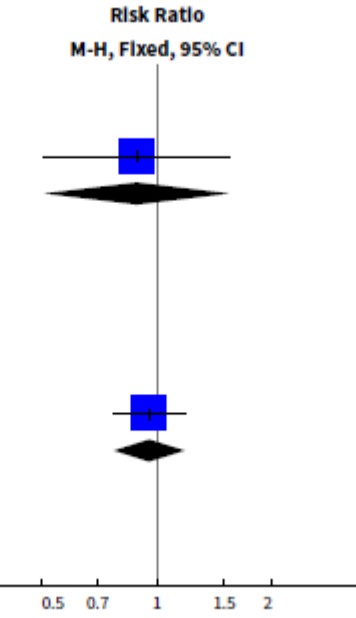
3. Change in growth/maturation

Analysis 1.3. Comparison 1 Statins versus control, Outcome 3 Change in puberty (Tanner stage ≧ 1 level).

Study or subgroup	Statins n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 At 6 months					
de Jongh 2002a	18/104	9/64		33.16%	1.23[0.59,2.57]
McCrindle 2003	39/140	15/47		66.84%	0.87[0.53,1.43]
Subtotal (95% CI)	**244**	**111**		**100%**	**0.99[0.66,1.5]**
Total events: 57 (Statins), 24 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.58, df=1(P=0.44); I^2=0%					
Test for overall effect: Z=0.04(P=0.97)					



Study or subgroup	Statins n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.2 At 1 year					
de Jongh 2002a	21/83	16/56		100%	0.89[0.51,1.54]
Subtotal (95% CI)	**83**	**56**		**100%**	**0.89[0.51,1.54]**
Total events: 21 (Statins), 16 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.43(P=0.67)					
1.3.3 At 2 years					
Wiegman 2004	63/104	68/107		100%	0.95[0.77,1.18]
Subtotal (95% CI)	**104**	**107**		**100%**	**0.95[0.77,1.18]**
Total events: 63 (Statins), 68 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.44(P=0.66)					

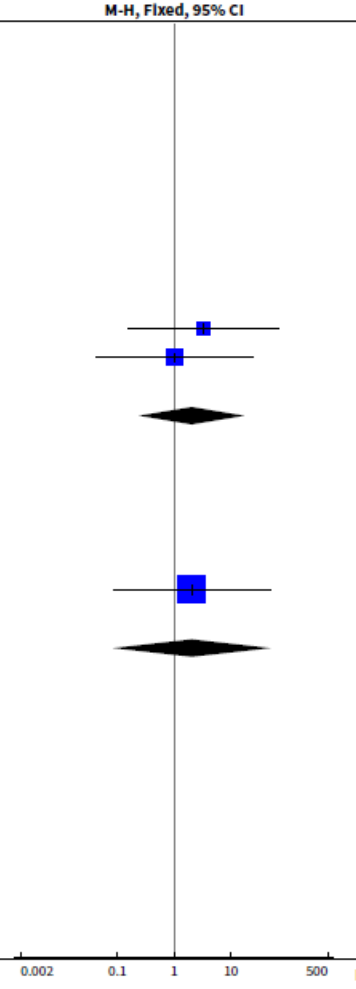


Other outcomes of interest

- ALT

Analysis 1.5. Comparison 1 Statins versus control, Outcome 5 Change in alanine aminotransferase levels (> 3x ULN).

Study or subgroup	Statins n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 At 1 month					
Braaskamp 2015a	0/76	0/27			Not estimable
Knipscheer 1996	0/54	0/18			Not estimable
Subtotal (95% CI)	**130**	**45**			**Not estimable**
Total events: 0 (Statins), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.5.2 At 6 months					
Clauss 2005	0/35	0/19			Not estimable
de Jongh 2002a	2/106	0/69		44.76%	3.27[0.16,67.12]
McCrindle 2003	1/140	0/47		55.24%	1.02[0.04,24.65]
Stein 1999	0/63	0/59			Not estimable
Subtotal (95% CI)	**344**	**194**		**100%**	**2.03[0.24,16.95]**
Total events: 3 (Statins), 0 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.27$, df=1(P=0.6); $I^2=0\%$					
Test for overall effect: Z=0.65(P=0.51)					
1.5.3 At 1 year					
de Jongh 2002a	1/86	0/58		100%	2.03[0.08,49.09]
Stein 1999	0/61	0/49			Not estimable
Subtotal (95% CI)	**147**	**107**		**100%**	**2.03[0.08,49.09]**
Total events: 1 (Statins), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.44(P=0.66)					
1.5.4 At 2 years					
Wiegman 2004	0/104	0/107			Not estimable
Subtotal (95% CI)	**104**	**107**			**Not estimable**
Total events: 0 (Statins), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

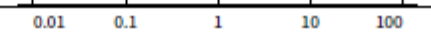


Other outcomes of interest

- CK

Analysis 1.6. Comparison 1 Statins versus control, Outcome 6 Myopathy: Change in creatine kinase levels (> 10x ULN).

Study or subgroup	Statins n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 At 1 month					
Avis 2010	4/130	0/46		100%	3.23[0.18,58.84]
Braaskamp 2015a	0/76	0/27			Not estimable
Knipscheer 1996	0/37	0/14			Not estimable
Subtotal (95% CI)	**243**	**87**		**100%**	**3.23[0.18,58.84]**
Total events: 4 (Statins), 0 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.79(P=0.43)					
1.6.2 At 6 months					
Clauss 2005	0/35	0/19			Not estimable
de Jongh 2002a	0/106	1/69		100%	0.22[0.01,5.28]
Subtotal (95% CI)	**141**	**88**		**100%**	**0.22[0.01,5.28]**
Total events: 0 (Statins), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.94(P=0.35)					
1.6.3 At 1 year					
de Jongh 2002a	1/86	1/58		100%	0.67[0.04,10.57]
Stein 1999	0/61	0/49			Not estimable
Subtotal (95% CI)	**147**	**107**		**100%**	**0.67[0.04,10.57]**
Total events: 1 (Statins), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.28(P=0.78)					

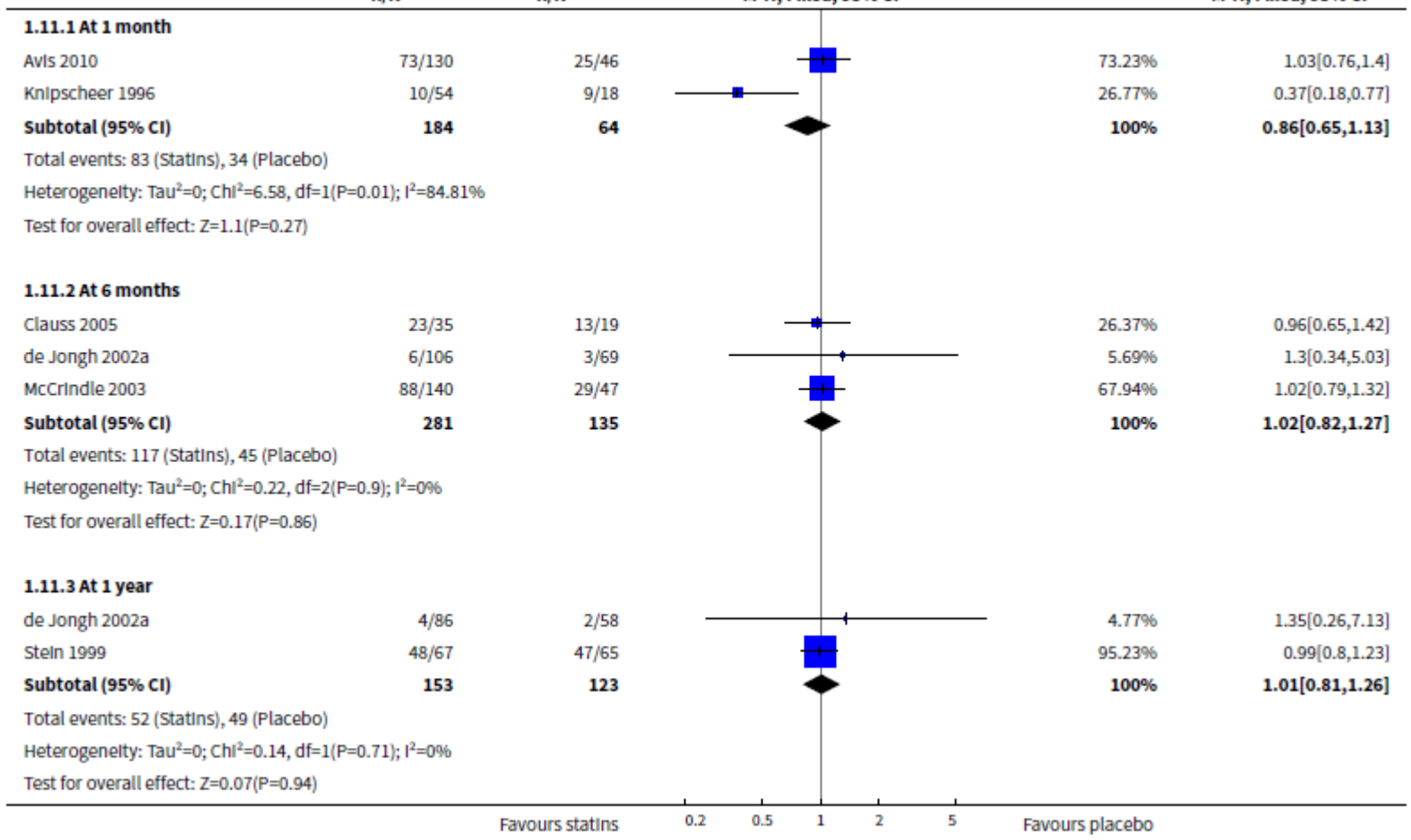


Other outcomes of interest

- Adverse events

Analysis 1.11. Comparison 1 Statins versus control, Outcome 11 Adverse events.

Study or subgroup	Statins n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.11.1 At 1 month					
Avis 2010	73/130	25/46		73.23%	1.03[0.76,1.4]
Knipscheer 1996	10/54	9/18		26.77%	0.37[0.18,0.77]
Subtotal (95% CI)	**184**	**64**		**100%**	**0.86[0.65,1.13]**
Total events: 83 (Statins), 34 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=6.58, df=1(P=0.01); I^2=84.81%					
Test for overall effect: Z=1.1(P=0.27)					
1.11.2 At 6 months					
Clauss 2005	23/35	13/19		26.37%	0.96[0.65,1.42]
de Jongh 2002a	6/106	3/69		5.69%	1.3[0.34,5.03]
McCrindle 2003	88/140	29/47		67.94%	1.02[0.79,1.32]
Subtotal (95% CI)	**281**	**135**		**100%**	**1.02[0.82,1.27]**
Total events: 117 (Statins), 45 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.22, df=2(P=0.9); I^2=0%					
Test for overall effect: Z=0.17(P=0.86)					
1.11.3 At 1 year					
de Jongh 2002a	4/86	2/58		4.77%	1.35[0.26,7.13]
Stein 1999	48/67	47/65		95.23%	0.99[0.8,1.23]
Subtotal (95% CI)	**153**	**123**		**100%**	**1.01[0.81,1.26]**
Total events: 52 (Statins), 49 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.14, df=1(P=0.71); I^2=0%					
Test for overall effect: Z=0.07(P=0.94)					



Overall results

Summary of findings for the main comparison.

Statins compared with placebo for children with familial hypercholesterolemia

Patient or population: children with familial hypercholesterolemia

Settings: outpatients

Intervention: statins

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Statins				
Change in carotid intima-media thickness (mm) - at 2 years Follow-up: 2 years	The mean change in carotid intima-media thickness was 0.005 mm in the placebo group.	The mean change in carotid intima-media thickness was 0.01 mm lower (0.03mm lower to 0.00mm lower) in the stains group.	NA	211 (1 study)	⊕⊕⊙⊙ **low**[1,4]	
Change in serum LDL cholesterol level (%) - at end of follow-up Follow-up: up to 48 weeks	The mean change in serum LDL cholesterol level ranged from a 5% increase to a 4% decrease across placebo groups.	The mean change in serum LDL cholesterol level was 32.15% lower (34.90% lower to 29.40% lower) in the stains group.	NA	669 (6 studies)	⊕⊕⊕⊕ **high**	Even with some concerns regarding risk of bias and heterogeneity, given the effect size, we regard this as high-quality evidence Heterogeneity: $I^2 = 89\%$ This outcome was also reported at at 1 month (228 participants, 3 studies), 6 months (528 participants, 4 studies) and at 1 year (254 participants, 2 studies). All pooled results were in favour of statins; the latter two analyses were also very heterogeneous ($I^2 > 85\%$)
Change in measures of growth and maturation: change in puberty proportion with Tanner stage ≧ 1 level - at 2 years Follow-up: 2 years	**636 per 1000**	**604 per 1000** (489 to 750 per 1000)	**RR 0.95** (95% CI 0.77 to 1.18)	211 (1 study)	⊕⊕⊙⊙ **low**[1,2]	This outcome was also reported at at 6 months (355 participants, 2 studies) and at 1 year (139 participants, 1 study). Results of analysis at all time points showed no significant differences between statins and placebo.

Statins in Children

Approved Medications in Pediatric Patients

Statin	Ages (yr)	Approved Daily Dose
Atorvastatin	10–17	10 mg starting; 20 mg maximum
Fluvastatin	10–16	20 mg starting; 80 mg maximum
Lovastatin	10–17	10 mg starting; 40 mg maximum
Pravastatin	8–13 14-18	20 mg starting; 20 mg maximum 40 mg starting; 40 mg maximum
Pitavastatin	8-16	2 mg stating; 4 mg maximum
Simvastatin	10–17	10 mg starting; 40 mg maximum
Rosuvastatin	7-17	5-20 mg starting; 20 mg maximum

Recommendations are from product inserts

8 if HeFH

7 if HoFH
8 if HeFH

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Slide modified from Saseen, JJ. Pharmacologic Therapies Part 1, NLA Foundations of Lipidology Course

Statins

- Prior to initiating:
  - Check to make sure no drug-drug interactions
  - Baseline liver panel (+/- CK)
  - Counsel about possible future drug-drug interactions,
  - Need for appropriate contraception
- Choice of statin is matter of preference
  - Start at lowest daily dose
- After 4 weeks check FLP, ALT, AST

	High-Intensity	Moderate-Intensity	Low-Intensity
LDL-C Lowering†	≥50%	30% to 49%	<30%
Statins	Atorvastatin (40 mg‡) 80 mg Rosuvastatin 20 (40 mg)	Atorvastatin 10 mg (20 mg) Rosuvastatin (5 mg) 10 mg Simvastatin 20–40 mg§	Simvastatin 10 mg
	-	Pravastatin 40 mg (80 mg) Lovastatin 40 mg (80 mg) Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 1–4 mg	Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg

Grundy, S.M. et al. 2018 Guideline on the Management of Blood Cholesterol. JACC.018;DOI:10.1016/j.jacc.2018.11.003.

Target LDL achieved

- Recheck labs:
  - 8 weeks
  - 3 months
  - 1st year
    - Q 3-4 months
  - 2nd year and beyond
    - Q 6 months

Target LDL not achieved

- Increase by one increment (usually 5mg or 10mg)
- Repeat labs in 4 weeks
- If still not achieved:
  - Consider increasing by one more increment

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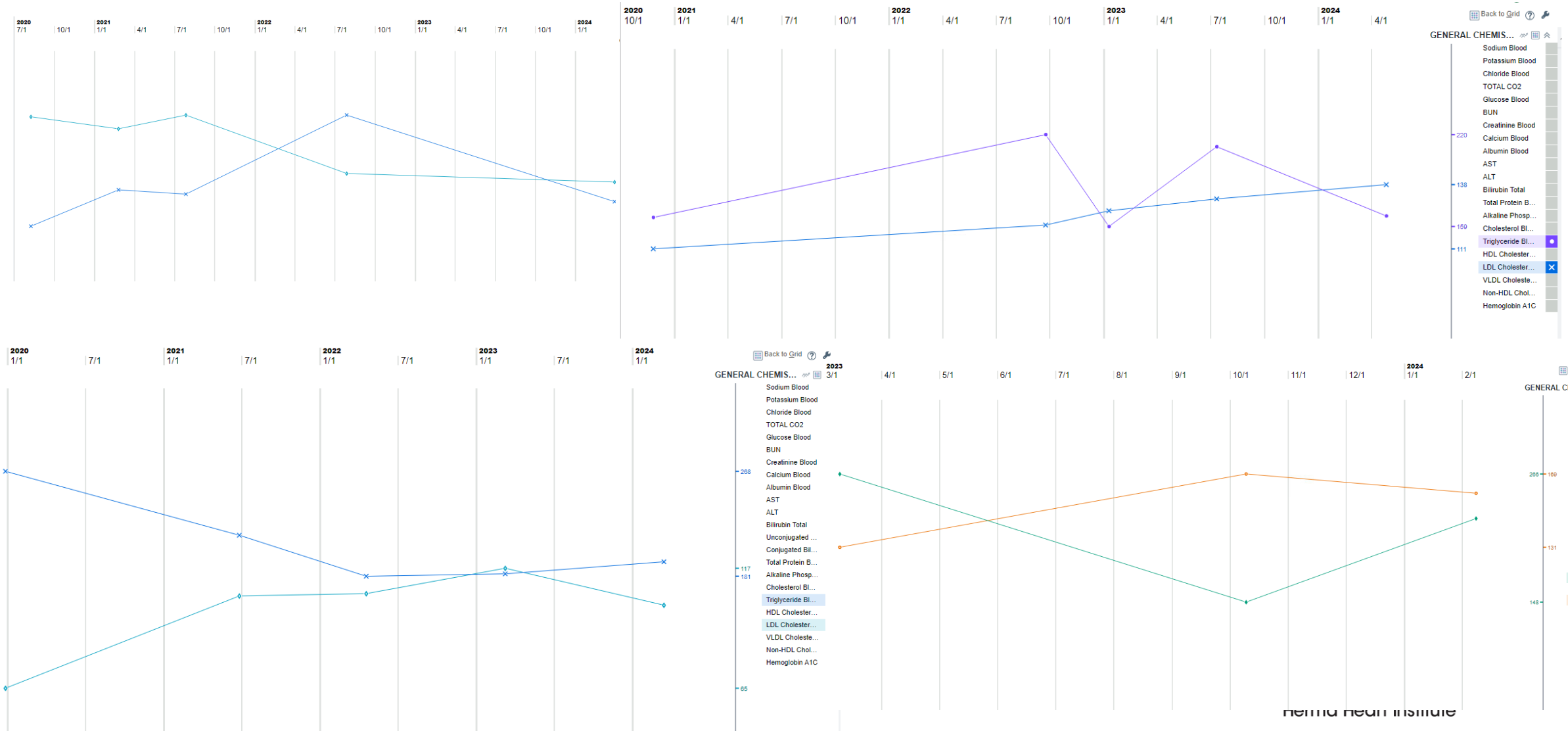
Statin Monitoring

- If myopathy-
  - Stop statin
  - Assess CK (worrisome if > 10x ULN)
  - Assess relation to exercise
  - May consider re-starting if symptoms and CK have normalized
- If elevated AST/ALT-
  - Stop statin or decrease dose
  - Worrisome if ≥ 3x ULN
  - Repeat labs in 2 weeks
  - May consider re-starting at lower dose (with close monitoring) when labs normalize
- Continue to monitor:
  - Compliance
  - Contraception

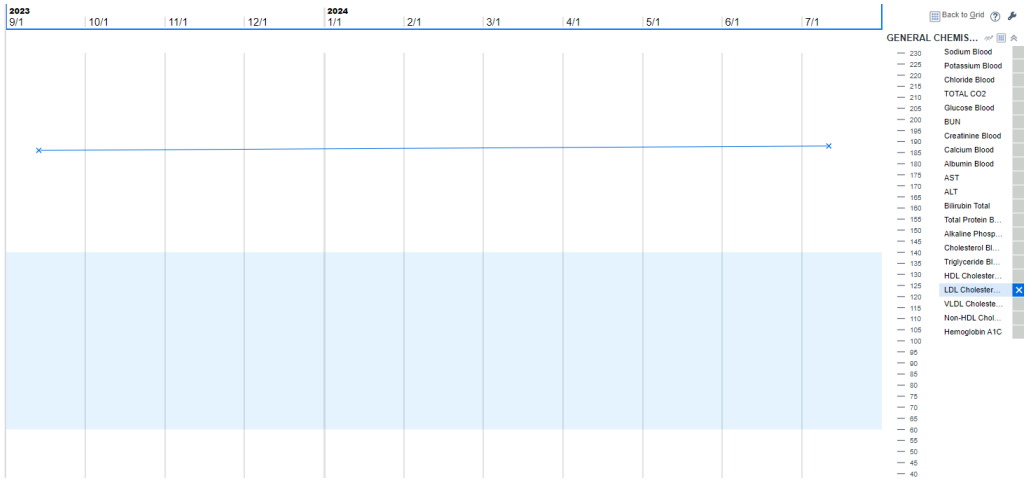
Multifactorial dyslipidemia

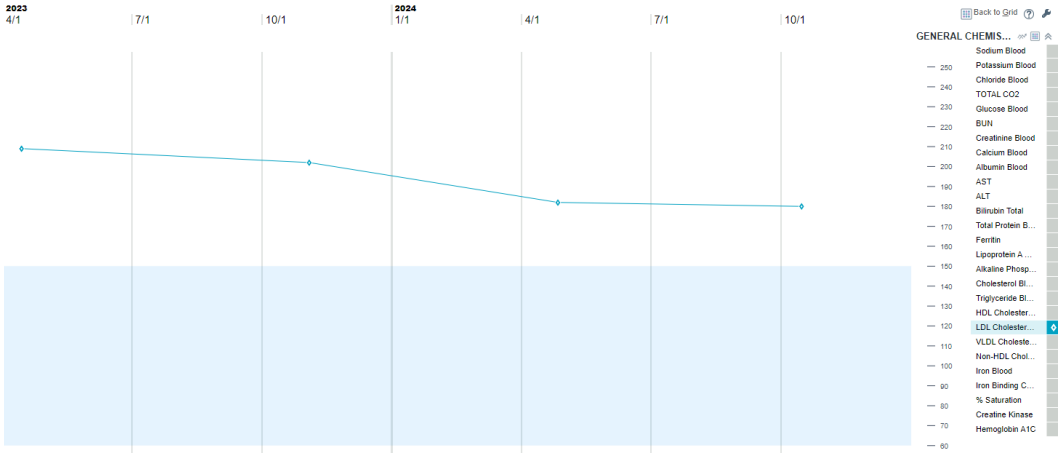
- More controversial
- Less data
- Threshold is likely higher
  - Lifestyle changes
  - Variable LDL exposure

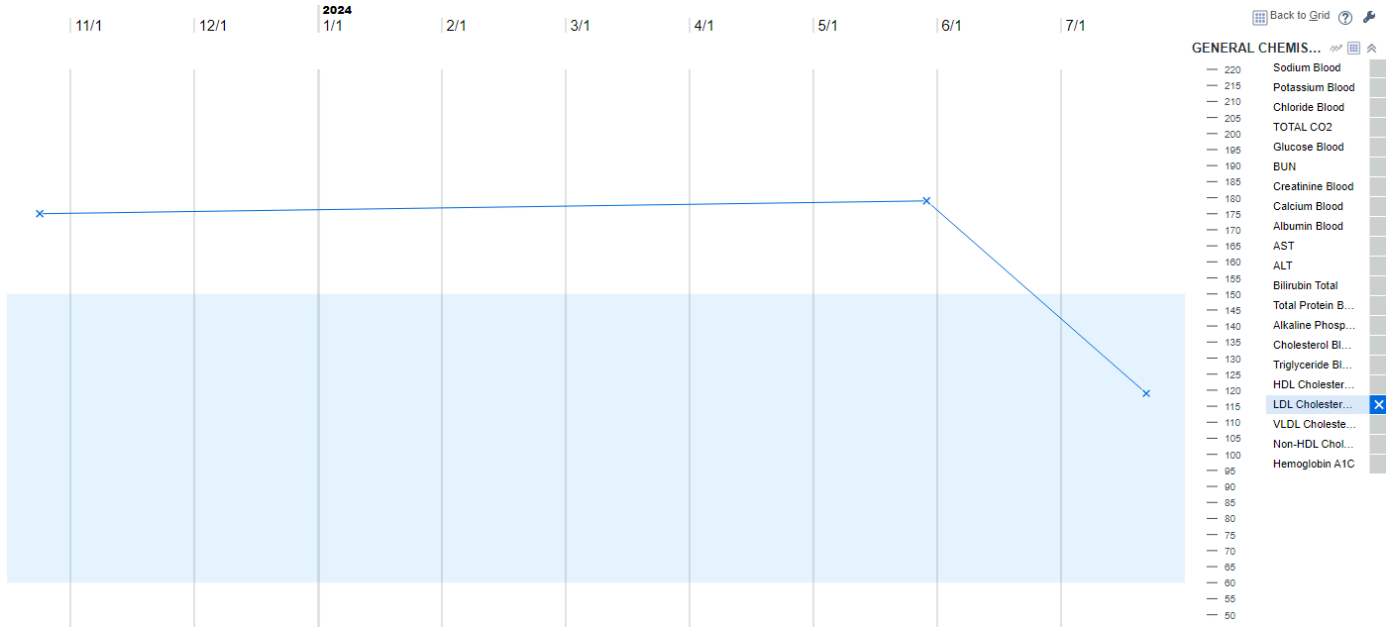
Multifactorial dyslipidemia



Multifactorial dyslipidemia







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2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

COR	LOE	RECOMMENDATIONS
I	B-R	1. A diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish is recommended to decrease ASCVD risk factors (S3.1-1–S3.1-11).
IIa	B-NR	2. Replacement of saturated fat with dietary monounsaturated and polyunsaturated fats can be beneficial to reduce ASCVD risk (S3.1-12, S3.1-13).
IIa	B-NR	3. A diet containing reduced amounts of cholesterol and sodium can be beneficial to decrease ASCVD risk (S3.1-9, S3.1-14–S3.1-16).
IIa	B-NR	4. As a part of a healthy diet, it is reasonable to minimize the intake of processed meats, refined carbohydrates, and sweetened beverages to reduce ASCVD risk (S3.1-17–S3.1-24).
III: Harm	B-NR	5. As a part of a healthy diet, the intake of *trans* fats should be avoided to reduce ASCVD risk (S3.1-12, S3.1-17, S3.1-25–S3.1-27).

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2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

I	B-NR	2. Adults should engage in at least 150 minutes per week of accumulated moderate-intensity or 75 minutes per week of vigorous-intensity aerobic physical activity (or an equivalent combination of moderate and vigorous activity) to reduce ASCVD risk (S3.2-3–S3.2-8).
IIa	B-NR	3. For adults unable to meet the minimum physical activity recommendations (at least 150 minutes per week of accumulated moderate-intensity or 75 minutes per week of vigorous-intensity aerobic physical activity), engaging in some moderate- or vigorous-intensity physical activity, even if less than this recommended amount, can be beneficial to reduce ASCVD risk (S3.2-5, S3.2-6).
IIb	C-LD	4. Decreasing sedentary behavior in adults may be reasonable to reduce ASCVD risk (S3.2-3, S3.2-9–S3.2-11).

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Physical Activity

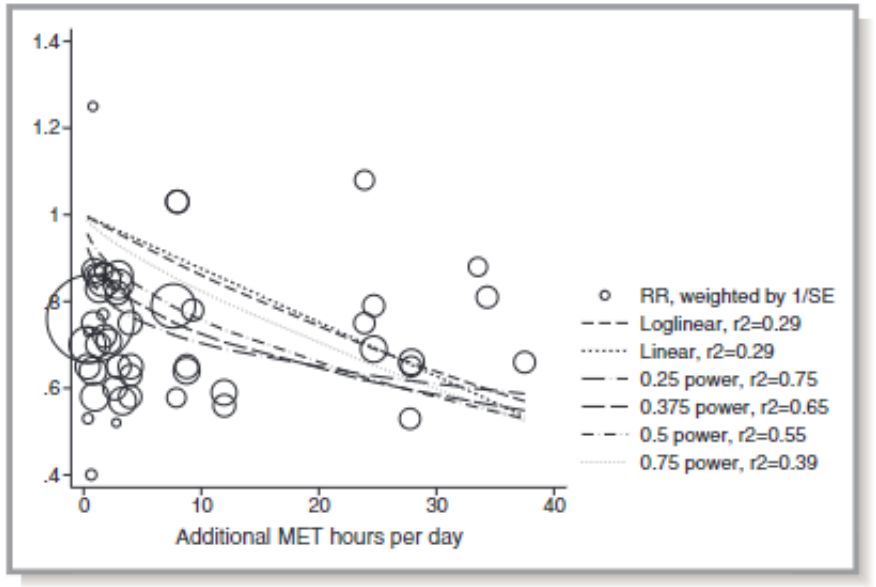

Figure 2. Relative risk for CVD mortality against MET hours per day. Results from 14 studies, including the 0.25 power transformation fit line as well as linear, log-linear, 0.375, 0.5, and 0.750 power transformations. Relative risk estimates are weighted by the inverse of the reported SE, with larger circles for results with greater weighting. The red line represents a log-linear transformation, and the orange line represents a 0.25 power transformation. CVD indicates cardiovascular disease; MET, metabolic equivalent of task; RR, relative risk.

Wahid, A., Manek, N., Nichols, M., Kelly, P., Foster, C., Webster, P., Kaur, A., Smith, C.F., Wilkins, E., Rayner, M., Roberts, N., Scarborough, P., n.d. Quantifying the Association Between Physical Activity and Cardiovascular Disease and Diabetes: A Systematic Review and Meta-Analysis.

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Risk Factors

- DM
- Family history of early ASCVD
  - Men < 55 years; Women < 65 years
- Current smoker
- High risk conditions
  - KD w/ aneurysms, s/p OHT, cancer survivor
- Inflammatory conditions
  - SLE, JIA, HIV
- CKD
- Lp(a) > 50 mg/dl or > 125 nmol/L
- HTN
- Obesity (BMI > 97th percentile)
- Persistently elevated TG (> 175 mg/dL)
- Ethnicity (e.g. SE Asian)

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Thank you!

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