Hot Topics in Pediatric HyperLipidemia

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July 22, 2022

Objectives:

Screening and Diagnosis of Common Lipid Disorders in Youth:

- Importance of screening and how to screen
- When to screen
- Who to screen

Common Causes of Hyperlipidemia

Non pharmacologic management

Pharmacologic management

Cascade Screening and Reverse Cascade Screening

What's the hype about Lp(a)?

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Pre-Talk Question #1:

If you are a physician, nurse practitioner, or physician assistant, answer the following. “I feel comfortable diagnosing familial hypercholesterolemia”

A. Yes, I think so
B. No
C. Not sure
D. Prefer not to answer

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Pre-Talk Question #2:

The following patient is most likely to have heterozygous familial hypercholesterolemia:

A. Patient X: 10 year old with LDL-c of 140mg/dL. No family history of premature coronary artery disease.
B. Patient Y: 10 year old with LDL-c of 160mg/dL. With lifestyle intervention, repeat LDL-c120mg/dL. Family history of premature coronary artery disease.
C. Patient Z: 10 year old with LDL-c of 190mg/dL. With lifestyle intervention, repeat LDL-c 190mg/dL. Family history of premature coronary artery disease.
D. Patient W: 10 year old with LDL-c of 120mg/dL, TG of 170mg/dL, and HDL-c of 29mg/dL. Family history unknown

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Pre-Talk Question #3:

Among persons with heterozygous familial hypercholesterolemia, the most effective option for reducing LDL-c level is the following:

A. Diet alone
B. Exercise alone
C. Statin
D. Not sure

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Scope of the Problem:

Dyslipidemia

is a risk factor for premature coronary artery disease, including heart attack and stroke.

component of **life's essential 8** (cholesterol, blood pressure, glucose, physical activity, smoking, diet, body mass index, *sleep*)

Treatment is essential for reducing the atherosclerotic risk burden in the US (and globally).

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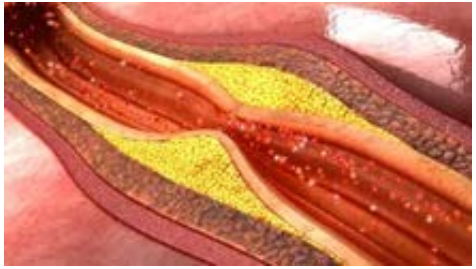
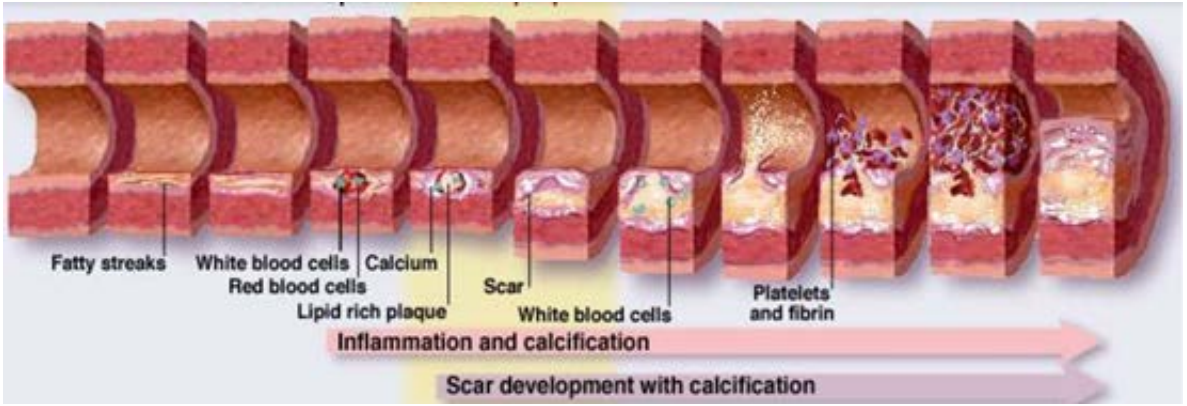
Gidding SS. J Pediatr 2022

Atherosclerosis:

Fatty streak deposition begins in the arteries of children as early as 8 years of age.





Berenson GS *et al* NEJM 1998
McGill HC *et al* Arterioscler Thromb Vasc Biol 1997

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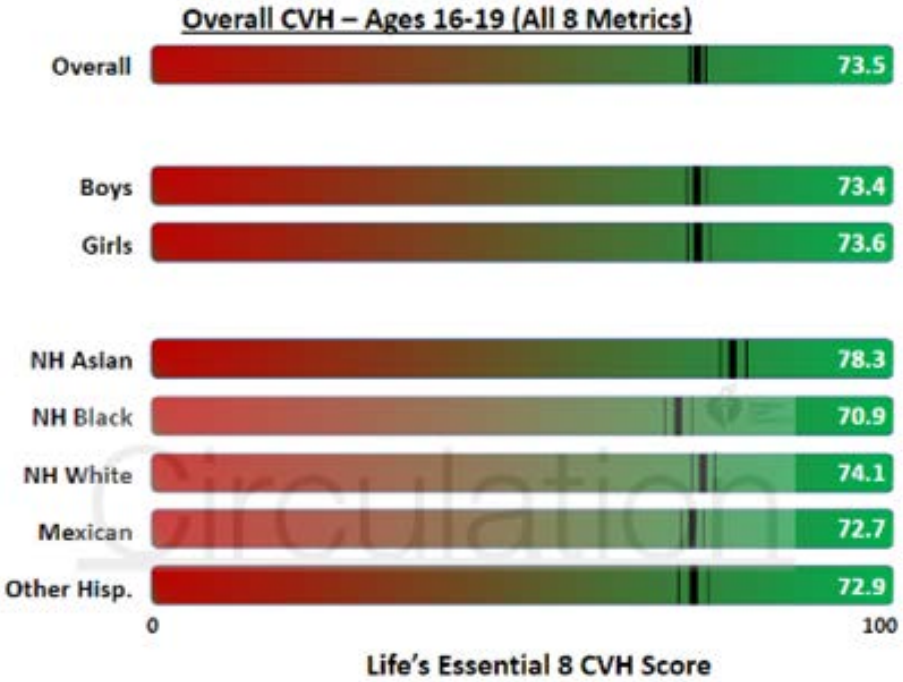

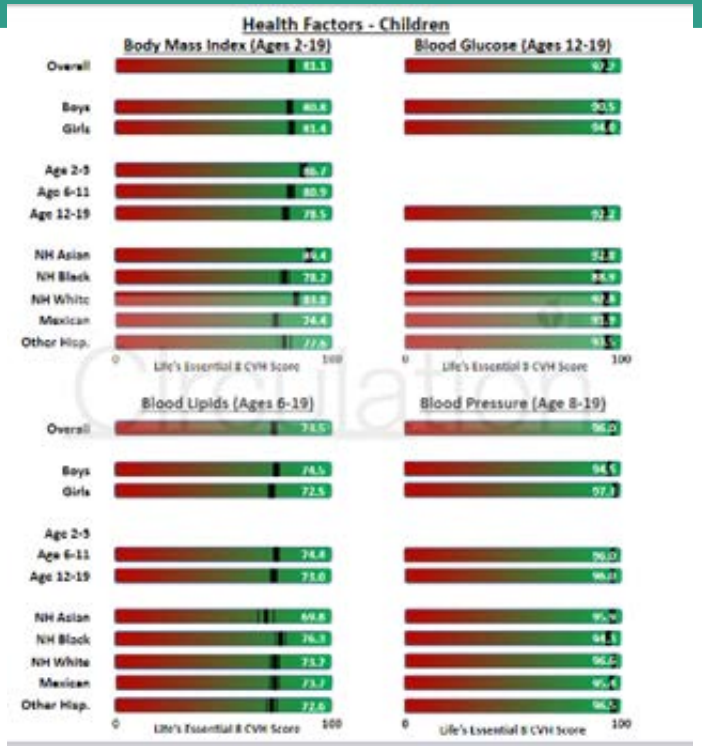

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Lloyd-Jones DM, *et al*. Circulation 2022

Lipid Panel

Total cholesterol (TC-c)

- Low density lipoprotein (LDL-c)
- High density lipoprotein (HDL-c)

Triglycerides (TG)

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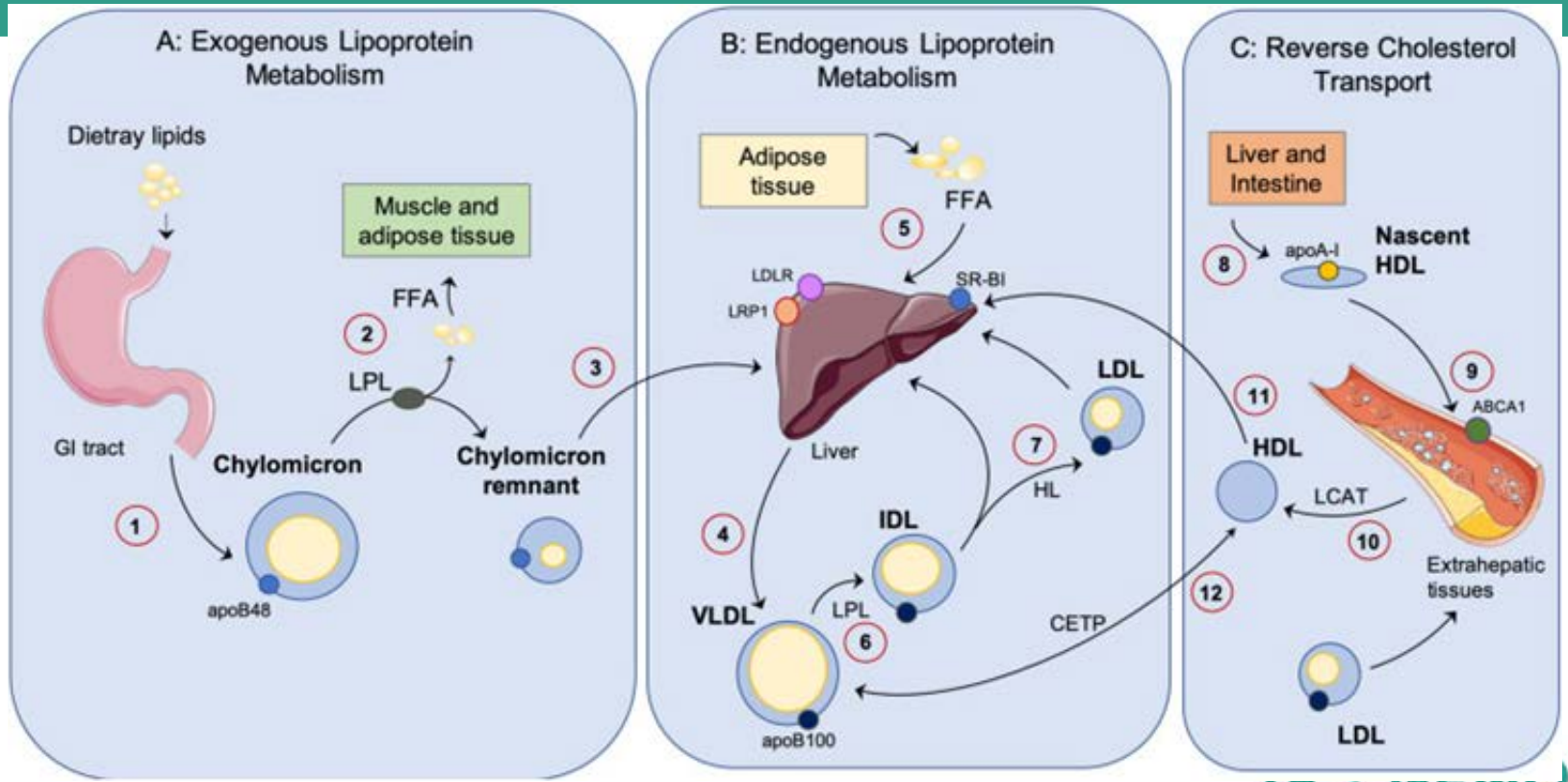
Components of lipid profile:



Stemmer K, *et al*. Adv Drug Deliv Rev 2020.

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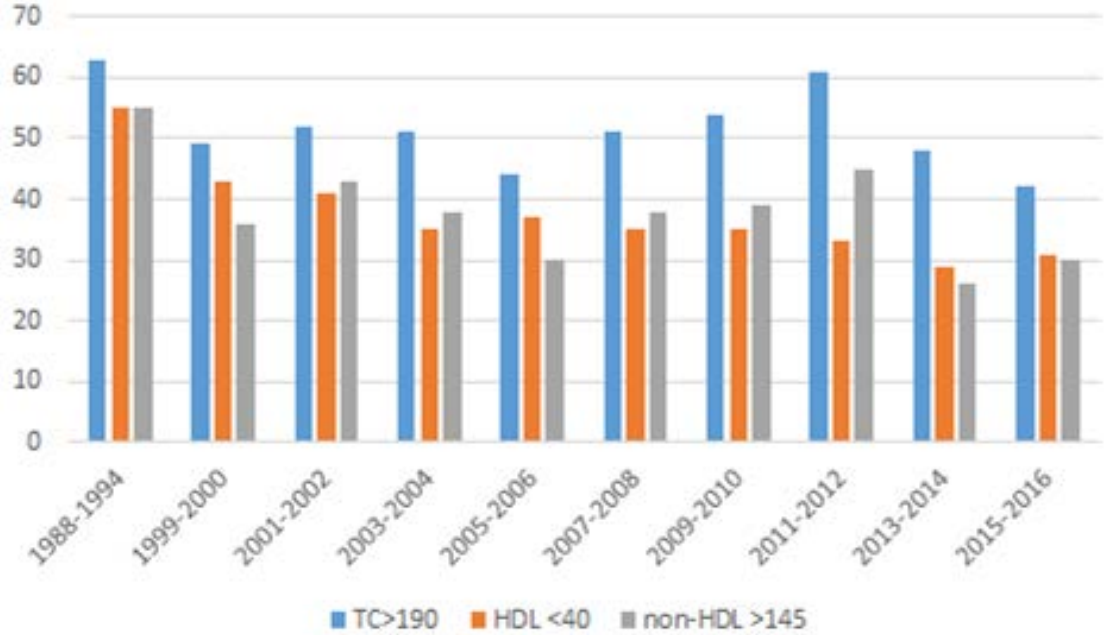
High Prevalence of Dyslipidemia in Children

Normal weight children: ¼ up to ½ of youth with dyslipidemia



Zachariah JP, *et al*. Am Heart J 2021

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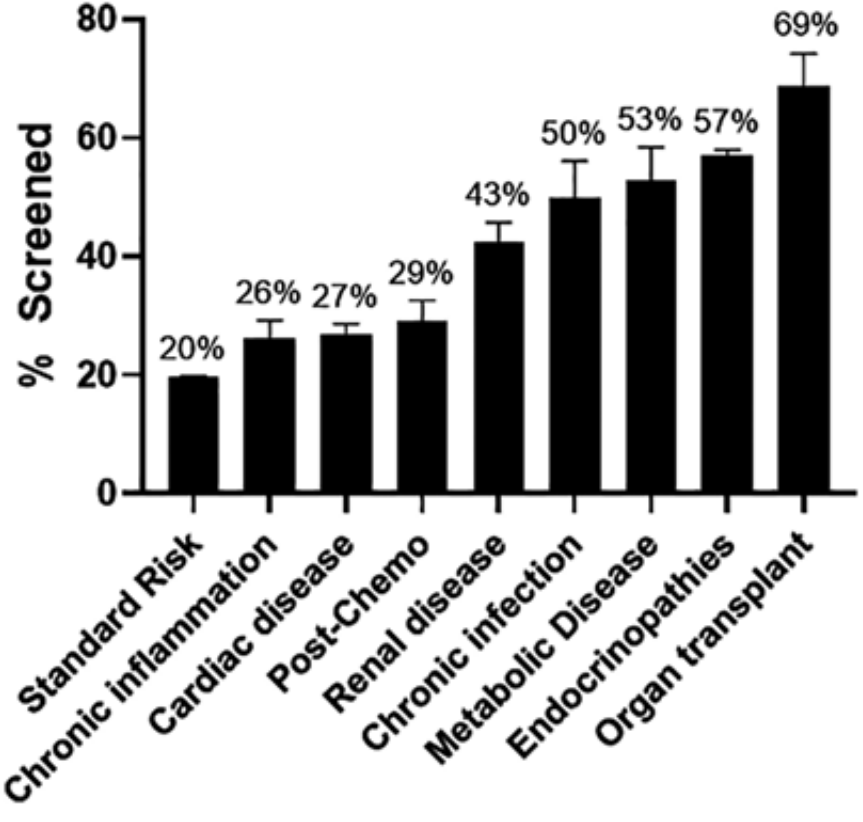
Screening for Dyslipidemia is Poor: Even Amongst the Highest Risk Patients



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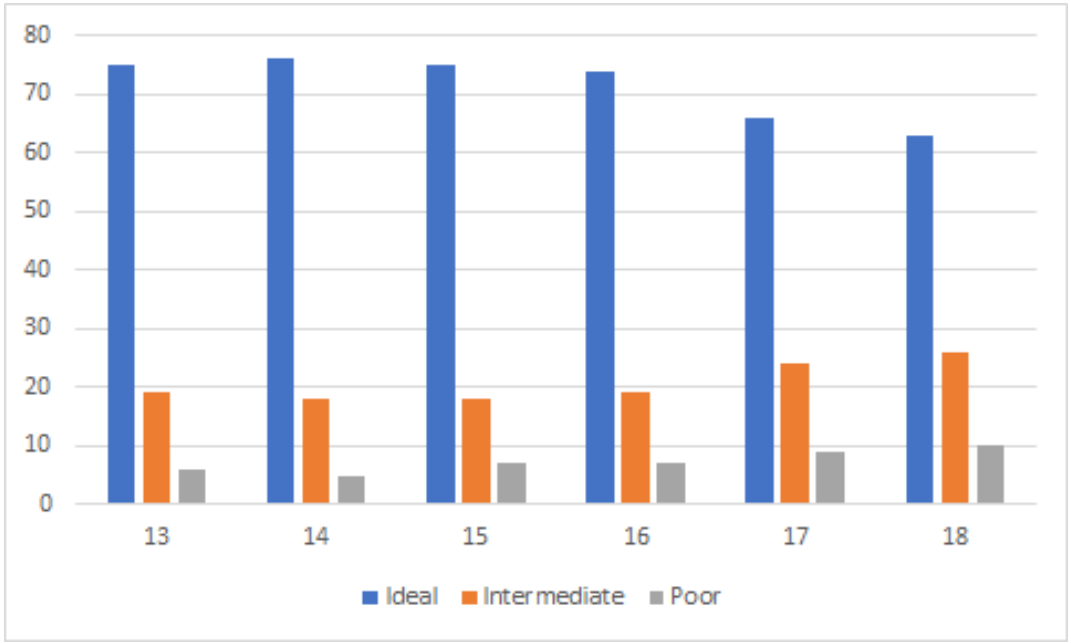
Percentage of Adolescents with Ideal Lipid Status Declines with Age

NHANES 2007-2018, Adolescents 13 to 18 years of age: TC score



Baker-Smith, CM *et al.* 2022. Unpublished Data

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Common Causes of Hyperlipidemia:

	High TC	High LDL-c	High TG	Low HDL
Heterozygous FH (22X increased risk of PCAD)	Statin; PCSK9 inhibitors, Ezetimibe			
Dyslipidemia of obesity			Omega-3 Rich Diet; Reduce sugar intake/SSB; Reduce carbs; increase exercise	
Combined Dyslipidemia				
Familial Combined Hyperlipidemia				

PCAD: premature coronary artery disease

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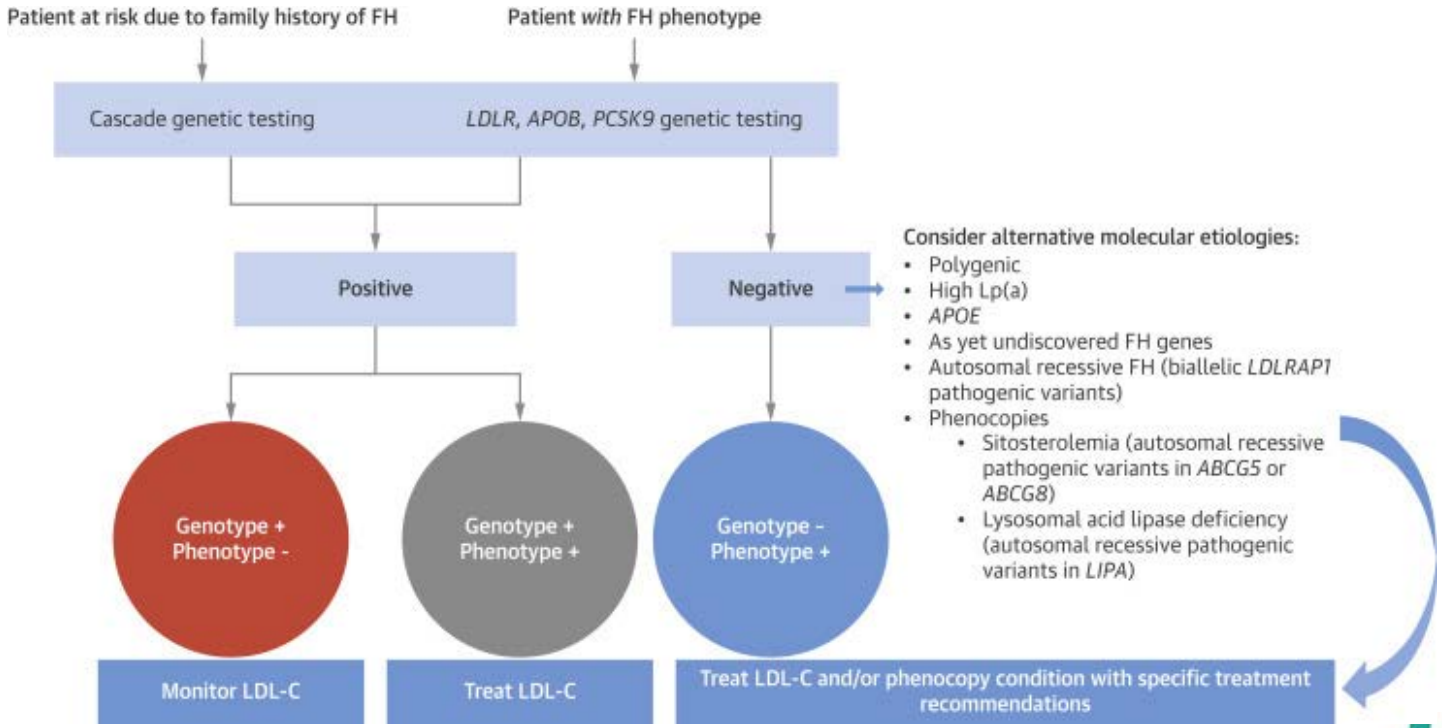
Baker-Smith CM and Peterson A. Curr Hypertens Rep. 2020.



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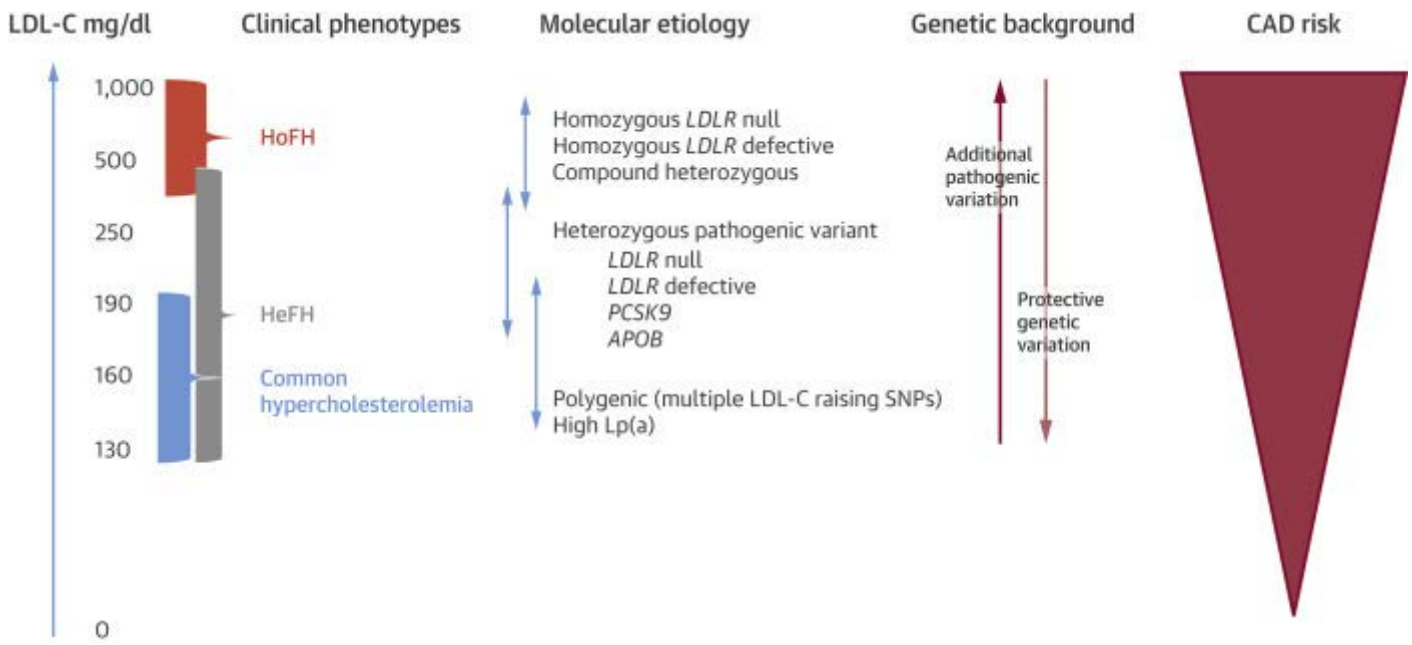

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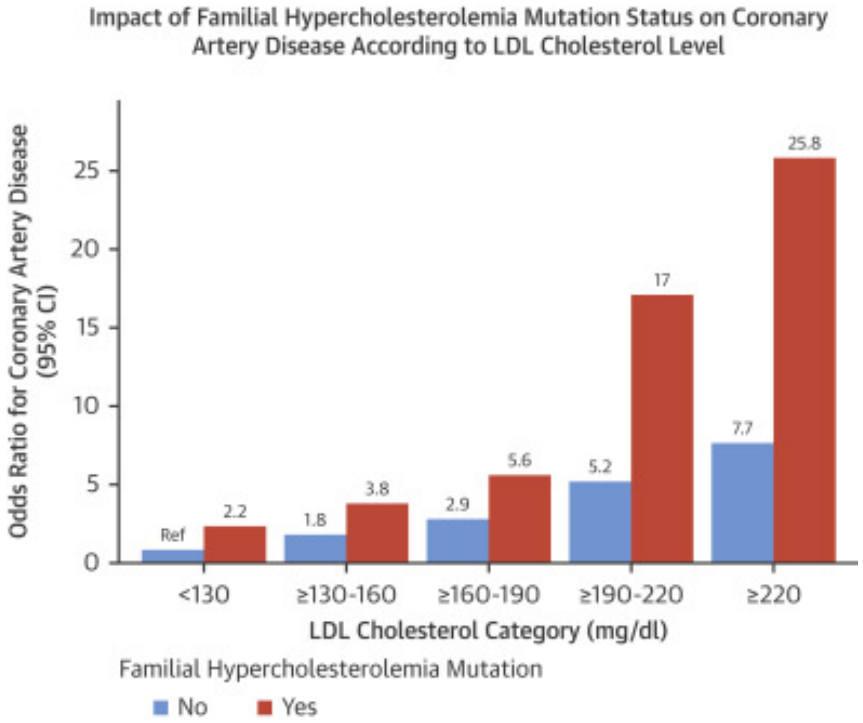

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Familial Hypercholesterolemia

Heterozygous familial hypercholesterolaemia: 1/200

Homozygous: 1/300,000

Cumulative risk of a fatal or non-fatal coronary event by the age of 60 without effective treatment : ≥ 50% in men and ≥ 30% in women; **22x greater risk for premature atherosclerotic cardiovascular disease (ASCVD)**

Etiology: monogenic mutation; variants in genes encoding proteins involved in clearance of LDL particles: LDLR, APOB or PCSK9

Each child/offspring has a 50% chance of inheriting an abnormal gene for FH

Neil HA *et al*. BMJ 2000

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Familial Hypercholesterolemia:

When to suspect:

LDL-c ≥ 190mg/dL in the absence of family history of premature coronary artery disease

LDL-c ≥ 160mg/dL in the **presence of a family history of premature atherosclerotic cardiovascular disease (ASCVD)**

FH FOUNDATION

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Strategies for Improving Recognition of Familial Hypercholesterolemia

Recognition of lipid profile consistent with FH

Genetic testing

- Cascade screening
- Reverse cascade screening

When is lipid testing recommended for ALL children?

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Universal Lipid Screening:

2 years of age if family history of premature coronary artery disease

ALL: 9 to 11 years of age

AGAIN, ALL: 17 to 21 years of age

Premature family history: myocardial infarction, stroke, peripheral vascular disease, coronary angiography, stent placement in first or second degree relative in men before 55 years of age or before 65 years of age in women.

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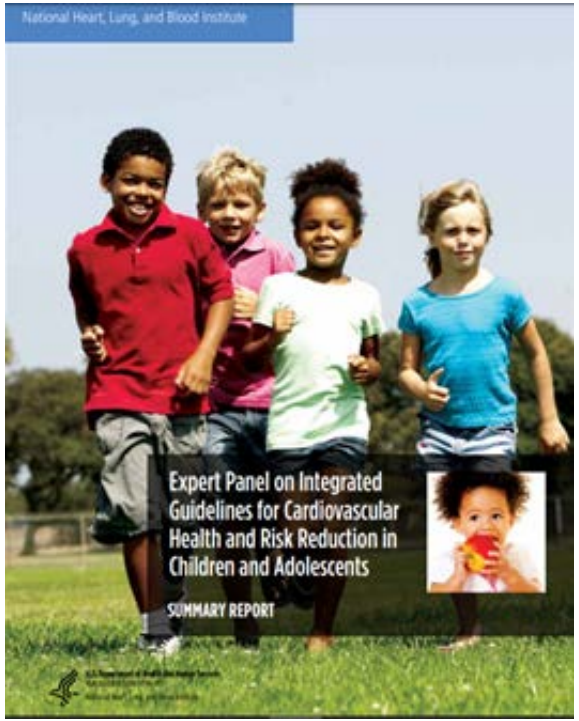
Importance of Genetic Testing:

Pathogenic genetic variant in an FH gene associated triple the risk for atherosclerotic cardiovascular disease (ASCVD) compared with those without a variant at any low-density lipoprotein-cholesterol (LDL-C) level

Lifelong exposure to elevated LDL-C levels matters



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Family Screening Matters

Potential utility of testing:

Identification of genetic syndromes:

- Familial hypercholesterolemia (FH)

Cascade screening and reverse cascade screening (start at age 2 years if family history of premature atherosclerotic cardiovascular disease (ASCVD))

Recommended for monogenic forms of hypercholesterolemia

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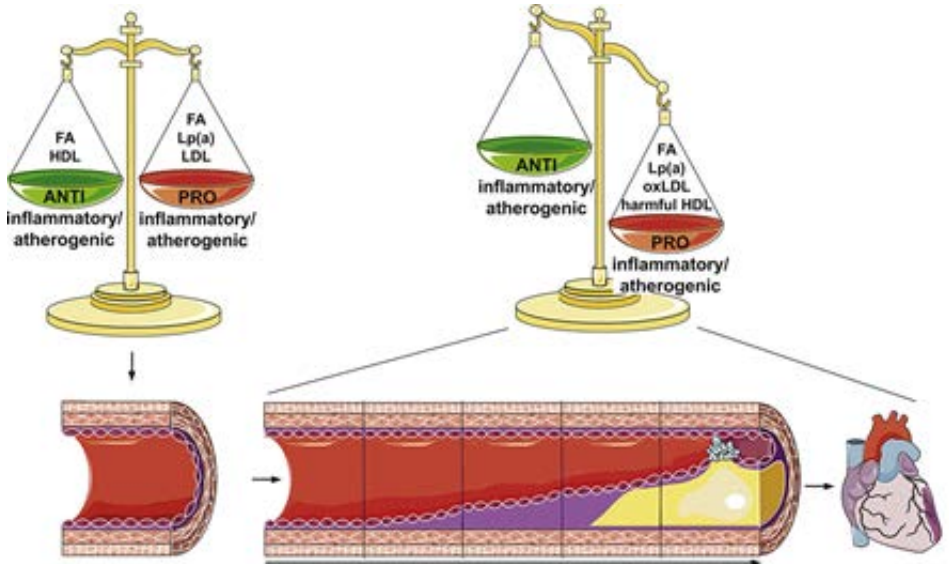
Brown EE *et al* J Clin Lipidol 2020

LDL-c:



"Every 10 mg/dl higher LDL-c contributes to a year of vascular aging. Someone in the FH range at age 25, say, would have the vasculature of a 40 year old."

non-HDL-c:

non-HDL-C (calculated: TC- HDL-c): more predictive of persistent dyslipidemia, atherosclerosis and future events than TC; non-fasting non-HDL-c is also accurate

Not routinely recommended: apoB, apoA-1, Lp(a)

Expert Panel on Integrated Guidelines. Pediatrics 2011

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Treatment of Dyslipidemia:

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Lifestyle Interventions:

- Balance calorie intake and physical activity to achieve or maintain a healthy body weight.
- Consume a diet rich in vegetables and fruits.
- Choose whole-grain, high-fiber foods.
- Consume fish, especially oily fish, at least twice a week.

AHA Nutrition Committee. Diet and Lifestyle Recommendations 2006

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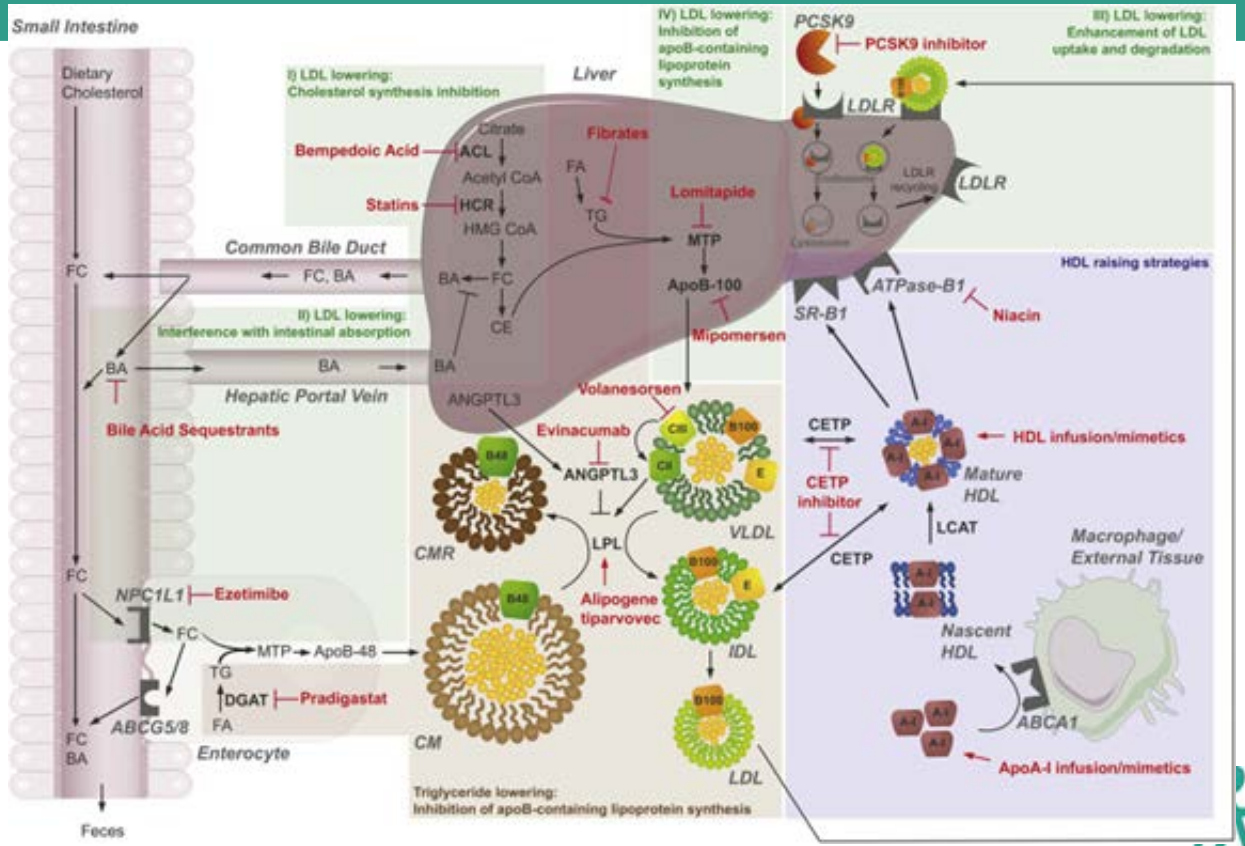
Table 5-1. AHA Dietary Targets and Healthy Diet Score for Defining Cardiovascular Health

	AHA target	Consumption range for alternative healthy diet score*	Alternative scoring range*
Primary dietary metrics†			
Fruits and vegetables	≥4.5 cups/d‡	0 to ≥4.5 cups/d‡	0–10
Fish and shellfish	2 or more 3.5-oz servings/wk (≥200 g/wk)	0 to ≥7 oz/wk	0–10
Sodium	≤1500 mg/d	≤1500 to >4500 mg/d	10–0
SSBs	≤36 fl oz/wk	≤36 to >210 fl oz/wk	10–0
Whole grains	3 or more 1-oz-equivalent servings/d	0 to ≥3 oz/d	0–10
Secondary dietary metrics†			
Nuts, seeds, and legumes	≥4 servings/wk (nuts/seeds, 1 oz; legumes, ½ cup)	0 to ≥4 servings/d	0–10
Processed meats	2 or fewer 1.75-oz servings/wk (≤100 g/wk)	≤3.5 to >17.5 oz/wk	10–0
Saturated fat	≤7% energy	≤7 to >15 (percent energy)	10–0
AHA Diet Score (primary)	Ideal: 4 or 5 dietary targets (≥80%) Intermediate: 2 or 3 dietary targets (40%–79%) Poor: <2 dietary targets (<40%)	Sum of scores for primary metrics	0 (worst)–100 (best)§ Ideal: 80–100 Intermediate: 40–79 Poor: <40
AHA Diet Score (secondary)	Ideal: 4 or 5 dietary targets (≥80%) Intermediate: 2 or 3 dietary targets (40%–79%) Poor: <2 dietary targets (<40%)	Sum of scores for primary and secondary metrics	0 (worst)–100 (best)§ Ideal: 80–100 Intermediate: 40–79 Poor: <40

AHA indicates American Heart Association; and SSBs, sugar-sweetened beverages.

*Consistent with other dietary pattern scores, the highest score (10) was given for meeting or exceeding the AHA target (eg, at least 4.5 cups of fruit and vegetables per day; no more than 1500 mg/d sodium), and the lowest score (0) was given for zero intake (protective factors) or for very high intake (harmful factors).

Pharmacologic Targets for Lipid Management:



Soppert J *et al*. Adv Drug Deliv Rev 2020

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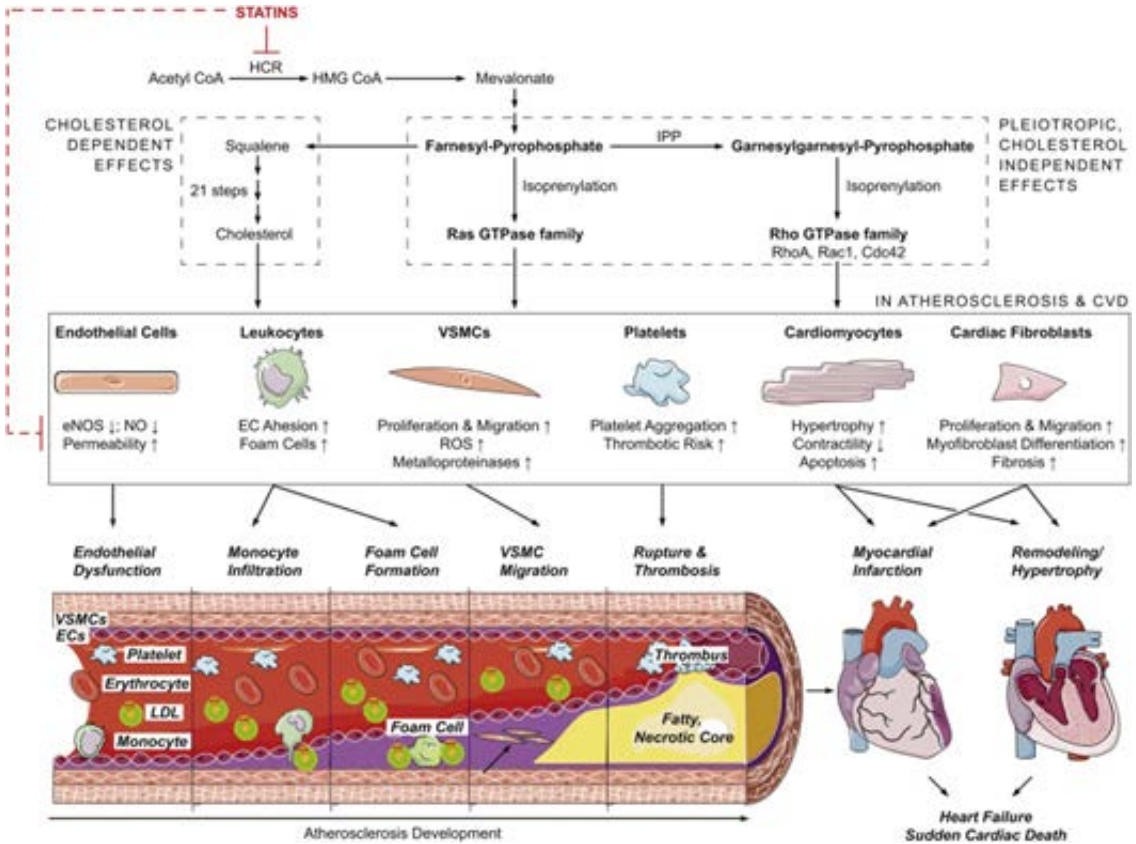
Statin Therapy:



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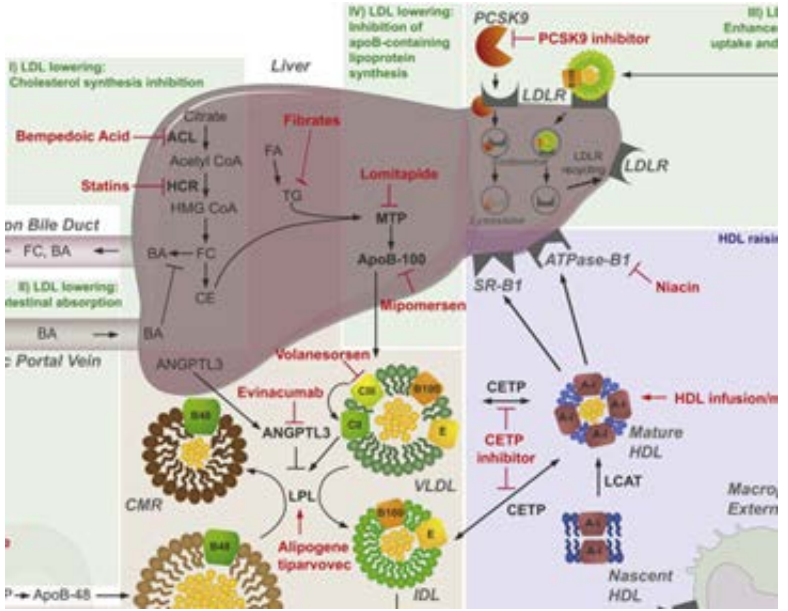
Statin Therapy:

Inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA), rate limiting step in cholesterol synthesis

Hydrophilic statins: pravastatin, rosuvastatin (more selective for hepatic tissue)

Enter hepatic cells passively; less specific: lovastatin, simvastatin, fluvastatin, atorvastatin, pitavastatin

Pleiotropic effects of statins. (JUPITER trial, IMPROVE-IT trial, ODYSSEY, FOURIER)



Soppert J *et al.* Adv Drug Deliv Rev. 2020.

Pesaro AE, et al J Cardiol 2012; Cannon CP et al. NEJM 2015; Sabatine MS et al. 2015. Schwartz GG et al NEJM 2018.

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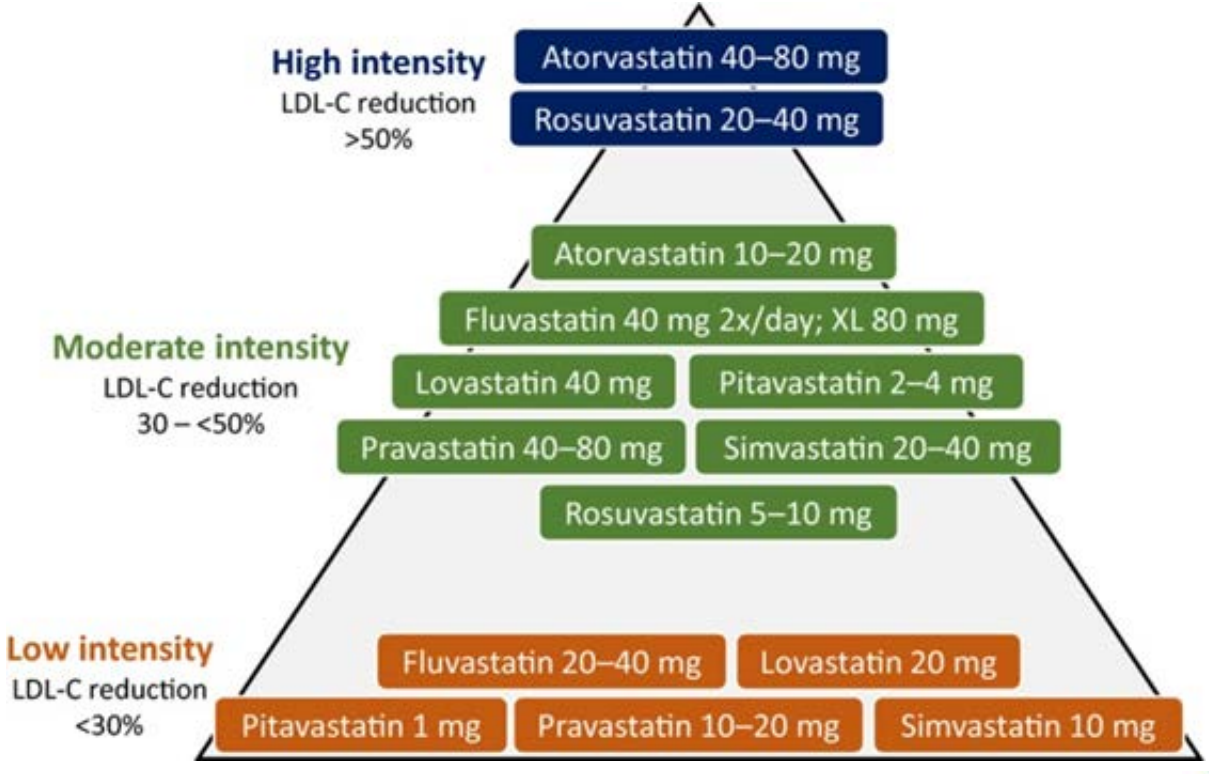
HMG-CoA Reductase Inhibitors: Pediatrics

Medication	Pediatric approvals and indications	Dosing	Comments
Atorvastatin (Lipitor)	age 10-17 y; heterozygous familial hypercholesterolemia (HFH)	10-20 mg/d Note (adults): high dose= 40-80mg	May be titrated at >= 4-wk intervals
Fluvastatin (Lescol)	age 10-16 y; HFH	20-80 mg/d	May be titrated at >= 6-wk intervals
Lovastatin (Mevacor)	age 10-17 y; HFH	10-40 mg/d	Initiated at 20mg/d for >=20% LDL reduction; may be titrated at >=4 wk intervals
Pravastatin (Pravachol)	**age 8-18 y**; HFH	20- 40 mg/d	Age 8-13 y: 20mg/d; Age 14- 18 y: 40mg/d
Rosuvastatin (Crestor)	age 10-17 y; HFH	5- 20 mg/d Note (adults): high dose= 20-40mg	May be titrated at >= 4-wk intervals; JUPITER study
Simvastatin (Zocor)	age 10-17 y; HFH	10-40 mg/d	May be titrated at >= 4-wk intervals

Treatment Options: Statins



McGowan MP *et al* J Am Heart Assoc 2019; Wiegman A *et al*. JAMA 2004

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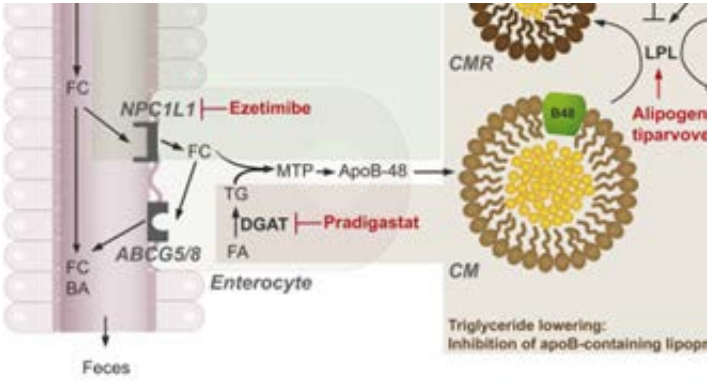
Ezetimibe:

Suppresses cholesterol absorption in the intestine by inhibiting the Niemann-Pick C1 like 1 (NPC1L1) protein

Dose: 10mg per day

FDA approved at age 10 years for hetFH

Added when maximum dose of LDL-c ineffective in controlling lipid level



Soppert J *et al.* Adv Drug Deliv Rev. 2020.

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Safety of Statin Therapy:

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.

ABSTRACT

BACKGROUND

Familial hypercholesterolemia is characterized by severely elevated low-density lipoprotein (LDL) cholesterol levels and premature cardiovascular disease. The short-term efficacy of statin therapy in children is well established, but longer follow-up studies evaluating changes in the risk of cardiovascular disease are scarce

From the Departments of Pediatrics (I.K.L., A.W., D.M.K., J.W.G.), Clinical Epidemiology, Biostatistics, and Bioinformatics (I.K.L., M.H.H., B.A.H.), and Vascular Medicine (I.K.L., J.J.P.K), Amsterdam University Medical Centers, Amsterdam,

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Effectiveness of Therapies:

Table 1 Lipid-lowering medications with approved indications for pediatric use

Class of medication and drug name	Approved pediatric age range	Approved pediatric indication	Clinical trial treatment duration	Clinical trial lipid outcome measure (% change from baseline)				Reference
				LDL-C	Apo B	TG	Lp(a)	
Selective cholesterol-absorption inhibitor								
Ezetimibe	10–17 years	HeFH	12 weeks	−28%	−22%	−6%	NR	Kusters et al. [27]
Bile-acid sequestrant								
Colesevelam	10–17 years	HeFH	8 weeks, 3.75 mg	−10.0%	−6.2%	+17.4%	NR	Stein et al. [32]
PCSK9 inhibitor								
Evolocumab	10–17 years	HoFH and HeFH	12 weeks (TESLA-B)	−23·1%	−19·2%	−1·4%	−9·4%	Raal et al. [15]
			48 weeks (TAUSSIG), ± apheresis	−23.3%	−16.2%	NR	−11.9%	Raal et al. [36]
			24 weeks (HAUSER-RCT)	−44.5%	−34.9%	NR	−7.4%	Santos et al. [37.••]
ANGPTL3 inhibitor								
Evinacumab	12–17 years	HoFH	24 weeks	−47.1%	−41.4%	−55.0%	−5.5%	Raal et al. [45.••]

This table lists the non-statin medications currently approved for use in pediatric patients, along with lipid outcome measures from select clinical trials that included subjects age 17 years or younger

HeFH heterozygous familial hypercholesterolemia, *HoFH* homozygous familial hypercholesterolemia, *NR* not reported, *RCT* randomized controlled trial, *LDL-C* low-density lipoprotein cholesterol, *Apo B* apolipoprotein B, *TG* triglyceride, *Lp(a)* lipoprotein(a), *PCSK9* proprotein convertase subtilisin/kexin type 9 serine protease, *ANGPTL3* angiopoietin-like 3

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Table 2 Pediatric studies on lipid-lowering medications with approved indications for adult use only

Class of medication and drug name	Age range of children studied	Indication studied in children	Duration of treatment	Reported lipid outcome measures (% change from baseline)				Reference
				Total cholesterol	LDL-C	TG	HDL-C	
Vitamin B3								
Niacin	4–14 years	Hypercholesterolemia, retrospective study, $n = 20$	~8 months	−12.6%	−16.8%	+13.2%	+3.6%	Colletti et al. [49]
Fibrates								
Bezafibrate	4–15 years	HeFH, crossover study, $n = 14$	6 months	−16%	NR	−33%	+15%	Wheeler et al. [54]
Bezafibrate (after sitosterol)	5.3–10.8 years	HeFH, crossover study, $n = 7$	3 months	−18%	−28%	-41%	+14.6%	Becker et al. [57]
Fenofibrate	4–19 years	Hyperlipidemia, $n = 17$	3 months	−22%	NR	−39%	NR	Steinmetz et al. [55]
Gemfibrozil	mean age 14 years	Metabolic syndrome, retrospective study, $n = 47$	~8 months	−14%	+6%	−57%	+20%	Smalley and Goldberg [56]
MTP Inhibitor								
Lomitapide	3–16 years	HoFH, case series, $n = 11$	20 months	NR	-58.4%	NR	NR	Ben-Omran T et al. [69]
Omega-3 Fatty Acids								
EPA + DHA	10–19 years	Hypertriglyceridemia, RCT, $n = 25$	6 months	−1.7%	+6.8%	−27.0%	+0.6%	de Ferranti et al. [75]
EPA + DHA + lifestyle	10–16 years	Obesity with hypertriglyceridemia, RCT, $n = 65$	12 weeks	−5.6%	NR	−44.1%	+2.0%	Huang et al. [76]
EPA + DHA	10–16 years	Hypertriglyceridemia, RCT, $n = 130$	12 weeks	−2.9%	NR	−39.1%	+3.8%	Del-Rio-Navarro et al. [77]
Small interfering RNA targeting hepatic PCSK9								
Inclisiran	12–17 years	HeFH, 1 year RCT, 1 year OLE, $n = 150$	2 years	Study is currently in progress				Clinicaltrials.gov [79]

This table lists non-statin medications that have been FDA-approved for use in adults, and may have been studied in children but are not currently approved for age < 18 years. Included are lipid outcome measures from studies that included subjects age 17 years or younger

Percent change from baseline is presented. Please see references for outcomes relative to placebo

HeFH heterozygous familial hypercholesterolemia, *HoFH* homozygous familial hypercholesterolemia, *NR* not reported, *RCT* randomized controlled trial, *LDL-C* low-density lipoprotein cholesterol, *TG* triglyceride, *HDL-C* high-density lipoprotein cholesterol, *MTP* microsomal triglyceride transfer protein, *EPA* eicosapentaenoic acid, *DHA* docosahexaenoic acid

PCSK9 Inhibitor: Evolocumab

Human monoclonal antibody directed against proprotein convertase subtilisin–kexin type 9 (PCSK9); prevents degradation of LDL receptor.

FDA approved for use in adolescents (13-17 years of age) with homozygous familial hypercholesterolemia (HoFH)

Now FDA approved (as of 9/2021) as an add on therapy for children and adolescents in receipt of statin and zetia (10 to 17 years of age) with heterozygous FH

Dose: 420 mg subcutaneously once monthly

Santos RD *et al* NEJM 2020

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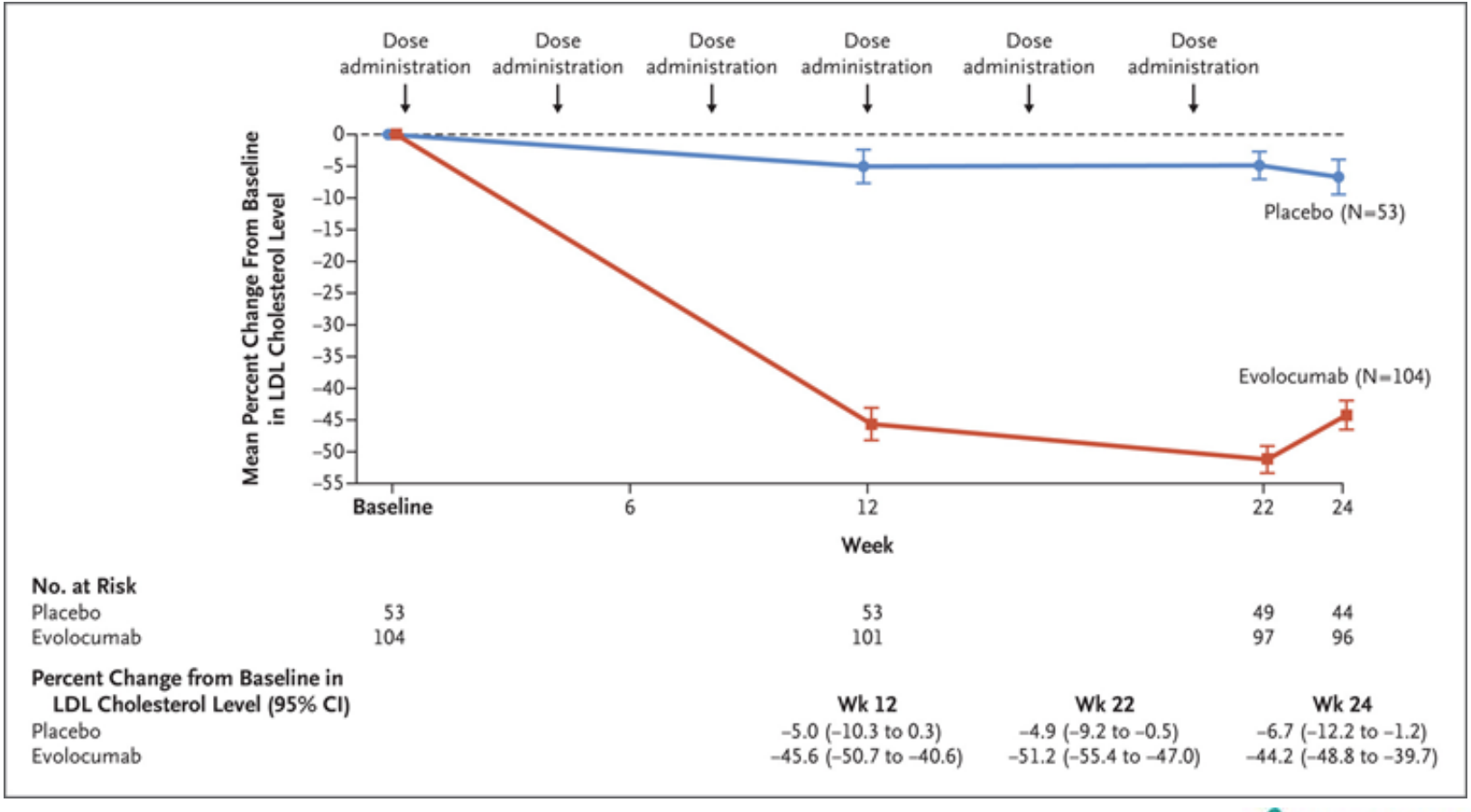

Santos RD *et al* NEJM 2020

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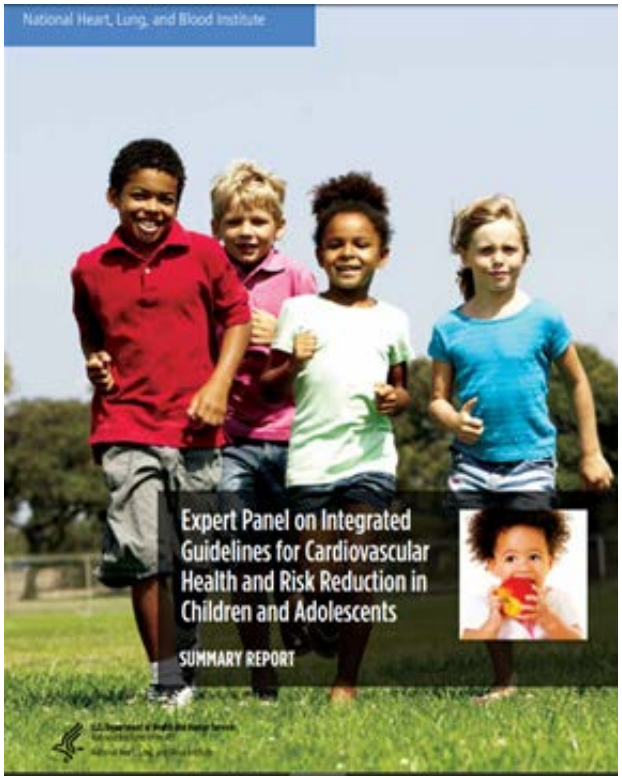
Practical Approach to Lipid Management:



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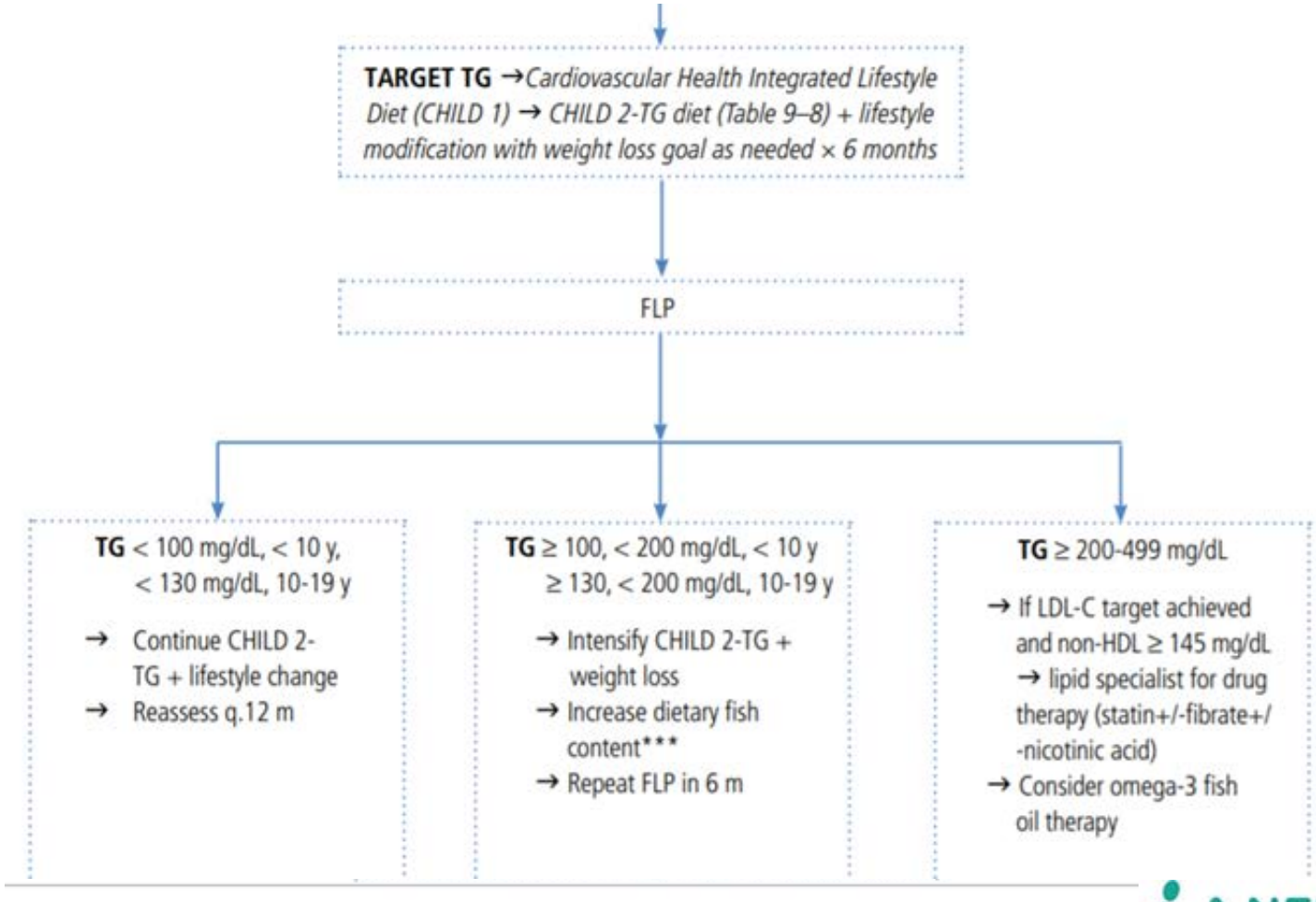

Expert Panel on Integrated Guidelines. Pediatrics 2011

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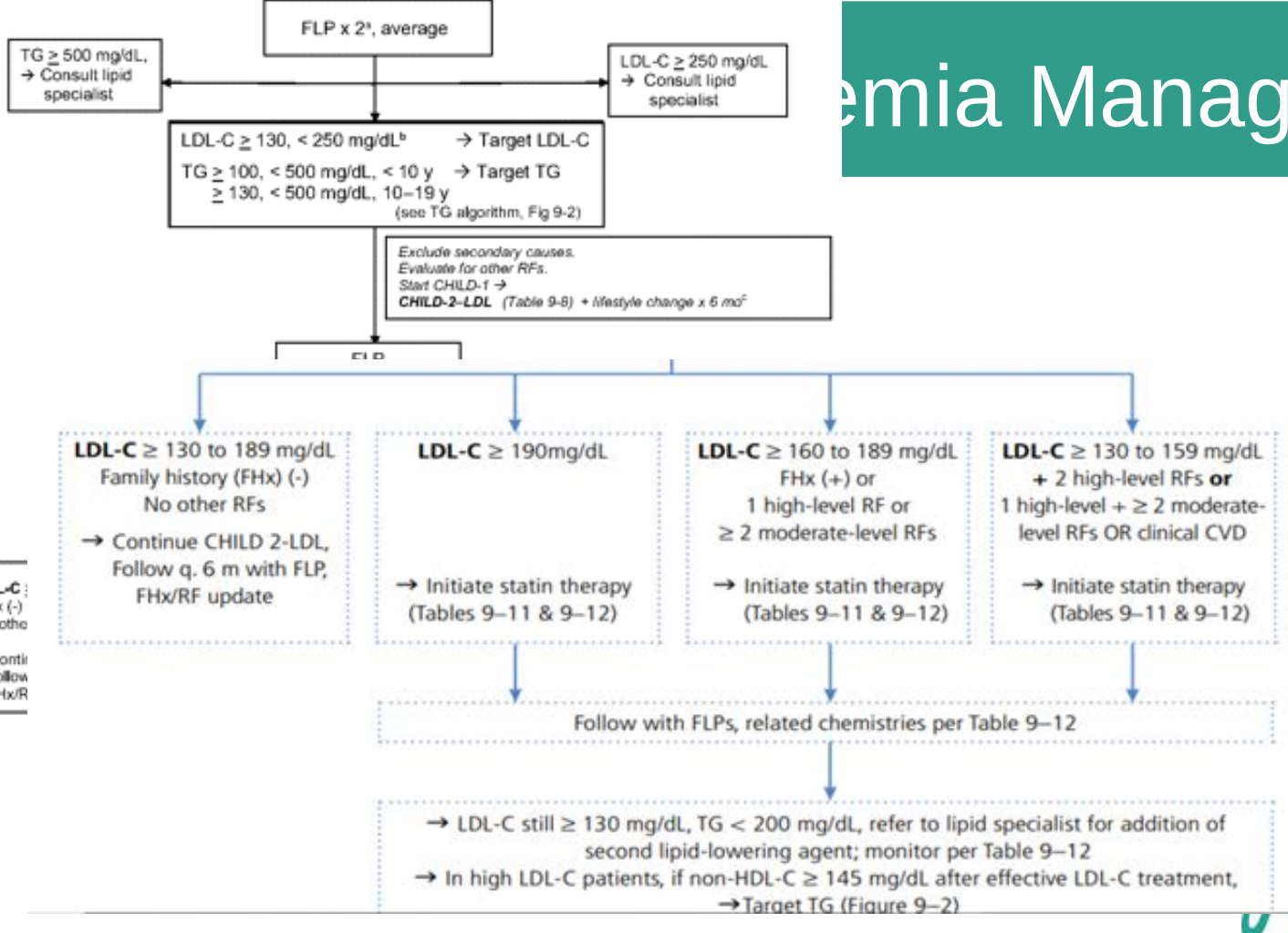
emia Management



Expert Panel on Integrated Guidelines. Pediatrics 2011

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Who is at greatest risk for premature ASCVD?

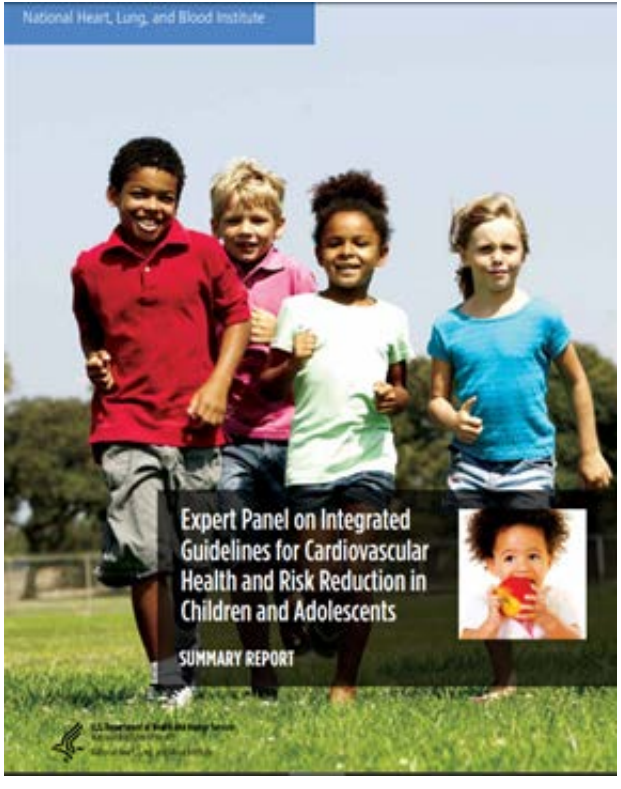

TABLE 9-6 Risk-Factor Definitions for Dyslipidemia Algorithms

Positive family history: myocardial infarction, angina, coronary artery bypass graft/stent/angioplasty, sudden cardiac death in parent, grandparent, aunt, or uncle at <55 y for males, <65 y for females

High-level RFs

- Hypertension that requires drug therapy (BP ≥ 99th percentile + 5 mm Hg)
- Current cigarette smoker
- BMI at the ≥97th percentile
- Presence of high-risk conditions (Table 9-7)
- (DM is also a high-level RF, but it is classified here as a high-risk condition to correspond with Adult Treatment Panel III recommendations for adults that DM be considered a CVD equivalent.)

TABLE 9-7 Special Risk Conditions

High risk

- T1DM and T2DM
- Chronic kidney disease/end-stage renal disease/post–renal transplant
- Post–orthotopic heart transplant
- Kawasaki disease with current aneurysms

Moderate risk

- Kawasaki disease with regressed coronary aneurysms
- Chronic inflammatory disease (systemic lupus erythematosus, juvenile rheumatoid arthritis)
- HIV infection
- Nephrotic syndrome

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TABLE 9-6 Risk-Factor Definitions for Dyslipidemia Algorithms

Positive family history: myocardial infarction, angina, coronary artery bypass graft/stent/angioplasty, sudden cardiac death in parent, grandparent, aunt, or uncle at <55 y for males, <65 y for females

High-level RFs

- Hypertension that requires drug therapy (BP ≥ 99th percentile + 5 mm Hg)
- Current cigarette smoker
- BMI at the ≥97th percentile
- Presence of high-risk conditions (Table 9-7)
- (DM is also a high-level RF, but it is classified here as a high-risk condition to correspond with Adult Treatment Panel III recommendations for adults that DM be considered a CVD equivalent.)

Moderate-level RFs

- Hypertension that does not require drug therapy
- BMI at the ≥95th percentile, <97th percentile
- HDL cholesterol < 40 mg/dL
- Presence of moderate-risk conditions (Table 9-7)

RF indicates risk factor.

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TABLE 9-7 Special Risk Conditions

High risk
T1DM and T2DM
Chronic kidney disease/end-stage renal disease/post–renal transplant
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Nephrotic syndrome

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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. Circulation.

4.4.4.3. Children and Adolescents

Recommendations for Children and Adolescents Referenced studies that support recommendations are summarized in Online Data Supplements 18, 19, 20, and 21.		
COR	**LOE**	**Recommendations**
I	A	1. In children and adolescents with lipid disorders related to obesity, it is recommended to intensify lifestyle therapy, including moderate caloric restriction and regular aerobic physical activity (S4.4.4.3-1–S4.4.4.3-4).
I	B-NR	2. In children and adolescents with lipid abnormalities, lifestyle counseling is beneficial for lowering LDL-C (S4.4.4.3-1–S.4.4.4.3-3, S4.4.4.3-5–S4.4.4.3-12).
IIa	B-R	3. In children and adolescents 10 years of age or older with an LDL-C level persistently 190 mg/dL (≥4.9 mmol/L) or higher or 160 mg/dL (4.1 mmol/L) or higher 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).
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).
IIa	B-NR	5. In children and adolescents found to have moderate or severe hypercholesterolemia, it is reasonable to carry out reverse-cascade screening of family members, which includes cholesterol testing for first-, second-, and when possible, third-degree biological relatives, for detection of familial forms of hypercholesterolemia (S4.4.4.3-22–S4.4.4.3-24).
		6. In children and adolescents with obesity or other metabolic risk factors, it

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Sample Case:

Component	Latest Ref Rng & Units	1:12 PM
Cholesterol, Total	100 - 169 mg/dL	
Triglycerides	0 - 89 mg/dL	
HDL	>39 mg/dL	
VLDL CHOLESTEROL	5 - 40 mg/dL	
LDL CHOLESTEROL	0 - 109 mg/dL	

Why does young adult lipid level matter?

Young adult LDL ≥100 mg/dl (compared with <100 mg/dl) was associated with a 64% increased risk for CHD, independent of later adult exposures

Zhang Y, et al. J ACC 2019.

Component	Latest Ref Rng & Units	**8/27/2021** 11:03 AM	**1/5/2022** 12:48 PM	**4/12/2022** 11:05 AM
Cholesterol, Total	100 - 169 mg/dL	300 (A)	285 (H)	267 (H)
Triglycerides	0 - 89 mg/dL		110 (A)	85 72
HDL	>39 mg/dL		42	37 (L) 41
VLDL CHOLESTEROL	5 - 40 mg/dL	20		
LDL CHOLESTEROL	0 - 109 mg/dL	238 (A)	234 (H)	214 (H)

ApoB mutation.

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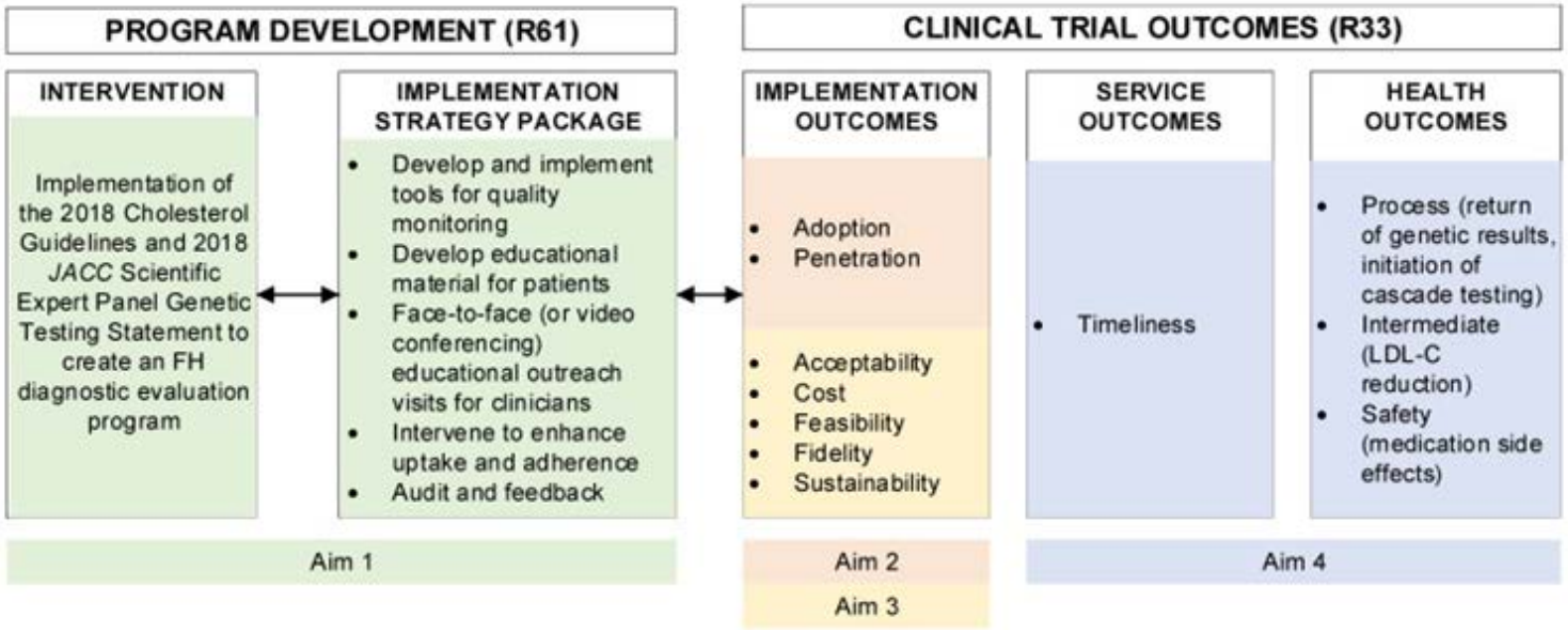
Implementation Science to Enhance Screening



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Lipoprotein (a)

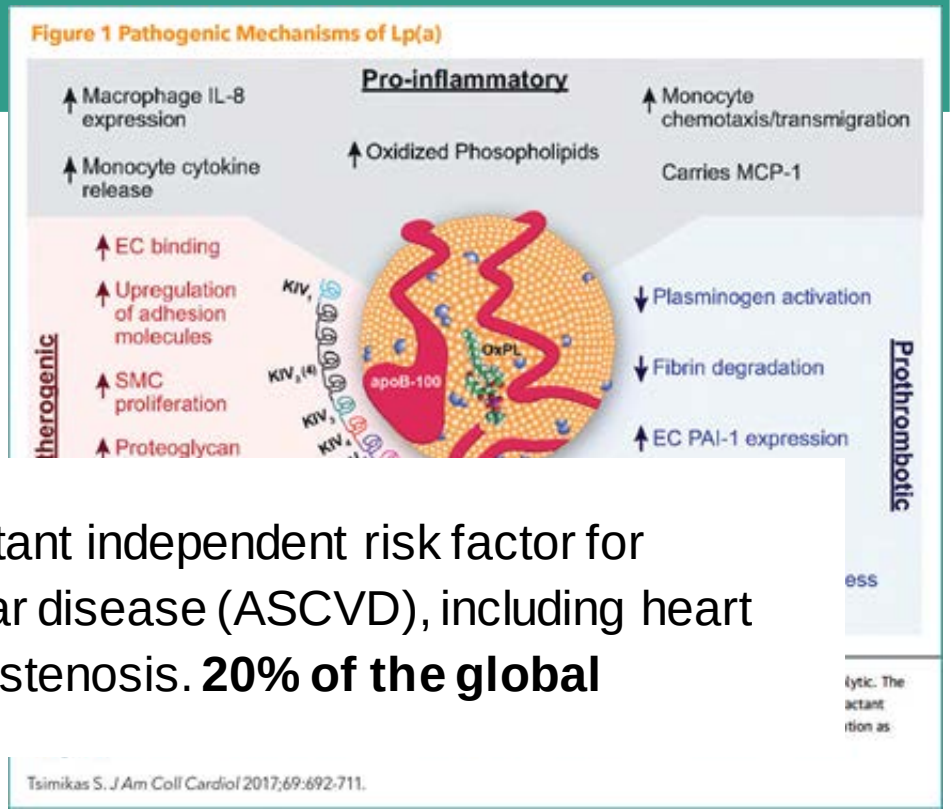
Composed of LDL-c and apolipoprotein (a) (apo[a])

Levels genetically determined

High plasma concentrations of Lp(a) assoc
wi
ca
inf
st

Lp(a) values ≥125 nmol/L (or ≥50 mg/dL)

Currently, not used for disease risk stratification*



High Lipoprotein(a) or Lp(a) is an important independent risk factor for premature atherosclerotic cardiovascular disease (ASCVD), including heart attacks, stroke, and calcific aortic valve stenosis. **20% of the global population has elevated Lp(a).**

Wilson DP, *et al*. J Clin Lipidol 2019

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Lipoprotein (a) cont'd:

Highly atherogenic lipoprotein

Independent risk factor for ASCVD including coronary heart disease (CHD) , stroke, peripheral arterial disease, and calcific aortic valve disease (CAVD) in the adult population

Lp(a) is the strongest independent genetic risk factor for both myocardial infarction (MI) and aortic stenosis (10), and inversely correlated with life expectancy (11).

More atherogenic than low density lipoprotein cholesterol (LDL-C) because of its pro-inflammatory and pro-thrombogenic properties.

Lp(a) in youth, data in the pediatric population suggests that it augments the risk of future ASCVD, is a risk factor for arterial ischemic stroke (AIS), and is possibly associated with venous thromboembolic events

Lp(a) is a highly hereditable disorder and although the genes for these two lipid disorders are not linked, when they occur jointly and/or in combination with other common risk factors such as diabetes and hypertension, they markedly accelerate the development of premature ASCVD,

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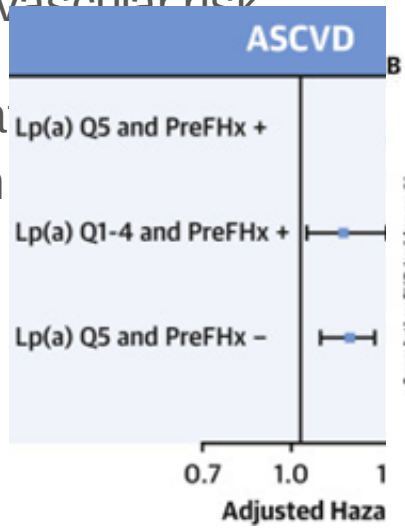
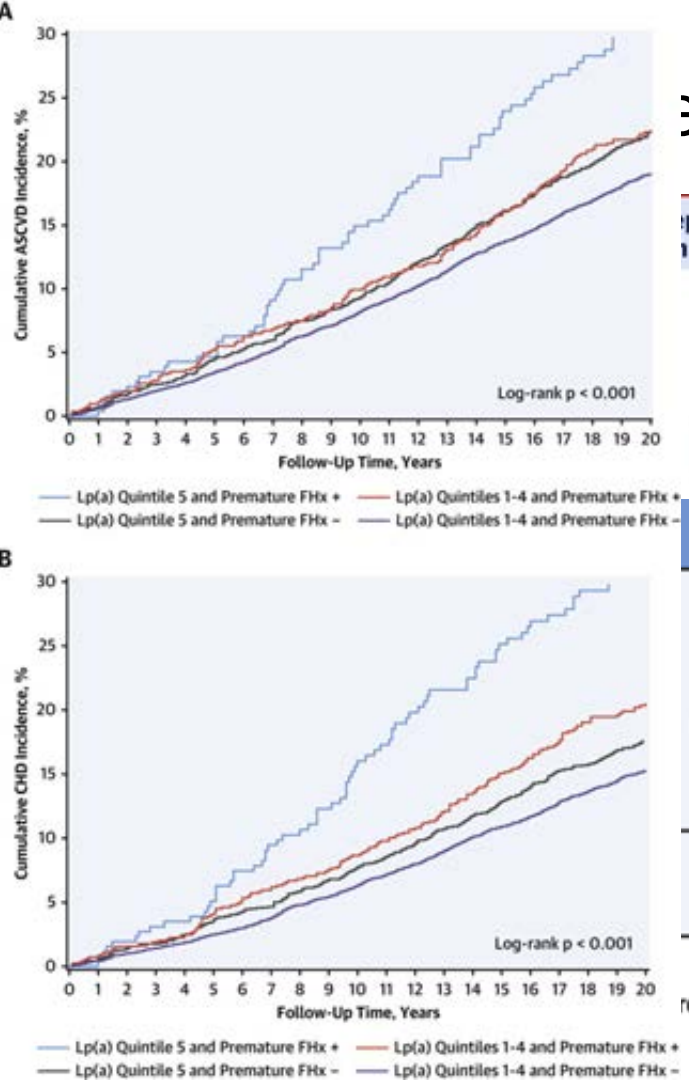
Wilson DP, *et al*. J Clin Lipidol 2019

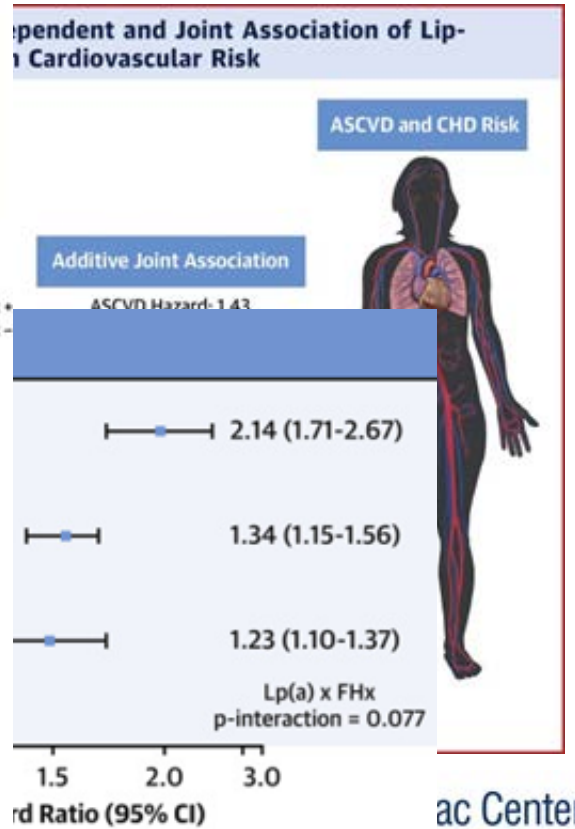
Lipoprotein(a) a edict CVD Risk

Elevated lipoprotein (a) a
family history of prematu
coronary artery disease
associated with
cardiovascular risk

Popula
Risk in



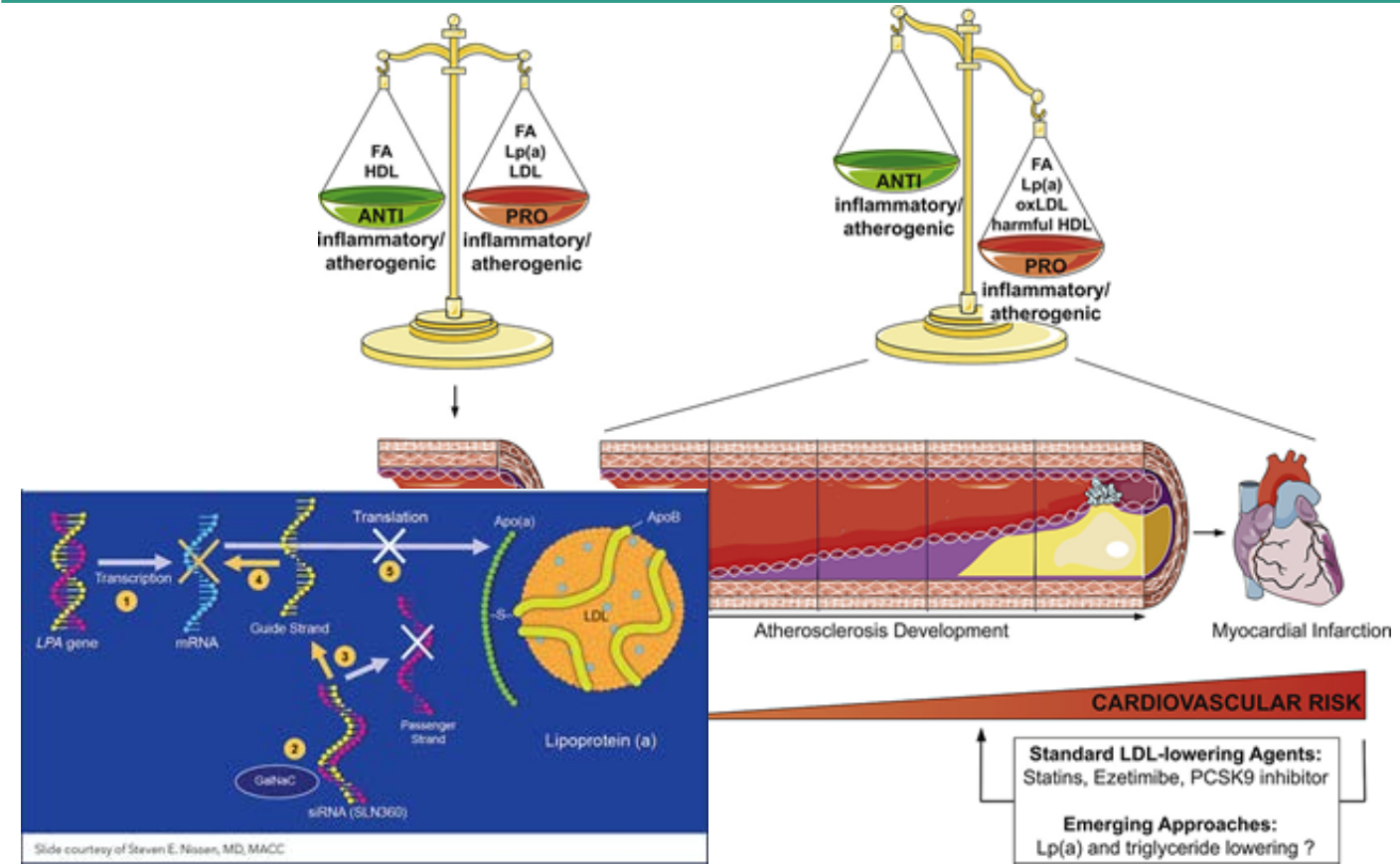




ac Center

Mehta A, *et al.* JACC. 2020

Lipoprotein (a)



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Secondary Causes of Dyslipidemia

Thyroid studies (TSH, Free T4)

Hemoglobin A1c (HgbA1c)

Medications and Other Potential Secondary Causes:

Obesity
Metabolic syndrome
Diuretics
Positive caloric balance
Alcohol consumption
Renal disease (Uremia, nephrotic syndrome)
Liver disease
Hypothyroidism
Pregnancy
Autoimmune disorders
Medications (corticosteroids, thiazide diuretics, non-cardioselective beta-blockers, oral estrogens, bile acid sequestrants, atypical psychotropic medications, isotretinoin)

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Familial Combined Hyperlipidemia

Most common inherited form of hypertriglyceridemia; Prevalence 0.5 to 2%

Associated with a 1.7 to 10 fold increased risk of premature CAD

Elevated serum TG due to elevated VLDL

Suspect Dx: affected family members and elevations in serum lipid levels triggered by weight gain

No single genetic etiology

Baker-Smith *et al*. Curr Hypertens Rep 2020
Zambon A *et al*. J Intern Med 2011

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Hypertriglyceridemia

Prevalence: 5.9% of normal weight children; 13.8% in overweight children; 24.1% in obese children

Associated with “atherogenic dyslipidemia”/ dyslipidemia of obesity:

High serum TG levels and low HDL-c

High TG/HDL-c ratio >2.27 associated 6X greater chance of insulin resistance (risk factor for type 2 diabetes mellitus)

CDC. MMWR 2010
Giannini C *et al* Diabetes Care 2011

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Summary of recommendations: Take Home #1

Screening for dyslipidemia at age 2 years (non-fasting; non-HDL) if family history of familial hypercholesterolemia and/or family history of premature coronary artery disease; parent with high cholesterol, moderate/high level risk factors/conditions

Screening for dyslipidemia at age 9-11 years

Screening for dyslipidemia age age 17-21 years

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Take Home #2: What the pediatrician can do

Check Labs!

Primordial prevention: counseling for the prevention of risk development (not smoking, low saturated fat diet, appropriate caloric intake and regular physical activity supporting the avoidance of diabetes)

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Final Take Home Message

We can help prevent the development of premature coronary artery disease via early screening, diagnosis and treatment of dyslipidemia; in particular, familial hypercholesterolemia

Screen all children 9 to 11 years of age (begin at 2 years of age if there is a family history familial hypercholesterolemia)

Repeat screening between 17 and 21 years of age

Lipid screening for identifying familial hypercholesterolemia and dyslipidemia of obesity.

Safe and effective treatment options available.

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Pre-Talk Question #1:

If you are a physician, nurse practitioner, or physician assistant, answer the following. “I feel comfortable diagnosing familial hypercholesterolemia”

A. Yes, I think so
B. No
C. Not sure
D. Prefer not to answer

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Pre-Talk Question #2:

The following patient is most likely to have heterozygous familial hypercholesterolemia:

A. Patient X: 10 year old with LDL-c of 140mg/dL. No family history of premature coronary artery disease.
B. Patient Y: 10 year old with LDL-c of 160mg/dL. With lifestyle intervention, repeat LDL-c120mg/dL. Family history of premature coronary artery disease.
C. Patient Z: 10 year old with LDL-c of 190mg/dL. With lifestyle intervention, repeat LDL-c 190mg/dL. Family history of premature coronary artery disease.
D. Patient W: 10 year old with LDL-c of 120mg/dL, TG of 170mg/dL, and HDL-c of 29mg/dL. Family history unknown

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Pre-Talk Question #3:

Among persons with heterozygous familial hypercholesterolemia, the most effective option for reducing LDL-c level is the following:

A. Diet alone
B. Exercise alone
C. Statin
D. Not sure

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Additional Slides:

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LDLR dependent strategies

Statin

PCSK9 inhibitors

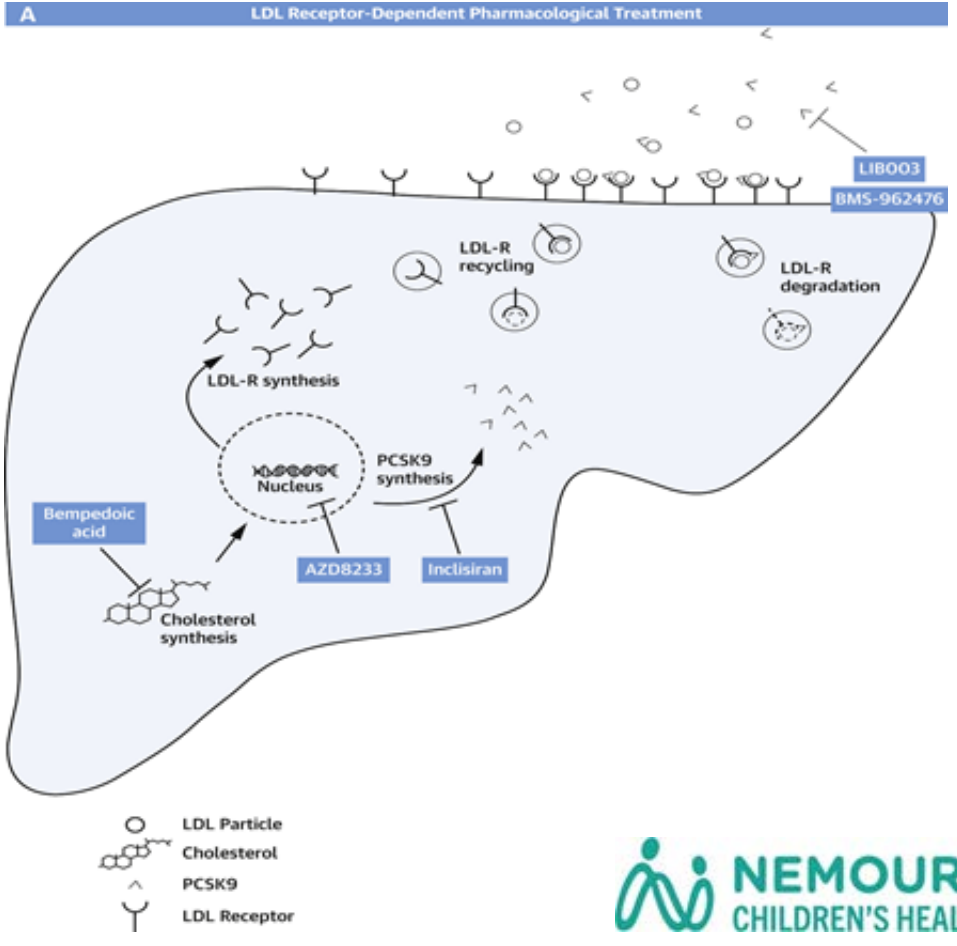
Bempedoic acid

AZD8233

Inclisiran

LIB003

BMS-962476



PCSK9 Inhibitor (Evolocumab-Repatha, alirocumab-Praluent)

LDLR receptor dependent

Interrupts the recycling process of LDLR after internalization (shortens the survival time)

At a constraint rate of LDL-R receptor synthesis, fewer receptors are expressed on the surface of the hepatocyte

Various approaches can be used to target PCSK9: differences vary by frequency of dosing required (biweekly, monthly for protein targeting interventions; twice per year with small interfering RNA (siRNA), to once in a lifetime DNA targeting approach)

Associated with 50% reduction in LDL-c

Efficacy of PCSK9 inhibition is still tied to residual LDLR activity. Patients with hoFH null-null mutations (<2% activity) show little to no response w/ mAbs

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LIB003

LDLR receptor dependent

Adnectin against PCSK9 (synthetic polypeptide designed to bind to targets); mode of action is similar to an antibody

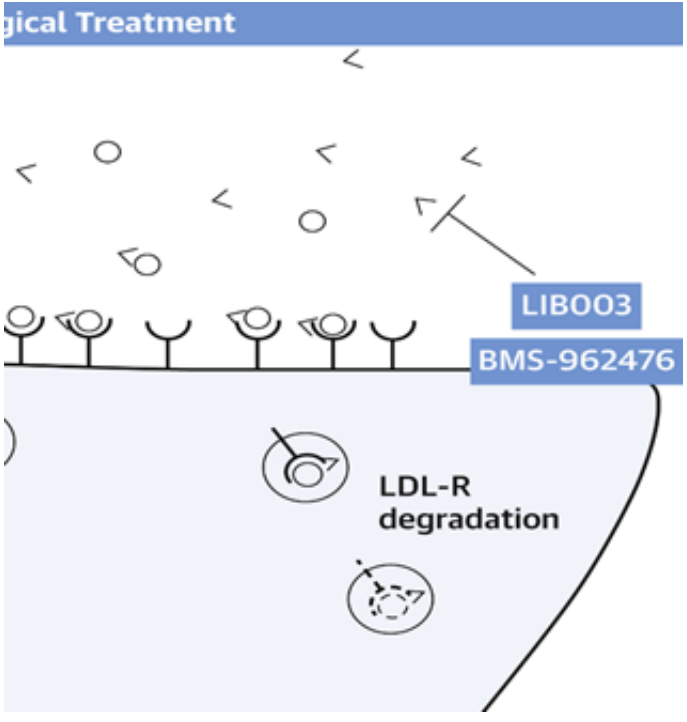
Recombinant fusion protein targeting PCSK9

Blocks binding of PCSK9 to LDLR

Monthly injection. 300mg dose

77% reduction in LDL-c at week 12

SE: Minimal injection site reactions



Inclisiran

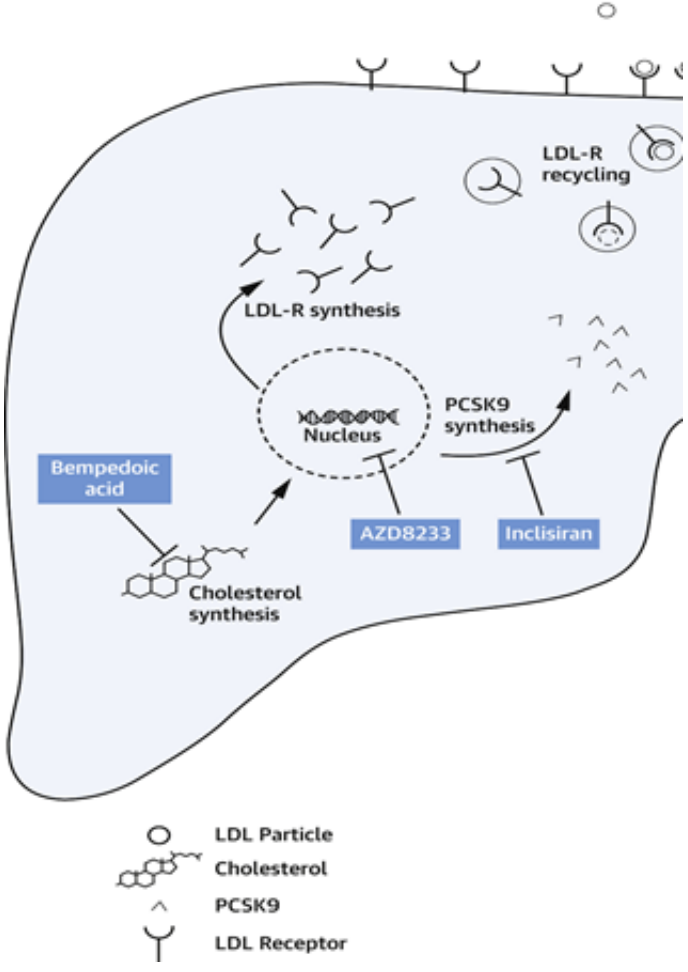
LDLR receptor dependent

siRNA again PCSK9

Anti-sense oligonucleotides against PCSK9; inhibits translation of PCSK9 mRNA

15mg oral or 25mg SC injection monthly

Additional 48% reduction in LDL-c among persons receiving statin and ezetimibe; Among HoFH patients, +3 to -37% reduction in LDL-c

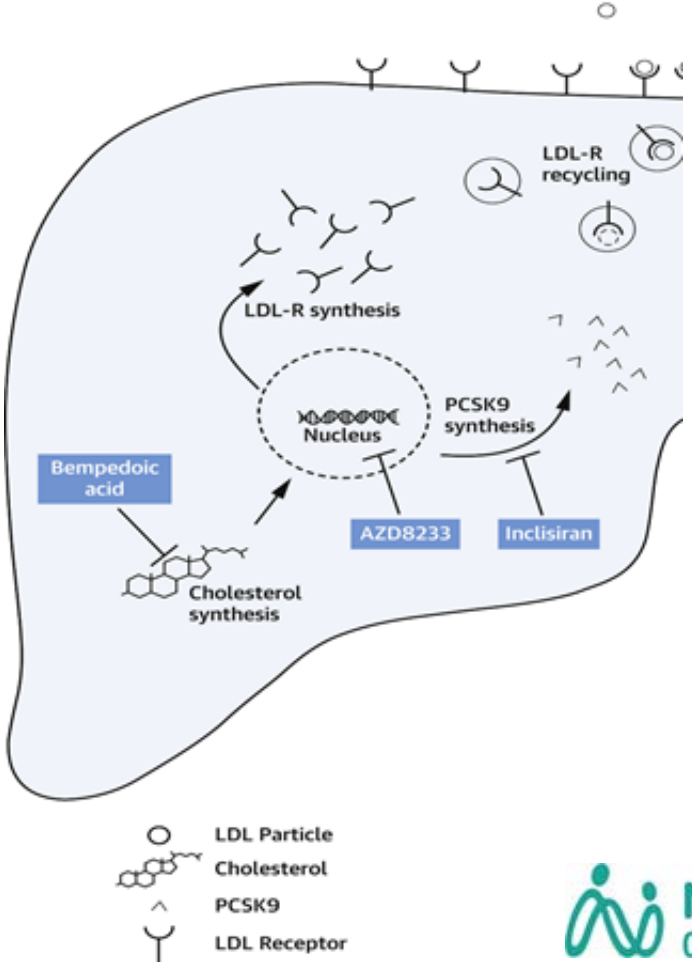


AZD8233

LDLR receptor dependent

Anti-sense oligonucleotides against PCSK9; inhibits translation of PCSK9 mRNA

Not yet demonstrated in FH, SQ injection of AZD8233 reduced circulating PCSK9 by 90% and LDL-c by 68% over 1 month; returning to baseline over 1 weeks



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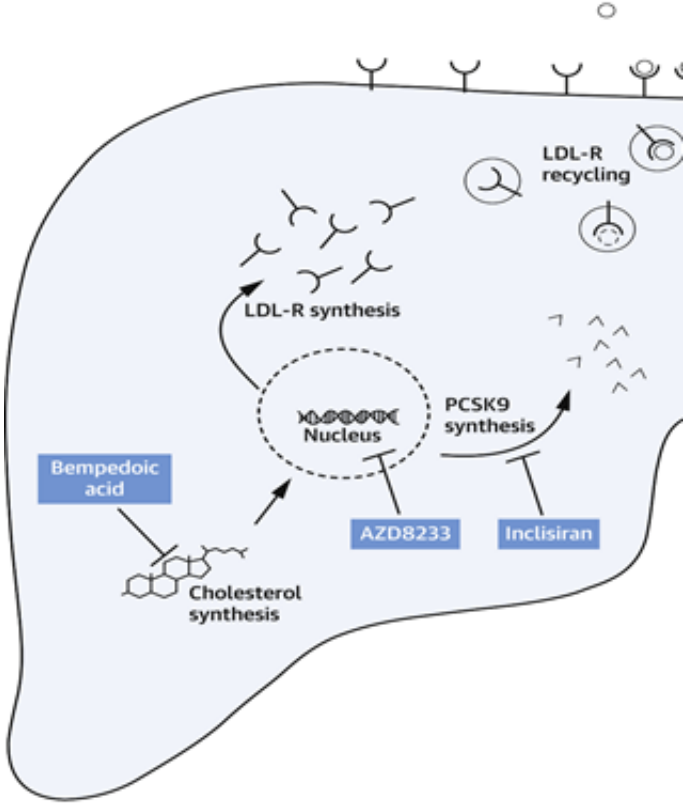
Bempedoic Acid

LDLR receptor dependent

Small molecule inhibiting adenosine triphosphate citrate lyase

Daily 180mg daily (½ life: 15-24 hours)

SE: Nasopharyngitis, myalgia, upper respiratory tract infection, urinary tract infection, arthralgia, dizziness, muscle spasms, diarrhea, increased risk of gout and tendon rupture



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Bempedoic Acid

Nexletol

MOA: adenosine triphosphate citrate lyase inhibitor; reduces LDL-c when used an adjunct to lipid-lowering therapy in patients with high cardiovascular disease (CVD) risk

Additional agent used in the management of patients with persistent elevations in serum LDL-c despite use of statin and ezetimibe; Efficacy demonstrated in the Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen) Harmony trial

Dose: 180mg (daily) (12.6% change from baseline LDL-c)

Ray KK *et al.* NEJM 2019

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LDLR independent strategies

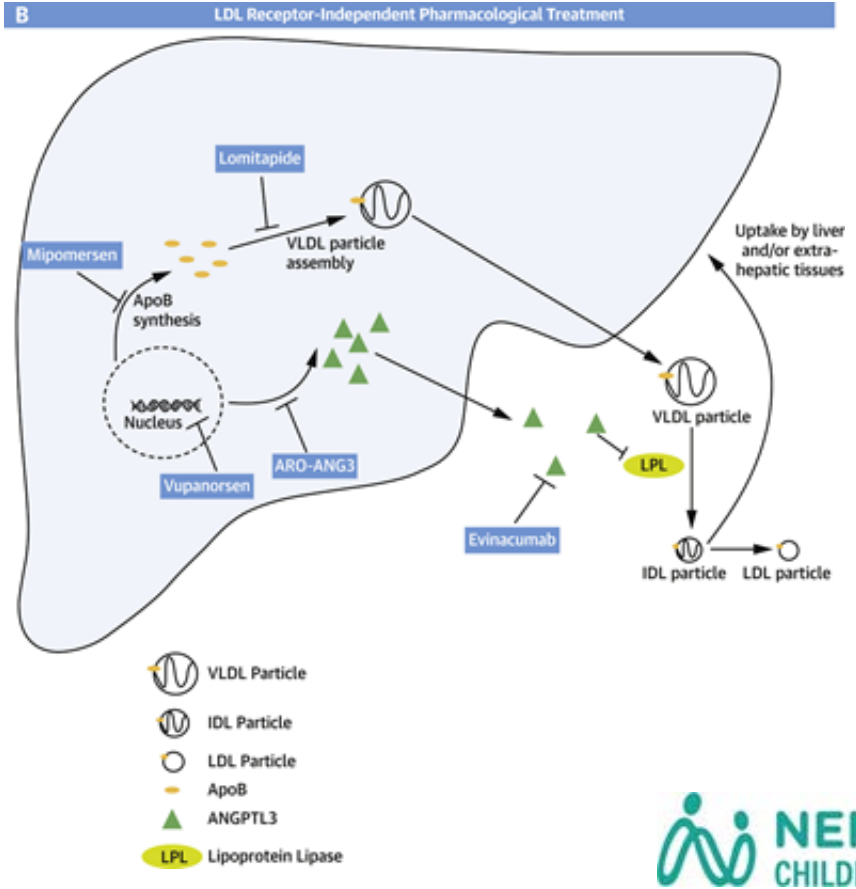
Lomitapide - not approved in children

Mipomersen

Vupanorsen

ARO-ANG3

Evinacumab



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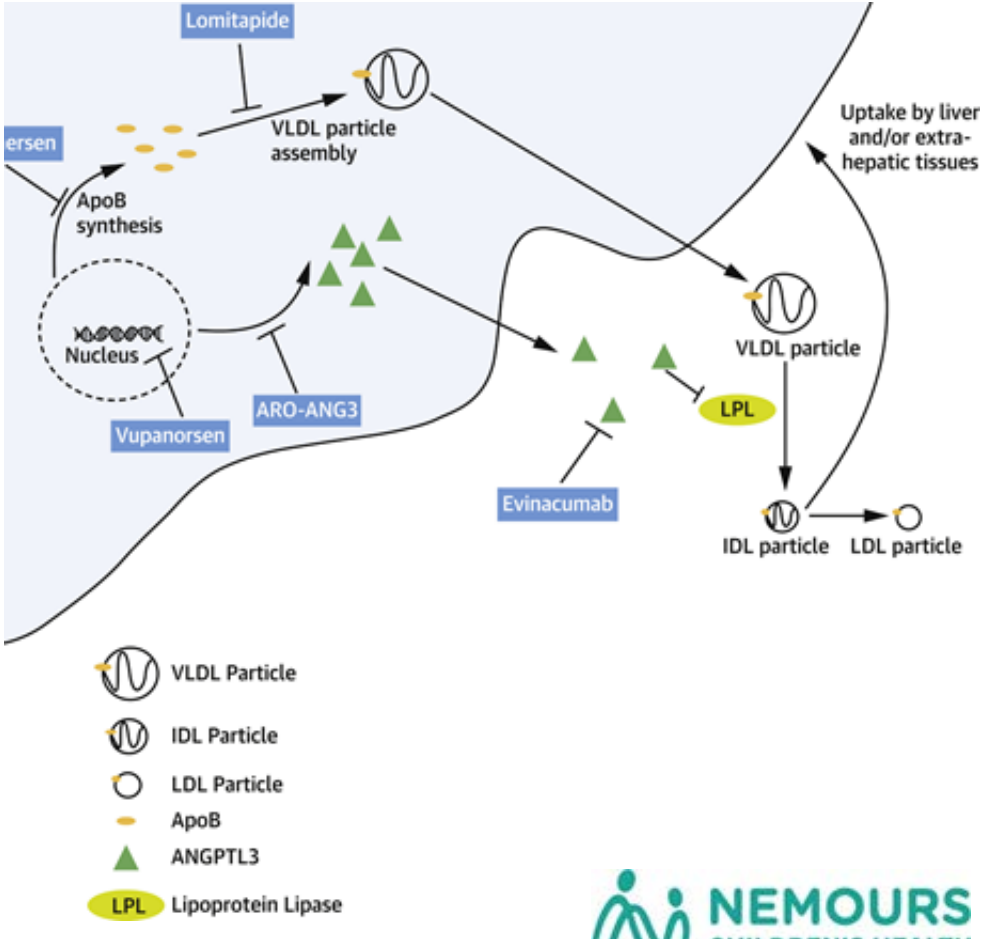
Evinacumab

LDLR receptor *in*dependent

Decreases ANGPTL3 levels→ increased lipoprotein lipase and endothelial lipase activity. (LL increases influx of free fatty acids into muscles and lipogenesis in adipose tissue); →enhanced LDL-c uptake, independent of LDLR; decreased VLDL synthesis

Effective in HoFH patients

Monthly injections



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Vupanorsen

LDLR receptor *in*dependent

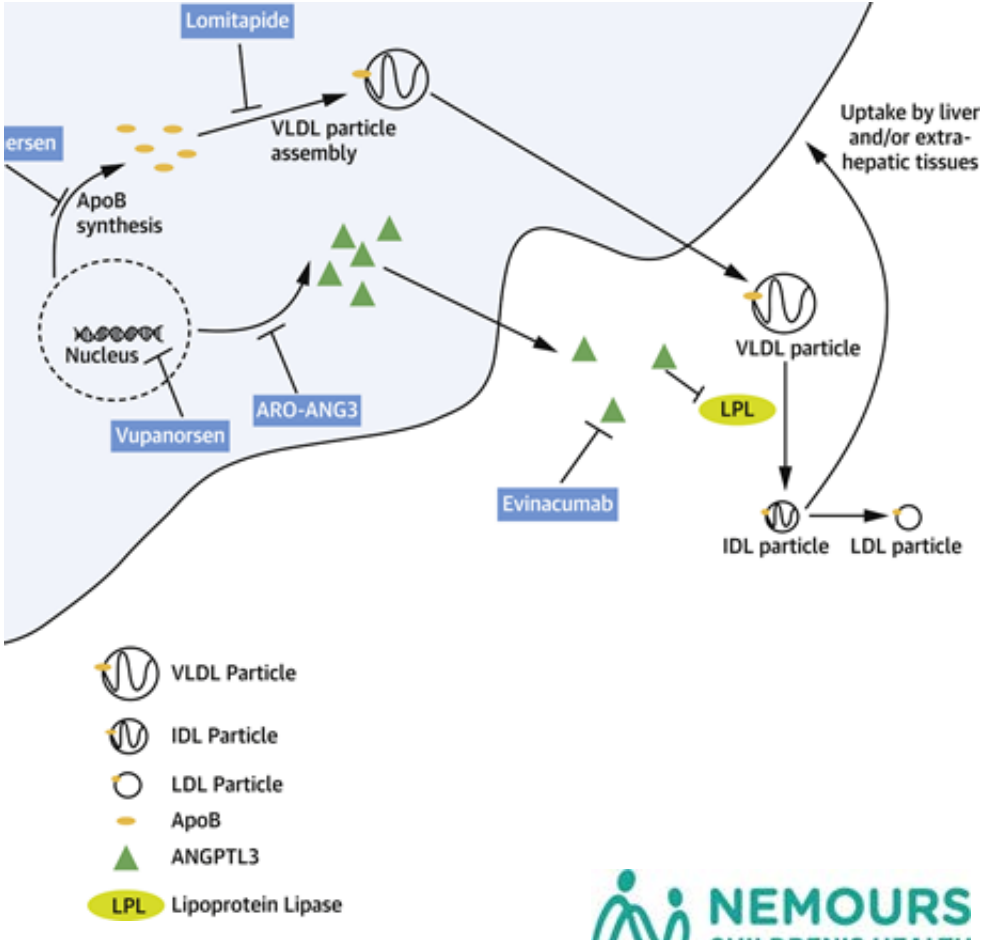
N-acetylgalactosamine modified ASO targeting hepatic ANGPTL3 mRNA

Site of inhibition within the nucleus of the hepatocyte

Reduction in TG by 44%; VLDL-c by 38%

More modest TG reduction among persons with hepatic steatosis, diabetes, and HTG

Focus of tx: combined dyslipidemia, chylomicronemia; **not approved in Peds**



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