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Algorithms for Treating Dyslipidemia in Youth

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Abstract

Purpose of Review The goal of this article is to review algorithms for treating dyslipidemia in youth, discuss pitfalls, propose enhanced algorithms to address pitfalls, and consider future directions.

Recent Findings The presence of modifiable and non-modifiable cardiovascular disease (CVD) risk factors during childhood is associated with CVD-related events in adulthood. Recent data has shown that childhood initiation of statin therapy in youth < 18 years of age with familial hypercholesterolemia reduces the risk of adult CVD. However, pediatric dyslipidemia remains undertreated in part due to a lack of primary health care providers with adequate understanding of screening guidelines and pediatric lipidologists with experience in treatment and follow-up of this unique population. Management algorithms have been published by the National Heart, Lung, and Blood Institute and American Heart Association as tools to empower clinicians to manage dyslipidemia. We propose enhanced algorithms, which incorporate recently approved pharmacotherapy to address the management gaps. Future algorithms based upon clinical risk scores may enhance treatment and improve outcomes.

Summary Algorithms for dyslipidemia management which target youth < 18 years of age are tools which empower clinicians to manage dyslipidemia in this unique population. Enhanced algorithms may help address pitfalls. We acknowledge the need for further risk assessment tools in pediatrics for tailored dyslipidemia management.

Keywords Dyslipidemia · Cardiovascular disease · Algorithms · Youth · Lipids

Introduction

Atherosclerosis and associated cardiovascular risk factors are known to develop in childhood and adolescence [1–3]. Many studies have shown that cardiovascular disease (CVD) risk factors in childhood, including dyslipidemia, progress into adult life and are associated with increased risk of premature CVD [4–7]. A large multi-cohort study evaluating long-term trajectories of cardiovascular health (defined by the American Heart Association (AHA) in 2010, based on body mass index (BMI), blood pressure (BP), cholesterol, glucose, diet, physical activity, smoking) showed that those with poor cardiovascular health in childhood experienced a more rapid progression in adulthood, and greater subclinical atherosclerosis [8]. Recently, a large prospective cohort study involving participants in the International Childhood and Cardiovascular Cohort consortium showed childhood CVD risk factors were also associated with fatal and nonfatal cardiovascular events in midlife [9•]. However, optimum management of risk factors in childhood has been shown to reduce risk of CVD in adulthood [10•]. Thus, it is essential to target cardiovascular risk factors, including dyslipidemia, in childhood with the goal of improving outcomes.

Screening and management guidelines for youth, as well as position statements, have previously been published with the intent of identifying and optimally managing cardiovascular risk factors at an early age with the goal of preventing or reducing the burden of atherosclerosis, the underlying cause of CVD in adulthood (see Table 1) [11–20, 21•].

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However, lipid screening in youth has been underutilized, and abnormal lipid values are undertreated [22–27]. A survey of US pediatricians conducted by the American Academy of Pediatrics (AAP) in 2013–2014 showed that only 30% performed universal screening at age 9–11 years. In that survey, 62% of responders considered lack of comfort in prescribing statins to be a major barrier to treatment, while 27% reported that lack of access to lipid specialists was a major barrier [22]. Suboptimal rates of screening fail to identify children who would likely benefit from early intervention.

Management algorithms have been created to provide tools for primary care providers and subspecialists to aid in management of dyslipidemia, as there is a lack of access to lipid specialists. Unique clinics targeting dyslipidemia in the pediatric population are often limited to large academic centers in medium- to large-sized cities [28]. We will review the currently available algorithms, discuss pitfalls, propose enhanced algorithms, and highlight future directions.

Definitions and Normative Values

Dyslipidemia is characterized by abnormal concentrations of lipids in the blood, which include elevated levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), triglycerides (TG), and low levels of high-density lipoprotein cholesterol (HDL-C), while the term hyperlipidemia generally refers to an increase in one or more lipid values. Hypercholesterolemia more specifically refers to high TC, high LDL-C, and/or high non-HDL-C. While the main focus has been to identify youth with elevated levels of LDL-C, studies have shown a predominant combined dyslipidemic pattern in children including moderately to severely elevated TG and non-HDL-C, reduced HDL-C, and minimally elevated or normal LDL-C, with increased small, dense LDL particles. Dyslipidemia places children at risk for early atherosclerotic disease [18, 29].

Normative lipid values in children are available and derived from population-based data from the Lipid Research Clinics Prevalence Study, a multicenter collaborative in the 1970s, which evaluated fasting lipoprotein profiles in over 13,000 children aged 0–19 years, and also from National Health and Nutrition Examination Survey III which evaluated over 7000 children aged 4–19 years from 1988–1994 [30–32]. Lipid levels vary by age and sex, along with race/ethnicity. Lipid levels initially increase from birth until 2 years of life, and then remain relatively stable until adolescence. During puberty, TC and LDL-C concentrations decrease initially, and then increase in the later teen years.

Table 1 Timeline of pediatric cholesterol guidelines, position statements, clinical reports

Year	Organization	Highlights
1992	National Cholesterol Education Program (NCEP), National Heart, Lung and Blood Institute (NHLBI) report, guidelines [11]	• Population approach with healthy lifestyle • Individualized approach based on family history
1998	American Association of Pediatrics (AAP) report [12]	• Population approach • Individualized approach • Patient risk factors including smoking, elevated BP, low high-density lipoprotein (HDL) cholesterol, severe obesity, diabetes mellitus, physical activity
2003	American Heart Association (AHA) guidelines [13]	• Similar to AAP, NHLBI
2006	AHA scientific statement for high-risk pediatric patients [14]	• Risk stratification based on high-risk pediatric conditions/diseases
2007	United States Preventative Services Task Force (USPTF) recommendations [15]	• Insufficient evidence for universal screening for dyslipidemia in children
2008	AAP report [16]	• Population approach • Individualized approach • Patient risk factors • Risk stratification based on risk conditions/diseases
2011	National Lipid Association (NLA), Familial Hypercholesterolemia (FH) guidelines [17]	• Universal screening in 9–11 years of age • Screening in ≥ 2 years with positive family history
2011	Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction, NHLBI report, guidelines [18]	• Population approach • Individualized approach • Patient risk factors • Risk stratification based on risk conditions/diseases • Universal screening 9–11 years of age; repeat 17–21 years of age
2016	USPTF recommendations [19]	• Insufficient evidence for universal lipid screening in children
2019	AHA/American College of Cardiology (ACC) guidelines [20]	• Similar to 2011 NHLBI
2019	AHA, scientific statement for high-risk pediatric patients [21•]	• Updated risk stratification and treatment algorithm for high-risk pediatric populations

Males experience a decrease in HDL-C where females have stable HDL-C until menopause. African American children tend to have higher TC and HDL-C and lower TG compared to other racial/ethnic groups [30–32].

Based on normative data, definitions for dyslipidemia in youth were initially published in 1992 from the National Cholesterol Expert Panel [33]. The updated recommendations from NHLBI in 2011 also incorporate data from the Bogalusa Heart study evaluating non-HDL levels, and these cutoffs matched the NCEP pediatric panel cutoffs for LDL-C (see Table 2) [18]. Of note, these abnormal definitions are based on population distributions, not health outcomes.

Screening Guidelines

The goal of screening is early detection and intervention of children at risk of developing CVD. Earlier guidelines targeted youth with an informative family history, risk factors, and medical conditions associated with high risk of premature cardiovascular disease. However, 30–60% of children with dyslipidemia are missed if family history is the only criteria used [18]. In addition, population screening at younger ages is highly sensitive for detection of high-risk conditions such as familial hypercholesterolemia (FH). A meta-analysis showed that population screening in children 1–9 years of age resulted in a detection rate of 96% for infants and children with FH, with a false positive rate of 1% [34]. Thus, the National Heart, Lung, and Blood Institute (NHLBI) guidelines added universal screening at 9–11 years, and in those with normal initial screening, repeat testing at 17–21 years [18]. While the U.S. Preventative Services Task Force concluded that evidence was insufficient to either recommend or not recommend universal cholesterol screening in children, the NHLBI guidelines have been endorsed by many organizations including the AAP, the National Lipid Association (NLA), the AHA, and the American College of Cardiology (ACC) [18, 20, 35]. Thus, universal screening is widely recommended to detect and create the opportunity of early treatment in children with dyslipidemia.

Table 2 Population-based acceptable, borderline-abnormal, and abnormal lipid concentrations in pediatrics

	Acceptable, mg/dL	Borderline-abnormal, mg/dL	Abnormal, mg/dL
TC	<170	170–199	≥200
LDL-C	<110	110–129	≥130
Non-HDL-C	<120	120–144	≥145
TG (0–9 years)	<75	75–99	≥100
TG (10–19 years)	<90	90–109	≥110
HDL-C	>45	40–45	<40

Values are from NCEP Expert Panel on Cholesterol Levels in Children. The cutoffs for borderline-abnormal and abnormal lipoprotein concentrations are represented by 75th and 95th percentiles (low cutoff of 10th percentile for HDL-C) of the population distribution age 2–19 years of age. Non-HDL-C levels are from the Bogalusa Heart study, which match the NCEP pediatric panel cutoffs for LDL-C [18]

TC total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *non-HDL-C* non-high-density lipoprotein-C, *TG* triglycerides, *HDL-C* high-density lipoprotein-C.

Management Algorithms Based on Guidelines and Position Statements

The 1992 NHLBI guidelines for cardiovascular risk reduction were the first to address lipid screening, definitions, and management in the pediatric population. These recommendations were updated in 2011, by an expert panel assembled to critically review subsequent evidence targeting both prevention of risk factors and future CVD by optimally managing risk factors. The intended audience were primary care providers and dietitians [18]. The AHA released a scientific statement in 2006, stratifying management of CVD risk reduction based on high-risk conditions/diseases that are associated with accelerated atherosclerosis and early CVD, directed to pediatric care providers and subspecialists who manage complex primary disease processes. This position statement was last updated in 2019 [21•]. We will summarize the dyslipidemia management algorithms that were derived from these guidelines and position statements.

The 2011 NHLBI dyslipidemia algorithm approaches management based upon the presence of an abnormal fasting or non-fasting lipid panel [18]. In general, if lipids levels are confirmed to be abnormal, the panel recommended an initial trial of lifestyle changes; if lifestyle alone was unsuccessful in reaching the desired goal, then pharmacology should be considered. At very elevated levels (LDL-C greater than or equal to 250 mg/dL and/or TG greater than or equal to 500 mg/dL), a lipid specialist should be consulted. The guidelines include statins, as well as instructions as to how to initiate and monitor statin therapy. It also lists additional agents to consider under direction of a lipid specialist, such as bile acid sequestrants and fibric acid derivatives. However, the list of lipid-lowering agents is limited to the medications which were available in the year that it was published. Also of note, currently none of the pharmacotherapies for hypertriglyceridemia is U.S. Food and Drug Administration (FDA) approved for use in childhood.

The 2019 AHA algorithm begins with, and focuses on, patient risk stratification [21•]. Patients are stratified by disease condition as high-risk, moderate-risk, or at-risk. These updated risk categories are based upon the magnitude of the risk for atherosclerotic-related pathology compared to the general population. This is followed by global risk

factor assessment. If 2 or more risk factors are present, then patients are reassigned to the next higher risk category. Once the risk category is established, then specific treatment goals are recommended. Depending on the risk category, there are different treatment thresholds, recommendations, and treatment goals. Treatment recommendations generally vary in terms of when to start pharmacotherapy in addition to lifestyle changes. Treatment recommendations for elevated LDL-C include statins, additional agents such as cholesterol absorption inhibitors, proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9) agents, and LDL apheresis for homozygous FH (HoFH). Pharmacotherapy recommendations for elevated triglycerides include off label use of fenofibrate, omega-3 fatty acids, and statins if non-HDL (or apolipoprotein B) is elevated.

Pitfalls and Future Directions

Despite having management algorithms, dyslipidemia in children is still poorly recognized and inadequately treated. From 1999 to 2016, the proportion of youths aged 6–19 years with ideal concentrations of lipids and apolipoprotein B, for example, has been reported to be only 47–51%. Those with adverse levels of lipids or apolipoprotein B comprised 19–25% [36]. There are many possible reasons for this that have previously been extensively discussed in the literature; however, we will focus on potential pitfalls of the algorithms.

The Pediatric Endocrine Society (PES) sponsors several special interest groups to address issues concerning endocrine-related disease in children, including lipid disorders. A PES subcommittee (Lipid Special Interest Group) created several algorithms in an attempt to fill gaps which are not addressed by existing guidelines and algorithms. Examples of these are included here as condition-specific algorithms.

One pitfall is not only the complexity of the comprehensive management algorithms, but there are also many different organizations with varying recommendations, creating even more confusion for the treating clinician on optimal management for certain patient populations. We propose simplifying clinical management by creating condition-specific algorithms. For example, dyslipidemia is frequently seen in patients with type 1 or type 2 diabetes and data show dyslipidemia in these populations is undertreated and undermanaged [37–40]. Therefore, we have created a diabetes-specific lipid algorithm incorporating recommendations from the AHA position statement, NHLBI guidelines, and American Diabetes Association (ADA) standards of care [18, 21•, 41, 42]. This includes starting statin pharmacotherapy simultaneously with lifestyle changes for LDL ≥ 130 mg/dL [21•]. We have not included an age-specific limit on when to start statin therapy, a departure from the ADA standards of care, due to availability of FDA-approved statins starting at age 7 years for HoFH and age 8 years for HeFH [43]. We also recommend initiation of pharmacotherapy earlier for TG > 400 mg/dL or TG ≥ 150 and non-HDL ≥ 145, with omega-3 fatty acids and considering fibrates, consistent with AHA recommendations, which differs slightly from the NHLBI guidelines and ADA recommendations. We have also incorporated non-HDL-C goals into this algorithm as it is a significant predictor of presence of atherosclerosis and persistent dyslipidemia and is accurate in a non-fasting state [18]. However, the primary endpoints are still LDL-C or TG levels, as most studies of medications and reducing cardiovascular risk have targeted primarily LDL-C and/or TG levels. In general, our algorithm provides more clinically relevant guidance than the AHA recommendations, for the clinician who manages this defined population. We see potential for creation of additional algorithms in the setting of other high-risk conditions (such as chronic kidney disease, Kawasaki disease, childhood cancer survivor, solid organ transplant) that may be useful to other pediatric subspecialists. In general, there is a need for simplification of algorithms to help with feasibility of guideline adherence (Fig. 1).

Another potential pitfall is the lack of consistent implementation of the algorithms in clinical practice, again perhaps from the complexity of algorithms. It has been reported that establishing clinical effectiveness of a clinical innovation is not enough to guarantee uptake into routine use and it may take at least 17–20 years to implement into clinical practice, with fewer than 50% of clinical innovations making it into general usage [44, 45]. Perhaps we need more research focusing on implementation science in this field.

A third potential pitfall of the algorithms is that they may not address the complexity of treating rare lipid disorders. There are no current algorithms for pediatric patients that include additional recommendations if first-line therapy is insufficient to achieve treatment goals, or if a patient exhibits statin intolerance. Newer pharmacotherapy options have been approved for use in children and adolescents in recent years. Thus, we propose a "Beyond Statin" supplemental algorithm to close this information gap, which includes new medications including proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9) inhibitors, and angiopoietin-like 3 (ANGPTL3) inhibitors (see Fig. 2) [46, 47]. This algorithm addresses the gap of treating rare lipid disorders, such as HoFH, but also encompasses other high-risk conditions when statins are insufficient (Fig. 2).

A fourth potential pitfall to the algorithms, specifically with the 2011 NHLBI guidelines, is that data is no longer up to date. However, the bigger issue may be that there is no single organization that speaks to the issues of management of pediatric dyslipidemia and/or timely updates. To achieve the goal of improving outcomes in youth with dyslipidemia, there needs to be more collaboration

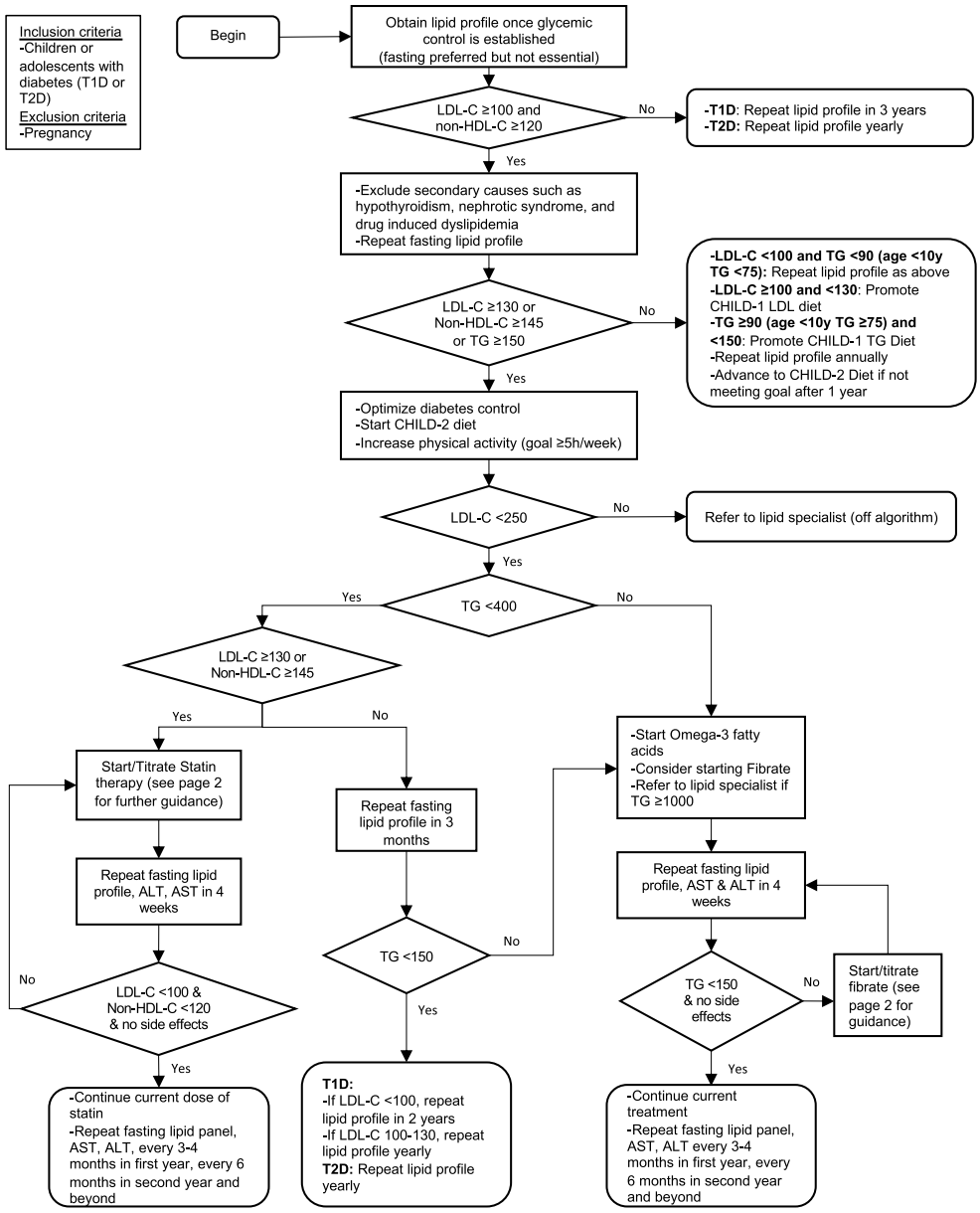
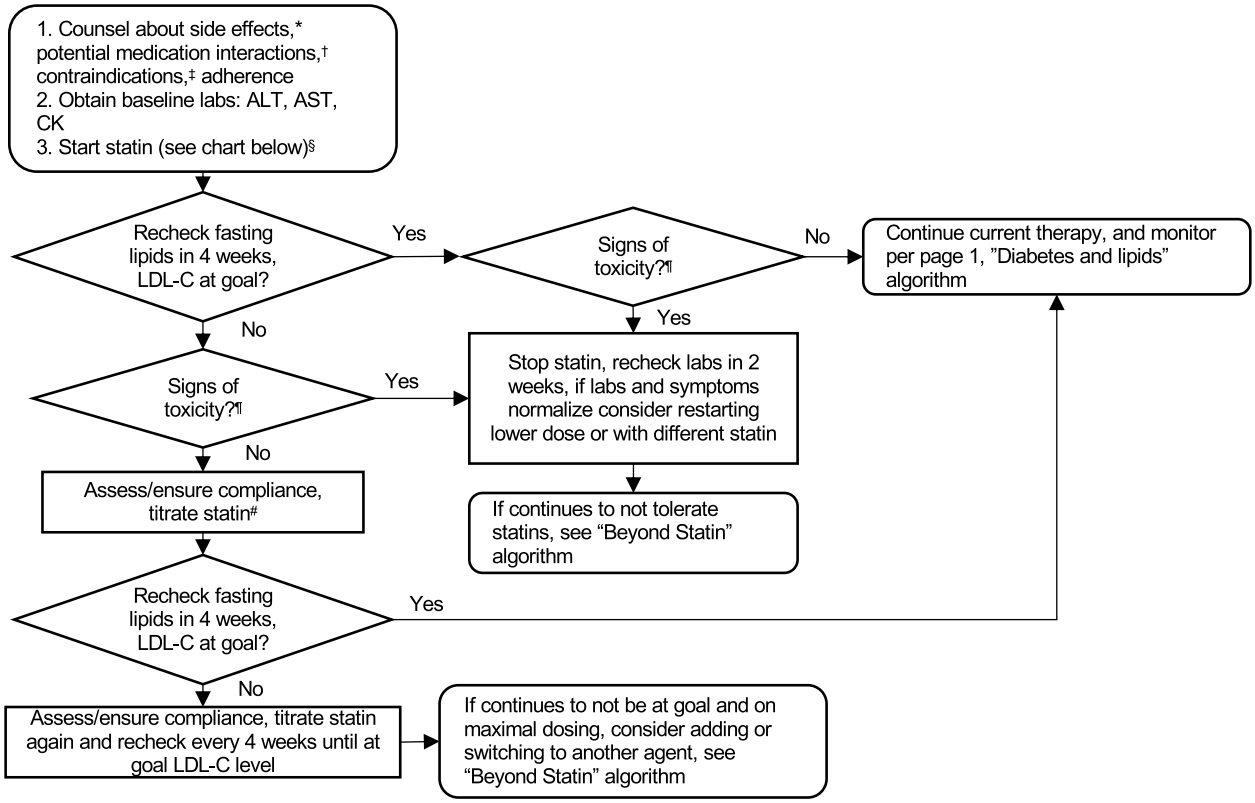


Fig. 1 Diabetes and lipids algorithm. This algorithm was developed by PES members to address dyslipidemia in type 1 and type 2 diabetes mellitus patients, based on the AHA position statement, NHLBI guidelines, and ADA standards of care. This algorithm includes a second page with instructions for starting statins, including recommendations for baseline labs, and counseling on side effects and contraindications, based on NHLBI guidelines. There is also a dose range table with anticipated lipid-lowering effects, incorporated from Jones et al. 1998. There are also general precautions about starting fibrate therapy, including counseling on side effects, drug interactions, and contraindications [18, 21•, 41, 42, 53]. *Side effects: muscle pain/cramps, weakness, myopathy. †Potential medication interactions: cyclosporine, niacin, fibric acid derivative, erythromycin, azole antifungal, HIV protease inhibitor. ‡Contraindicated in pregnancy, known teratogen. For female patients consider contraception or gynecology referral. Also contraindicated in nursing mothers, acute liver disease, hypersensitivity to statin. §Currently statins are approved for children starting age 7 years for HoFH and age 8 years for HeFH. ¶Toxicity = AST, ALT > 3 × ULN, or CK > 10 × ULN (check CK if concern for myopathy). #2 × dose = ↓ 6% LDL-C. αOf note, TG lowering medications in adults with diabetes have shown inconsistent results with improved CVD benefit [54]. βSide effects: muscle toxicity, hepatotoxicity. If on fibrate and statin, higher risk of muscle toxicity. γDrug interactions: coumarin anticoagulants, immunosuppressants, bile acid resins. δContraindications: severe renal dysfunction, acute liver disease, gall bladder disease, hypersensitivity to fibrate, nursing mothers. *T1D* type 1 diabetes mellitus, *T2D* type 2 diabetes mellitus, *LDL-C* low-density lipoprotein cholesterol, *non-HDL* non-high-density lipoprotein, *TG* triglyceride, *y* years of age, *CHILD-1* Cardiovascular Health Integrated Lifestyle-1, *CHILD-2* Cardiovascular Health Integrated Lifestyle-2, *ALT* alanine transaminase, *AST* aspartate aminotransferase, *CK* creatinine kinase, *ULN* upper limit of normal, *HoFH* homozygous familial hypercholesterolemia, *HeFH* heterozygous familial hypercholesterolemia, *EPA* eicosapentaenoic acid, *DHA* docosahexaenoic acid

Statin initiation



Lipid Lowering Dose Ranges

Drug	Strength	Dose	% ↓LDL-C	% ↑HDL-C	% ↓Trigs	% ↓TC
Lovastatin	10 mg	10 mg QD	22%	4%	5%	12%
	20 mg	20 mg QD	29%	7%	12%	21%
	40 mg	40 mg QD	31%	5%	2%	23%
	80 mg	80 mg QD	48%	8%	13%	36%
Atorvastatin	10 mg	10 mg QD	38%	6%	13%	28%
	20 mg	20 mg QD	46%	5%	20%	35%
	40 mg	40 mg QD	51%	5%	32%	40%
	80 mg	80 mg QD	54%	1%	25%	42%
Fluvastatin	20 mg	20 mg QD	17%	1%	5%	13%
	40 mg	40 mg QD	23%	3%	13%	19%
	80 mg XL	80 mg QD	35%	8%	11%	20%
Pravastatin	10 mg	10 mg QD	19%	10%	3%	13%
	20 mg	20 mg QD	24%	3%	15%	18%
	40 mg	40 mg QD	34%	6%	10%	24%
Rosuvastatin	5 mg	5 mg QD	45%	13%	35%	33%
	10 mg	10 mg QD	52%	14%	10%	36%
	20 mg	20 mg QD	55%	8%	23%	40%
	40 mg	40 mg QD	63%	10%	28%	46%
Simvastatin	5 mg	5 mg QD	24%	7%	12%	17%
	10 mg	10 mg QD	28%	7%	12%	21%
	20 mg	20 mg QD	35%	5%	17%	26%
	40 mg	40 mg QD	41%	10%	15%	30%
	80 mg	80 mg QD	47%	12%	36%	36%

Triglyceride management (off label in pediatrics[α])

Omega-3 fatty acids

1. Recommended dose is 4g/day DHA/EPA

Fibrates

1. Counsel about side effects,[β] potential drug interactions,[γ] and contraindications[δ]
2. Prefer fenofibrate initially due to fewer side effects, better tolerated, and only once daily dosing
3. Check baseline AST, ALT and again in 4 weeks to monitor on fibrate. If AST, ALT >3x ULN, stop fibrate, consider restarting at lower dose once labs normalize or refer to lipid specialist

Fig. 1 (continued)

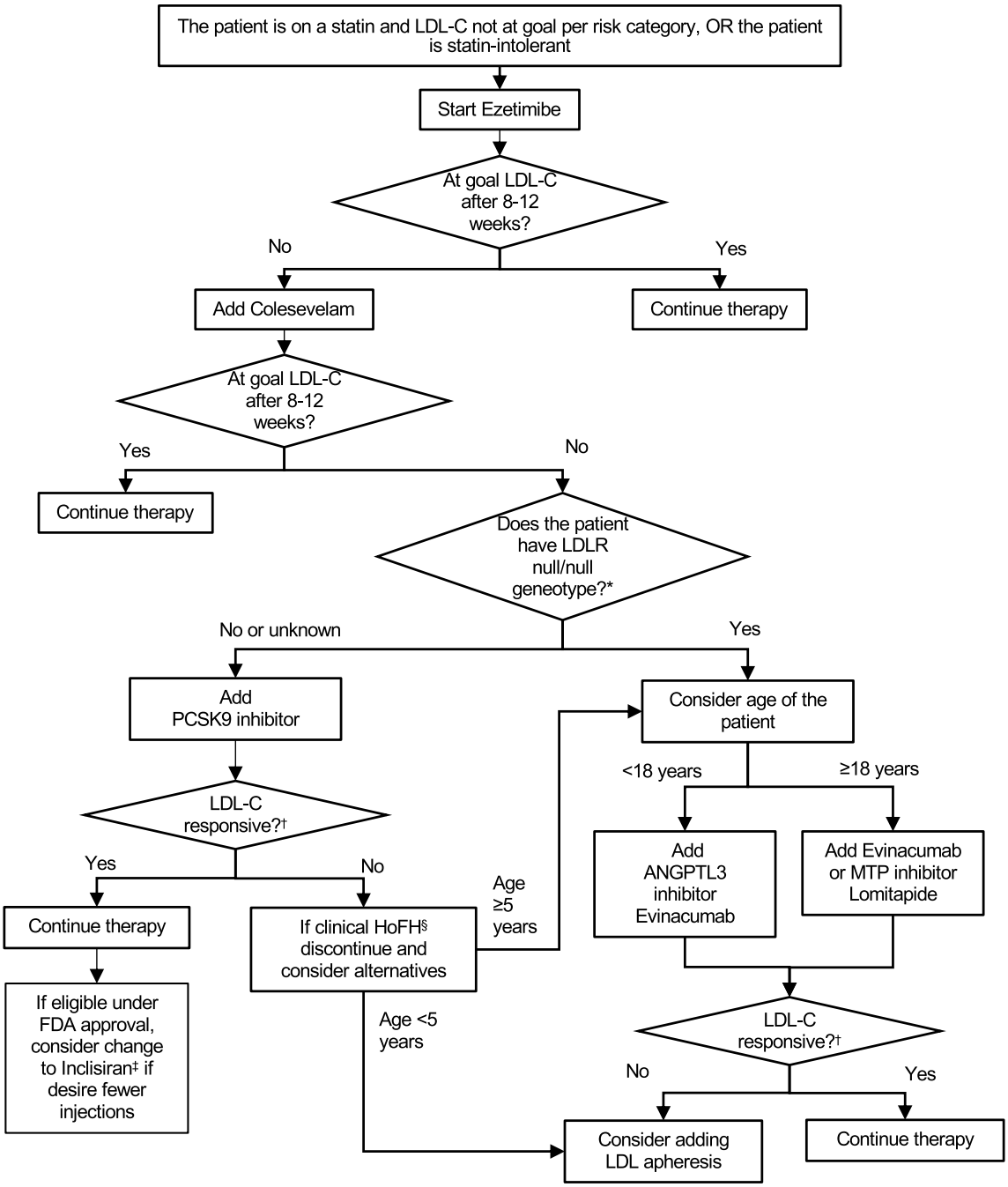
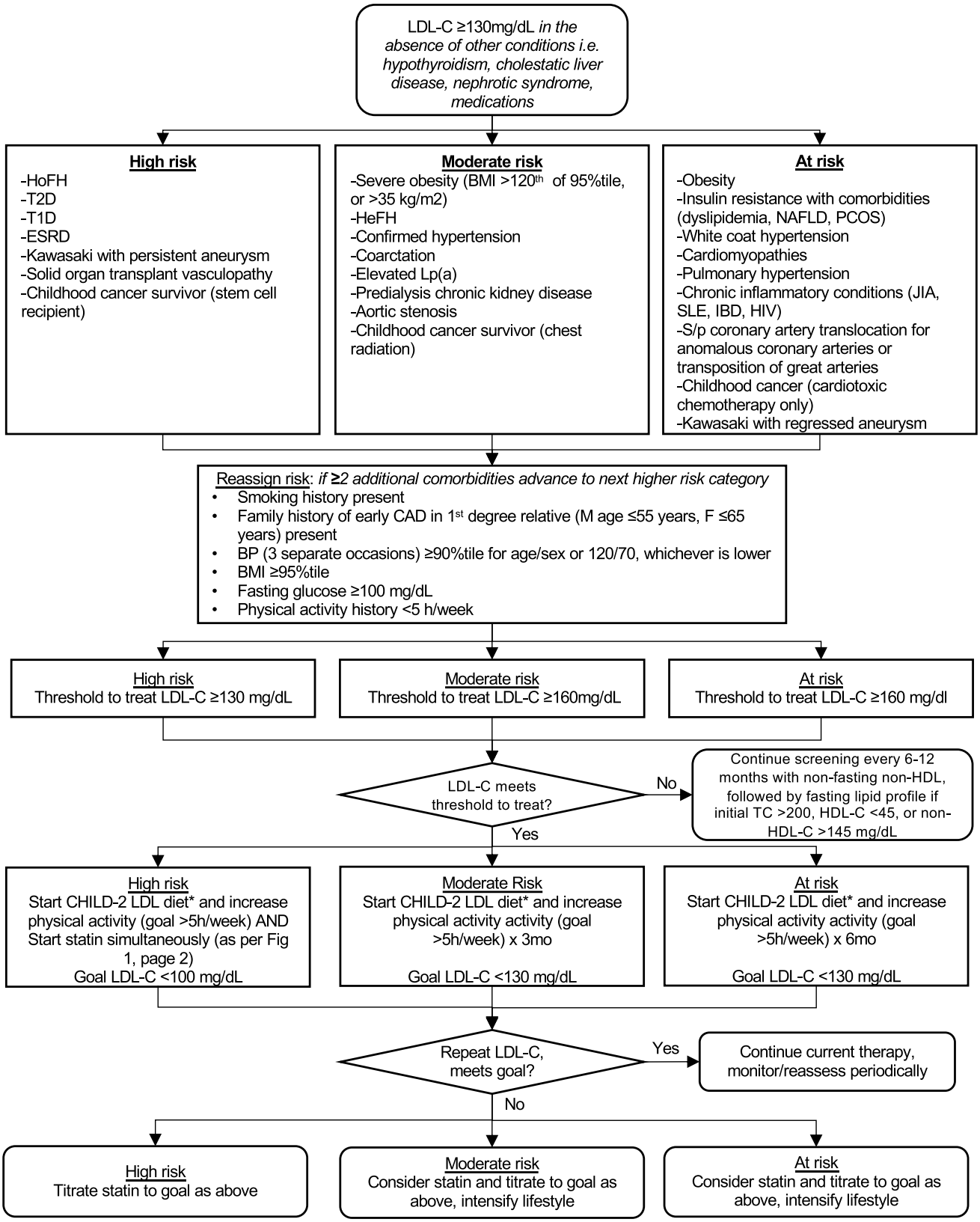


Fig. 2 Beyond statins algorithm. This algorithm was developed by PES members to address management of hypercholesterolemia in the event that statins are insufficient, or a patient is intolerant to statins. This algorithm includes medications for HoFH that have been very recently approved by the FDA. The decision branch points for therapeutic options are based on age and available information on genetic mutations, since PCSK9 inhibitor response depe-ds on LDL receptor function. The PES algorithm for members includes a table summarizing anticipated LDL-C lowering effects and drug safety information [46, 47, 55]. *Genetic testing is currently not an exclusive criteria for defining familial hypercholesterolemia, and not all patients with clinical FH have identifiable mutations. Thus, the decision branch encompasses patients whose genetics are unknown. †In severe cases, initial LDL-C goal may be ≥ 50% reduction from baseline, and clinical judgment is required to evaluate responsiveness. ‡At this time Inclisiran is only FDA-approved for age 18 years and older. §HoFH is clinically diagnosed when a person has an untreated LDL-C level > 500 mg/dL, with either the presence of cutaneous or tendinous xanthomas before the age of 10 years or documentation of untreated LDL-C levels of > 250 mg/dL in both parents [56]. *LDL-C* low-density lipoprotein cholesterol, *LDLR* LDL receptor, *PCSK 9* proprotein convertase subtilisin/kexin type 9 serine protease, *HoFH* homozygous familial hypercholesterolemia, *ANGPTL3* angiopoietin-like 3, *MTP* microsomal triglyceride transfer protein


LDL-C ≥130mg/dL *in the absence of other conditions i.e. hypothyroidism, cholestatic liver disease, nephrotic syndrome, medications*
High risk
-HoFH
-T2D
-T1D
-ESRD
-Kawasaki with persistent aneurysm
-Solid organ transplant vasculopathy
-Childhood cancer survivor (stem cell recipient)
Moderate risk
-Severe obesity (BMI >120th of 95%tile, or >35 kg/m2)
-HeFH
-Confirmed hypertension
-Coarctation
-Elevated Lp(a)
-Predialysis chronic kidney disease
-Aortic stenosis
-Childhood cancer survivor (chest radiation)
At risk
-Obesity
-Insulin resistance with comorbidities (dyslipidemia, NAFLD, PCOS)
-White coat hypertension
-Cardiomyopathies
-Pulmonary hypertension
-Chronic inflammatory conditions (JIA, SLE, IBD, HIV)
-S/p coronary artery translocation for anomalous coronary arteries or transposition of great arteries
-Childhood cancer (cardiotoxic chemotherapy only)
-Kawasaki with regressed aneurysm
Reassign risk: *if ≥2 additional comorbidities advance to next higher risk category*
• Smoking history present
• Family history of early CAD in 1st degree relative (M age ≤55 years, F ≤65 years) present
• BP (3 separate occasions) ≥90%tile for age/sex or 120/70, whichever is lower
• BMI ≥95%tile
• Fasting glucose ≥100 mg/dL
• Physical activity history <5 h/week
High risk
Threshold to treat LDL-C ≥130 mg/dL
Moderate risk
Threshold to treat LDL-C ≥160mg/dL
At risk
Threshold to treat LDL-C ≥160 mg/dl
LDL-C meets threshold to treat?
No
Continue screening every 6-12 months with non-fasting non-HDL, followed by fasting lipid profile if initial TC >200, HDL-C <45, or non-HDL-C >145 mg/dL
Yes
High risk
Start CHILD-2 LDL diet* and increase physical activity (goal >5h/week) AND Start statin simultaneously (as per Fig 1, page 2)
Goal LDL-C <100 mg/dL
Moderate Risk
Start CHILD-2 LDL diet* and increase physical activity activity (goal >5h/week) x 3mo
Goal LDL-C <130 mg/dL
At risk
Start CHILD-2 LDL diet* and increase physical activity activity (goal >5h/week) x 6mo
Goal LDL-C <130 mg/dL
Repeat LDL-C, meets goal?
Yes
Continue current therapy, monitor/reassess periodically
No
High risk
Titrate statin to goal as above
Moderate risk
Consider statin and titrate to goal as above, intensify lifestyle
At risk
Consider statin and titrate to goal as above, intensify lifestyle

◂**Fig. 3** LDL-C management in high-risk pediatric patients. This algorithm was developed by PES members and includes the basic management strategy for elevated LDL-C, adapted from the AHA position statement. It also includes a second page with instructions for starting statins, including recommendations for baseline labs, and counseling on side effects and contraindications, and a dose range table with anticipated lipid-lowering effects, same as previous figure (see Fig. 1) [18, 21•, 53]. *See reference for more information on CHILD-2 LDL lowering diet [57]. *LDL-C* low-density lipoprotein cholesterol, *HoFH* homozygous familial hypercholesterolemia, *T2D* type 2 diabetes mellitus, *T1D* type 1 diabetes mellitus, *ESRD* end-stage renal disease, *BMI* body mass index, *HeFH* heterozygous familial hypercholesterolemia, *Lp(a)* lipoprotein (a), *NAFLD* nonalcoholic fatty liver disease, *PCOS* polycystic ovary syndrome, *JIA* juvenile idiopathic arthritis, *SLE* systemic lupus erythematosus, *IBD* inflammatory bowel disease, *HIV* human immunodeficiency virus, *CAD* coronary artery disease, *M* male, *F* female, *BP* blood pressure, *h* hours, *non-HDL* non-high-density lipoprotein, *TC* total cholesterol, *HDL-C* high-density lipoprotein, *CHILD-2 LDL* Cardiovascular Health Integrated Lifestyle-2 low-density lipoprotein diet

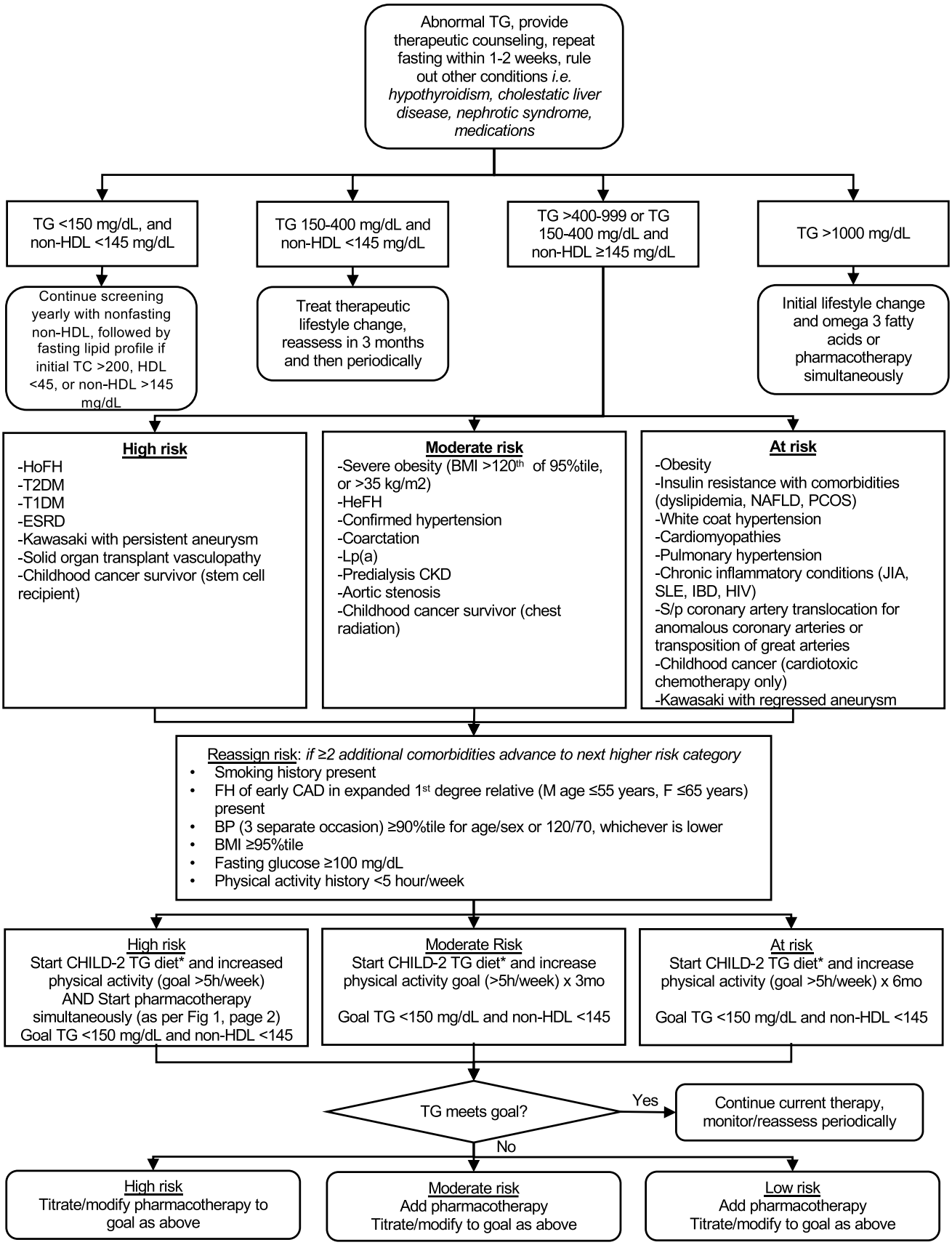
among organizations including the National Lipid Association, American Heart Association, Pediatric Endocrine Society, and American Academy of Pediatrics. The latest NHLBI algorithm was published in 2011 and lacks updated evidence showing even more support for early intervention for hypercholesterolemia in children. There is now more data showing that statin therapy is effective and safe among pediatric patients. Meta-analyses have shown effectiveness of statin therapy in children with FH without adverse side effects [48, 49]. A recent large longitudinal study of pediatric patients with FH who started statin therapy and were followed for 20 years showed slowed progression of carotid media intima thickness and reduced risk of CV disease in adulthood [10•]. Another study in children with type 1 diabetes showed that statin therapy for 2–4 years was effective in improving lipid profiles without adverse side effects [50]. The AHA position statement takes the recent data into account; however, it does not provide detailed framework of drug initiation and monitoring. We have adapted the algorithm in the AHA position statement to create easy-to-follow management algorithms (see Figs. 3 and 4) that include pharmacotherapy initiation and monitoring, adapted from the NHLBI guidelines (see Fig. 1) [21•]. The AHA position statement recommends simultaneously initiation of pharmacotherapy with lifestyle in the high-risk group, as there is data supporting the fact that higher risk patients such as those with FH do benefit from early treatment [10•].

Lastly, there is a lack of outcome studies in the pediatric literature, in comparison to adults, which hampers our ability to predict whether pediatric algorithms are safe and effective. Therefore, precise risk assessment tools are not available for pediatric care. Even our definitions of dyslipidemia and treatment thresholds in youth are generally "borrowed" from adult data, and based on normative data, not outcomes-based data. Given the nature of preventive care for children, and the long interval prior to a CVD-related event, other approaches are needed such as prospective longitudinal and indirect studies of risk. Unlike adult algorithms that are based on risk scores generated from risk of atherosclerotic CVD-related morbidity and mortality, pediatric algorithms are not based on expected risk of atherosclerotic CVD [18, 51]. Perhaps this nebulous concept of atherosclerotic CVD risk has prevented wider acceptance and implementation of these guidelines and algorithms. We need to create an improved system for developing a more specific risk score for patients to individualize treatment.

There are a few studies evaluating proposed risk scores in youth. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) risk score was developed from initial observations of well-defined risk factors, measured postmortem in young adults, which correlated to the amount of advanced atherosclerosis in coronary arteries and abdominal aorta in women and men dying accidentally. This risk score was applied to a longitudinal cohort, Cardiovascular Risk Development in Young Adults (CARDIA), who were young adults, age 18–30 years, and followed for 30 years. At 15 years of follow-up, they found that the PDAY score was highly predictive of atherosclerotic cardiovascular disease events later in life [52]. It remains to be seen if this can be applied to the younger population. Recently, a large international prospective study over 35 years analyzed five risk factors including BMI, systolic BP, total cholesterol level, TG level, and youth smoking, with the use of age- and sex-specific *z*-scores, and with a combined-risk *z*-score that was calculated as the unweighted mean of the five risk *z*-scores [9•]. A comparable adult combined-risk *z*-score was analyzed jointly with the childhood risk factors. It was found that the childhood combined-risk *z*-score and the change in the combined-risk *z*-score between childhood and adulthood were associated with CV events in midlife. This was the first study showing childhood risk factors were associated with clinical events in adulthood. It remains unclear if this type of risk score can be generalized for wider use. Nevertheless, these studies are promising.

Conclusions

Despite guideline and statement-based algorithms for screening and management of dyslipidemia in youth, there are still low rates of screening and treatment. Algorithms have been created to facilitate initiation of management among youth by general pediatricians, pediatric endocrinologists, and preventative cardiologists. We propose a few enhanced algorithms based upon expert opinion to address potential gaps and pitfalls to the existing algorithms, including a diabetes-specific and beyond statin algorithm, to add more resources for clinicians. We also acknowledge the need


Abnormal TG, provide therapeutic counseling, repeat fasting within 1-2 weeks, rule out other conditions *i.e. hypothyroidism, cholestatic liver disease, nephrotic syndrome, medications*
TG <150 mg/dL, and non-HDL <145 mg/dL
TG 150-400 mg/dL and non-HDL <145 mg/dL
TG >400-999 or TG 150-400 mg/dL and non-HDL ≥145 mg/dL
TG >1000 mg/dL
Continue screening yearly with nonfasting non-HDL, followed by fasting lipid profile if initial TC >200, HDL <45, or non-HDL >145 mg/dL
Treat therapeutic lifestyle change, reassess in 3 months and then periodically
Initial lifestyle change and omega 3 fatty acids or pharmacotherapy simultaneously
High risk
-HoFH
-T2DM
-T1DM
-ESRD
-Kawasaki with persistent aneurysm
-Solid organ transplant vasculopathy
-Childhood cancer survivor (stem cell recipient)
Moderate risk
-Severe obesity (BMI >120th of 95%tile, or >35 kg/m2)
-HeFH
-Confirmed hypertension
-Coarctation
-Lp(a)
-Predialysis CKD
-Aortic stenosis
-Childhood cancer survivor (chest radiation)
At risk
-Obesity
-Insulin resistance with comorbidities (dyslipidemia, NAFLD, PCOS)
-White coat hypertension
-Cardiomyopathies
-Pulmonary hypertension
-Chronic inflammatory conditions (JIA, SLE, IBD, HIV)
-S/p coronary artery translocation for anomalous coronary arteries or transposition of great arteries
-Childhood cancer (cardiotoxic chemotherapy only)
-Kawasaki with regressed aneurysm
Reassign risk: *if ≥2 additional comorbidities advance to next higher risk category*
• Smoking history present
• FH of early CAD in expanded 1st degree relative (M age ≤55 years, F ≤65 years) present
• BP (3 separate occasion) ≥90%tile for age/sex or 120/70, whichever is lower
• BMI ≥95%tile
• Fasting glucose ≥100 mg/dL
• Physical activity history <5 hour/week
High risk
Start CHILD-2 TG diet* and increased physical activity (goal >5h/week) AND Start pharmacotherapy simultaneously (as per Fig 1, page 2)
Goal TG <150 mg/dL and non-HDL <145
Moderate Risk
Start CHILD-2 TG diet* and increase physical activity goal (>5h/week) x 3mo
Goal TG <150 mg/dL and non-HDL <145
At risk
Start CHILD-2 TG diet* and increase physical activity (goal >5h/week) x 6mo
Goal TG <150 mg/dL and non-HDL <145
TG meets goal?
Yes
Continue current therapy, monitor/reassess periodically
No
High risk
Titrate/modify pharmacotherapy to goal as above
Moderate risk
Add pharmacotherapy
Titrate/modify to goal as above
Low risk
Add pharmacotherapy
Titrate/modify to goal as above

◂**Fig. 4** TG management in high-risk pediatric patients. This algorithm was developed by PES members and applies the risk stratification approach utilized in the AHA position statement [21•] to the management of hypertriglyceridemia. The narrative and tabular information regarding TG evaluation is integrated into the algorithm along with the composition of a recommended diet (CHILD-2 TG), and the pharmacotherapy options. *See reference for more information on CHILD-2 TG lowering diet [57]. *TG* triglyceride, *CHILD-2 TG* Cardiovascular Health Integrated Lifestyle-2 triglyceride, *EPA* eicosapentaenoic acid, *DHA* docosahexaenoic acid, *non-HDL* non-high-density lipoprotein, *ApoB* apolipoprotein B-100, *HDL-C* high-density lipoprotein cholesterol, *HoFH* homozygous familial hypercholesterolemia, *T2DM* type 2 diabetes mellitus, *T1DM* type 1 diabetes mellitus, *ESRD* end-stage renal disease, *BMI* body mass index, *HeFH* heterozygous familial hypercholesterolemia, *Lp(a)* lipoprotein (a), *CKD* chronic kidney disease, *NAFLD* nonalcoholic fatty liver disease, *PCOS* polycystic ovary syndrome, *JIA* juvenile idiopathic arthritis, *SLE* systemic lupus erythematosus, *IBD* inflammatory bowel disease, *HIV* human immunodeficiency virus, *CAD* coronary artery disease, *M* male, *F* female, *BP* blood pressure

for further risk assessment tools in youth for more tailored dyslipidemia management.

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Declarations

Conflict of Interest The authors have no financial or non-financial interests that are directly or indirectly related to the work submitted.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Berenson GS, Srinivasan SR, Bao W, Newman WP, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. Bogalusa study. N Engl J Med. 1998;338:1650–6.
2. Strong J, Malcom G, McMahan A. Prevalence and extent of atherosclerosis in adolescents and young adults: Implications for prevention from the pathobiological determinants of atherosclerosis in youth study. JAMA. 1999;281:727–35. https://doi.org/10.1001/jama.281.8.727.
3. Mcgill HC, Mcmahan AC, Zieske AW, Malcom GT, Tracy RE, Strong J, et al. Effects of Nonlipid Risk Factors on Atherosclerosis in Youth With a Favorable Lipoprotein Profile. Circulation. 2001;103:1546–50.
4. Davis PH, Dawson JD, Riley WA, Lauer RM. Carotid Intimal-Medial Thickness Is Related to Cardiovascular Risk Factors Measured From Childhood Through Middle Age. Circulation. 2001;104:2815–9.
5. Raitakari OT, Juonala M, Kähö M, Taittonen L, Laitinen T, Mäki-Torkko N, et al. Cardiovascular Risk Factors in Childhood and Carotid Artery Intima-Media Thickness in Adulthood The Cardiovascular Risk in Young Finns Study. JAMA. 2003;209:2277–83.
6. Koskinen JS, Kytö V, Juonala M, Viikari JSA, Nevalainen J, Kähönen M, et al. Childhood risk factors and carotid atherosclerotic plaque in adulthood: The Cardiovascular Risk in Young Finns Study. Atherosclerosis. 2020;293:18–25.
7. Juhola J, Magnussen CG, Viikari JSA, Kähönen M, Hutri-Kähönen N, Jula A, et al. Tracking of serum lipid levels, blood pressure, and body mass index from childhood to adulthood: The cardiovascular risk in young Finns study. J Pediatr. 2011;159:584–90.
8. Allen NB, Krefman AE, Labarthe D, Greenland P, Juonala M, Kähönen M, et al. Cardiovascular Health Trajectories from Childhood Through Middle Age and Their Association with Subclinical Atherosclerosis. JAMA Cardiol. 2020;5:557–66.
9.• Jacobs DR, Woo JG, Sinaiko AR, Daniels SR, Ikonen J, Juonala M, et al. Childhood Cardiovascular Risk Factors and Adult Cardiovascular Events. N Engl J Med. 2022;386:1877–88. **This was the first paper to show childhood CVD risk factors are associated with clinical CVD events in adulthood**.
10.• Luirink IK, Wiegman A, Kusters DM, Hof MH, Groothoff JW, de Groot E, et al. 20-Year Follow-up of Statins in Children with Familial Hypercholesterolemia. N Engl J Med. 2019;381:1547–56. **This paper was the first to show that childhood initiation of statin therapy in familial hypercholesterolemia decreases CVD risk in childhood**.
11. National Cholesterol Education Program (NCEP): Highlights of the report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Pediatrics. 1992;89(3):495–501
12. American Academy of Pediatrics Committee on Nutrition. Cholesterol in Childhood. Pediatrics. 1998;101:141–7.
13. Kavey R-EW, Daniels SR, Lauer RM, Atkins DL, Hayman LL, Taubert K. American Heart Association Guidelines for Primary Prevention of Atherosclerotic Cardiovascular Disease Beginning in Childhood. Circulation. 2003;107:1562–6.
14. Kavey REW, Allada V, Daniels SR, Hayman LL, McCrindle BW, Newburger JW, et al. Cardiovascular risk reduction in high-risk pediatric patients: A scientific statement from the American Heart Association expert panel on population and prevention science; the councils on cardiovascular disease in the young, epidemiology and prevention, nutrition, physical activity and metabolism, high blood pressure research, cardiovascular nursing, and the kidney in heart disease. Circulation. 2006;114:2710–38.
15. Haney EM, Huffman LH, Bougatsos C, Freeman M, Steiner RD, Nelson HD. Screening and treatment for lipid disorders in children and adolescents: systematic evidence review for the US Preventive Services Task Force. Pediatrics. 2007;120(10):e189–214. https://doi.org/10.1542/peds.2006-1801.
16 Daniels SR, Greer FR. Committee on Nutrition. Lipid screening and cardiovascular health in childhood. Pediatrics. 2008;122:198–208.
17 Daniels SR, Gidding SS, De Ferranti SD. Pediatric aspects of familial hypercholesterolemias: Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5(3):S30–7.
18. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children

and adolescents: Summary report. Pediatrics. 2011;128:Suppl 5(Suppl 5):S213–56. https://doi.org/10.1542/peds.2009-2107C.
19. Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW, García FAR, et al. Screening for lipid disorders in children and adolescents US Preventive Services Task Force recommendation statement. JAMA. 2016;316:625–33.
20. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 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. J Am Coll Cardiol. 2019;73:e285-350.
21.• de Ferranti SD, Steinberger J, Ameduri R, Baker A, Gooding H, Kelly AS, et al. Cardiovascular Risk Reduction in High-Risk Pediatric Patients: A Scientific Statement From the American Heart Association. Circulation. 2019;139:E603–34. **This was the updated scientific statement management algorithm for cardiovascular risk reduction in high-risk pediatric patients**.
22. de Ferranti SD, Rodday AM, Parsons SK, Cull WL, O'Connor KG, Daniels SR, et al. Cholesterol Screening and Treatment Practices and Preferences: A Survey of United States Pediatricians. J Pediatr. 2017;185:99-105.e2.
23. Khoury M, Rodday AM, Mackie AS, Gill P, McLaughlin T, Harris KC, et al. Pediatric Lipid Screening and Treatment in Canada: Practices, Attitudes, and Barriers. Can J Cardiol. 2020;36:1545–9.
24. Berger JH, Chen F, Faerber JA, O'Byrne ML, Brothers JA. Adherence with lipid screening guidelines in standard- and high-risk children and adolescents. Am Heart J. 2021;232:39–46.
25. Gooding HC, Rodday AM, Wong JB, Gillman MW, Lloyd-Jones DM, Leslie LK, et al. Application of pediatric and adult guidelines for treatment of lipid levels among US adolescents transitioning to young adulthood. JAMA Pediatr. 2015;169:569–74.
26 Sriram S, St. Sauver JL, Jacobson DJ, Fan C, Lynch BA, Cristiani V, et al. Temporal trends in lipid testing among children and adolescents: A population based study. Prev Med Rep. 2017;8:267–72.
27. Dixon DB, Kornblum AP, Steffen LM, Zhou X, Steinberger J. Implementation of lipid screening guidelines in children by primary pediatric providers. J Pediatr. 2014;164:572–6.
28. Liebeskind A, Warden BA, Sikand G, Duell PB, Guyton JR. JCL Roundtable: Lipid clinic operations. J Clin Lipidol. Elsevier Ltd; 2019;13(4):511–21. https://doi.org/10.1016/j.jacl.2019.07.011.
29. Kavey REW. Combined dyslipidemia in childhood. J Clin Lipidol. Elsevier Ltd; 2015;9(5Suppl):S41–56. https://doi.org/10.1016/j.jacl.2015.06.008.
30. Hickman TB, Briefel RR, Carroll MD, Rifkind BM, Cleeman JI, Maurer KR, et al. Distributions and Trends of Serum Lipid Levels among United States Children and Adolescents Ages 4–19 Years: Data from the Third National Health and Nutrition Examination Survey 1. Preventative Medicine. 1998;27:879–90.
31 Tamir I, Heiss G, Glueck C, Christensen B, Kwiterovich P, Rifkind B. Lipid and lipoprotein distributions in white children ages 6–19 yr. The lipid research clinics program prevalence study. J Chron Dis. 1981;34:27–39.
32. Christensen Charles Glueck B, Kwiterovich P, Chase G, Heiss G, Mowery R, Tamir I, et al. Plasma cholesterol and triglyceride distributions in 13,665 children and adolescents: the prevalence study of the lipid research clinics program. Pediatr Res. 1980;14(3):194–202. https://doi.org/10.1203/00006450-198003000-00004.
33. National Cholesterol Education Program (NCEP): Highlights of the report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. Pediatrics. 1992;89:495–501.
34. Wald DS, Bestwick JP, Wald NJ. Child-parent screening for familial hypercholesterolaemia: screening strategy based on a meta-analysis. BMJ. 2007;335:599.
35. Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW, García FAR, et al. Screening for lipid disorders in children and adolescents US Preventive Services Task Force recommendation statement. JAMA. 2016;316:625–33.
36. Perak AM, Ning H, Kit BK, De Ferranti SD, Van Horn LV, Wilkins JT, et al. Trends in Levels of Lipids and Apolipoprotein B in US Youths Aged 6 to 19 Years, 1999–2016. JAMA. 2019;321:1895–905.
37. Kershnar AK, Daniels SR, Imperatore G, Palla SL, Petitti DB, Pettitt DJ, et al. Lipid abnormalities are prevalent in youth with type 1 and type 2 diabetes: the SEARCH for Diabetes in Youth Study. J Pediatr. 2006;149:314–9.
38. Ahmadizar F, Souverein P, de Boer A, Maitland-van der Zee AH. Undertreatment of hypertension and hypercholesterolaemia in children and adolescents with type 1 diabetes: long-term follow-up on time trends in the occurrence of cardiovascular disease, risk factors and medications use. Br J Clin Pharmacol. 2018;84(4):776–85. https://doi.org/10.1111/bcp.13482.
39. Kim G, DeSalvo D, Guffey D, Minard CG, Cephus C, Moodie D, et al. Dyslipidemia in adolescents and young adults with type 1 and type 2 diabetes: a retrospective analysis. Int J Pediatr Endocrinol. 2020;2020.
40. Jackson S, Creo A, Kumar S. Are Clinicians Aggressive Enough in Treating Diabetes-Related Hyperlipidemia in Youth? Curr Atheroscler Rep. 2022;24(6):471–81. https://doi.org/10.1007/s11883-022-01020-y.
41. Elsayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. Children and Adolescents: Standards of Care in Diabetes—2023. Diabetes Care. 2023;46:S230–53.
42. Chiang JL, Maahs DM, Garvey KC, Hood KK, Laffel LM, Weinzimer SA, et al. Type 1 diabetes in children and adolescents: A position statement by the American Diabetes Association. Diabetes Care. 2018;41:2026–44.
43. Bansal N, Kumar S, Brar PC. Update on management of paediatric dyslipidaemia. Curr Opin Endocrinol Diabetes Obes. 2023;30:52–64.
44. Bauer MS, Kirchner JA. Implementation science: What is it and why should I care? Psychiatry Res. 2020;283:112376. https://doi.org/10.1016/j.psychres.2019.04.025.
45. Galaviz KI, Barnes GD. Implementation science opportunities in cardiovascular medicine. Circ Cardiovasc Qual Outcomes. 2021;14(7):e008109. https://doi.org/10.1161/CIRCOUTCOMES.121.008109.
46 McGowan MP, Hosseini Dehkordi SH, Moriarty PM, Duell PB. Diagnosis and treatment of heterozygous familial hypercholesterolemia. J Am Heart Assoc. 2019;8:e013225.
47. Rosenson RS. Existing and emerging therapies for the treatment of familial hypercholesterolemia. J Lipid Res. 2021;62:100060. https://doi.org/10.1016/j.jlr.2021.100060.
48. Anagnostis P, Vaitsi K, Kleitsioti P, Mantsiou C, Pavlogiannis K, Athyros VG, et al. Efficacy and safety of statin use in children and adolescents with familial hypercholesterolaemia: a systematic review and meta-analysis of randomized-controlled trials. Endocrine. 2020;69(2):249–61. https://doi.org/10.1007/s12020-020-02302-8.
49. Vuorio A, Kuoppala J, Kovanen PT, Humphries SE, Tonstad S, Wiegman A, et al. Statins for children with familial hypercholesterolemia. Cochrane Database Syst Rev. 2019;2019(11):CD006401. https://doi.org/10.1002/14651858.CD006401.pub5.
50. Marcovecchio ML, Chiesa ST, Bond S, Daneman D, Dawson S, Donaghue KC, et al. ACE Inhibitors and Statins in Adolescents with Type 1 Diabetes. N Engl J Med. 2017;377:1733–45.

51. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 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. Circulation. 2019;140(11):e596–646. https://doi.org/10.1161/CIR.0000000000000678.
52. Gidding SS, Colangelo LA, Nwabuo CC, Lewis CE, Jacobs DR, Schreiner PJ, et al. PDAY risk score predicts cardiovascular events in young adults: the CARDIA study. Eur Heart J. 2022;43:2892–900.
53. Jones P, Kafonek S, Laurora I, Hunninghake D. Comparative Dose Efficacy Study of Atorvastatin Versus Simvastatin, Pravastatin, Lovastatin, and Fluvastatin in Patients With Hypercholesterolemia (The CURVES Study). Am J Cardiol. 1998;81:582–7.
54. Alexopoulos AS, Qamar A, Hutchins K, Crowley MJ, Batch BC, Guyton JR. Triglycerides: Emerging targets in diabetes care? review of moderate hypertriglyceridemia in diabetes. Curr Diab Rep. 2019;19(4):13. https://doi.org/10.1007/s11892-019-1136-3.
55. Butt WZ, Yee JK. The Role of Non-statin Lipid-Lowering Medications in Youth with Hypercholesterolemia. Curr Atheroscler Rep. 2022;24:379–89.
56. Raal FJ, Rosenson RS, Reeskamp LF, Hovingh GK, Kastelein JJP, Rubba P, et al. Evinacumab for Homozygous Familial Hypercholesterolemia. N Engl J Med. 2020;383:711–20. https://doi.org/10.1056/NEJMoa2004215.
57. Williams LA, Wilson DP, et al. Nutritional management of pediatric dyslipidemia. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hofland J, Kalra S, Kaltsas G, Kapoor N, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, New M, Purnell J, Sahay R, Shah AS, Singer F, Sperling MA, Stratakis CA, Trence DL, Wilson DP, et al., editors. Endotext Endotext South Dartmouth (MA). South Dartmouth (MA): MDText.com, Inc.; 2023. p. 2000.