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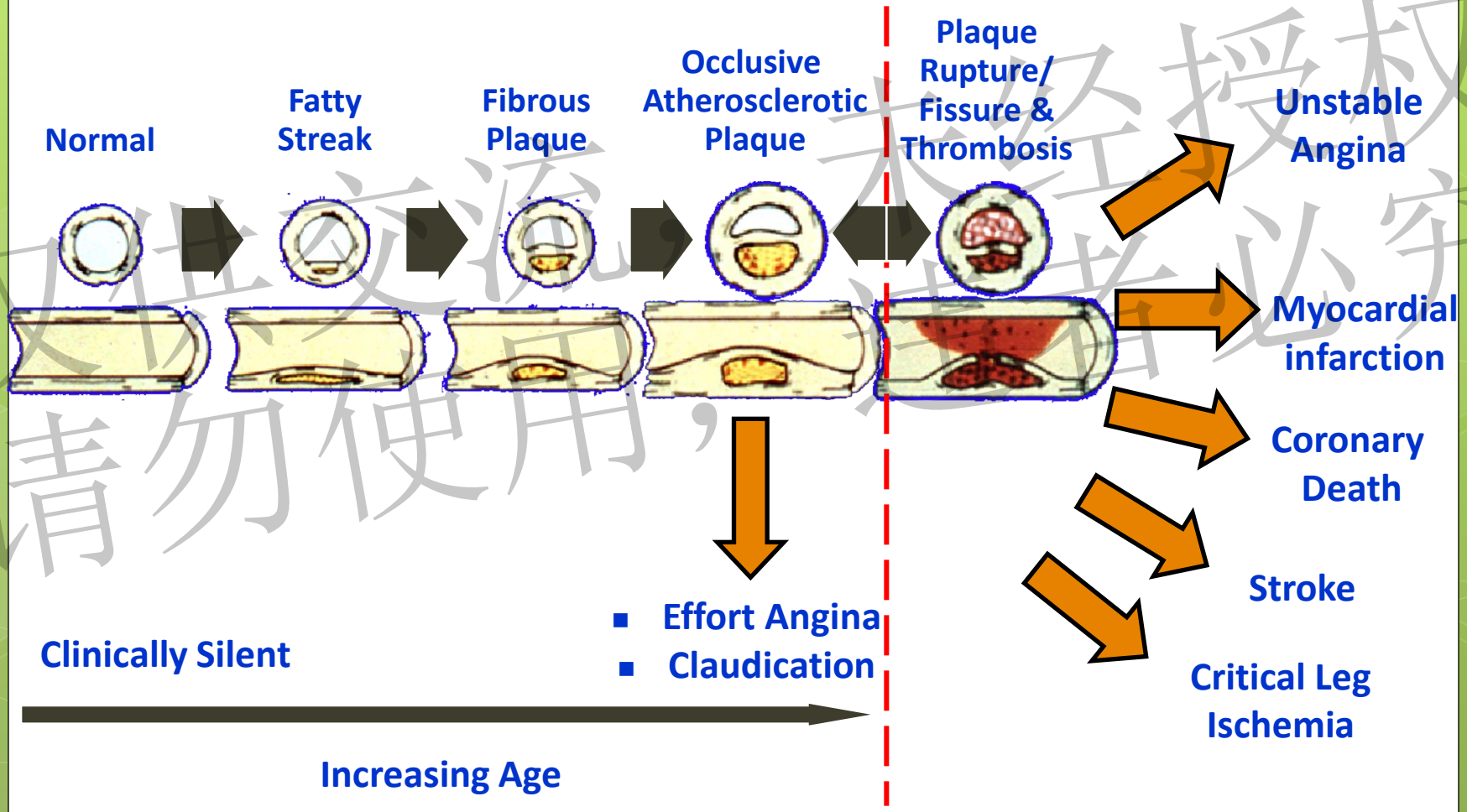
Approach to dyslipidaemia in paediatrics

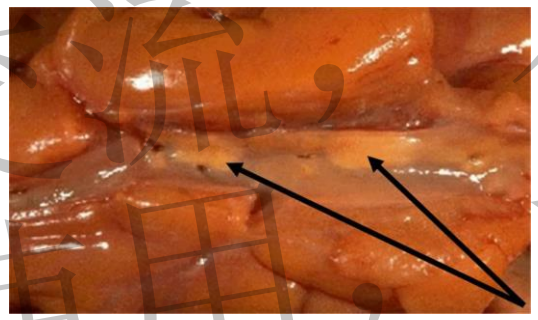
PT Cheung

Atherosclerosis: A Progressive Process



The Fatty Streak

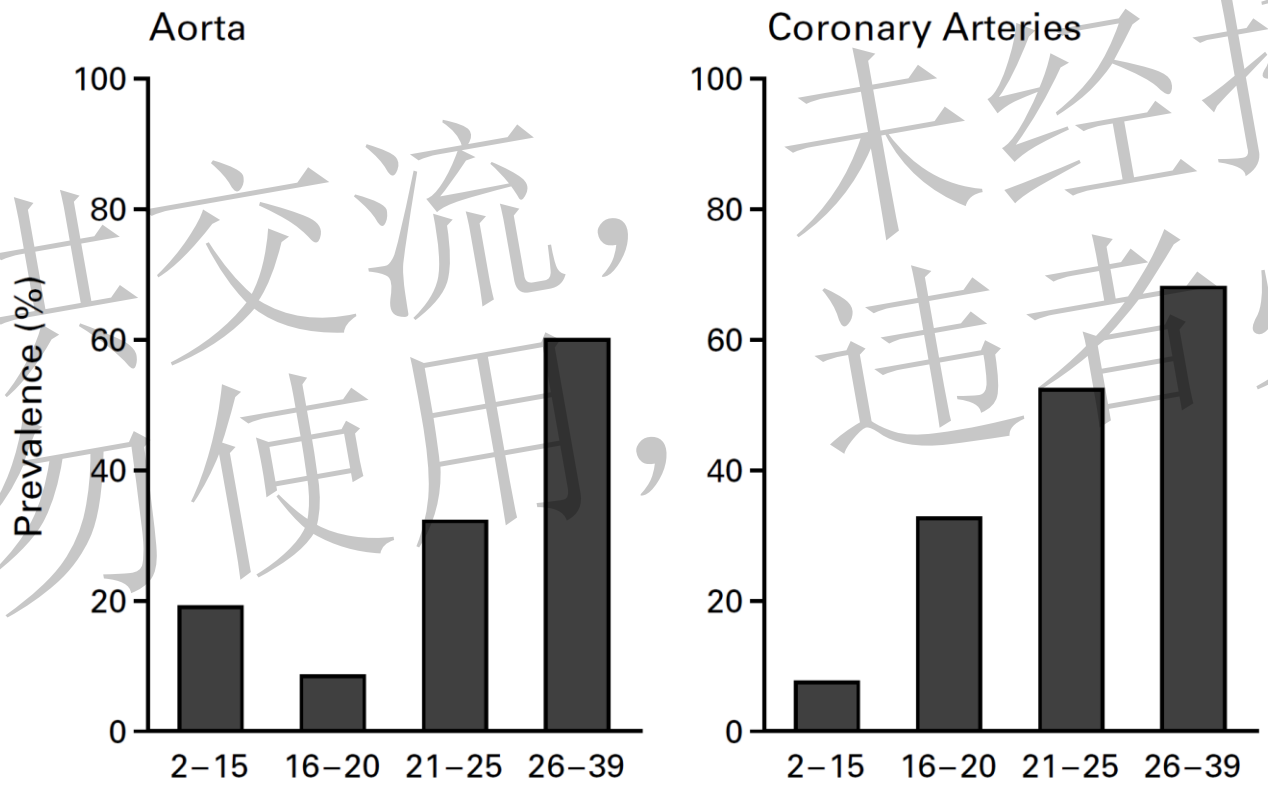
- Fatty streaks are the first signs of atherosclerosis that are visible without magnification
- They consist of lipid-containing foam cells in the arterial wall just beneath the endothelium.



- There are two yellowish fatty streaks beneath the thin endothelial lining of the artery shown above
- These lesions occur in the aorta and coronary arteries of most people by age 20
- Over time, they can evolve into atherosclerotic plaques or they can remain stable or even regress

Link between hyperlipidemia and atherosclerosis is well established in children and adolescent

The Prevalence of Fibrous-Plaque Lesions in the Aorta and Coronary Arteries in 204 Children and Young Adults, According to Age



There is a consistent trend toward a greater prevalence of coronary-artery lesions **with increasing age** (P=0.001)

N Engl J Med **1998**;338:1650-6

Risk-Factor Variable	Aorta		Coronary Arteries	
	Fatty Streaks	Fibrous Plaques	Fatty Streaks	Fibrous Plaques
Body-mass index	0.33†	0.24‡	0.41§	0.29†
Systolic blood pressure	0.31†	0.17	0.47§	0.41§
Diastolic blood pressure	0.14	0.10	0.18	0.24‡
Total cholesterol	0.54§	0.15	0.26‡	0.23
LDL cholesterol	0.54§	0.16	0.29‡	0.32†
HDL cholesterol	−0.03	0.05	−0.14	−0.12
Triglycerides	0.23	0.26‡	0.32†	0.37†

* Values shown are Spearman correlation coefficients

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

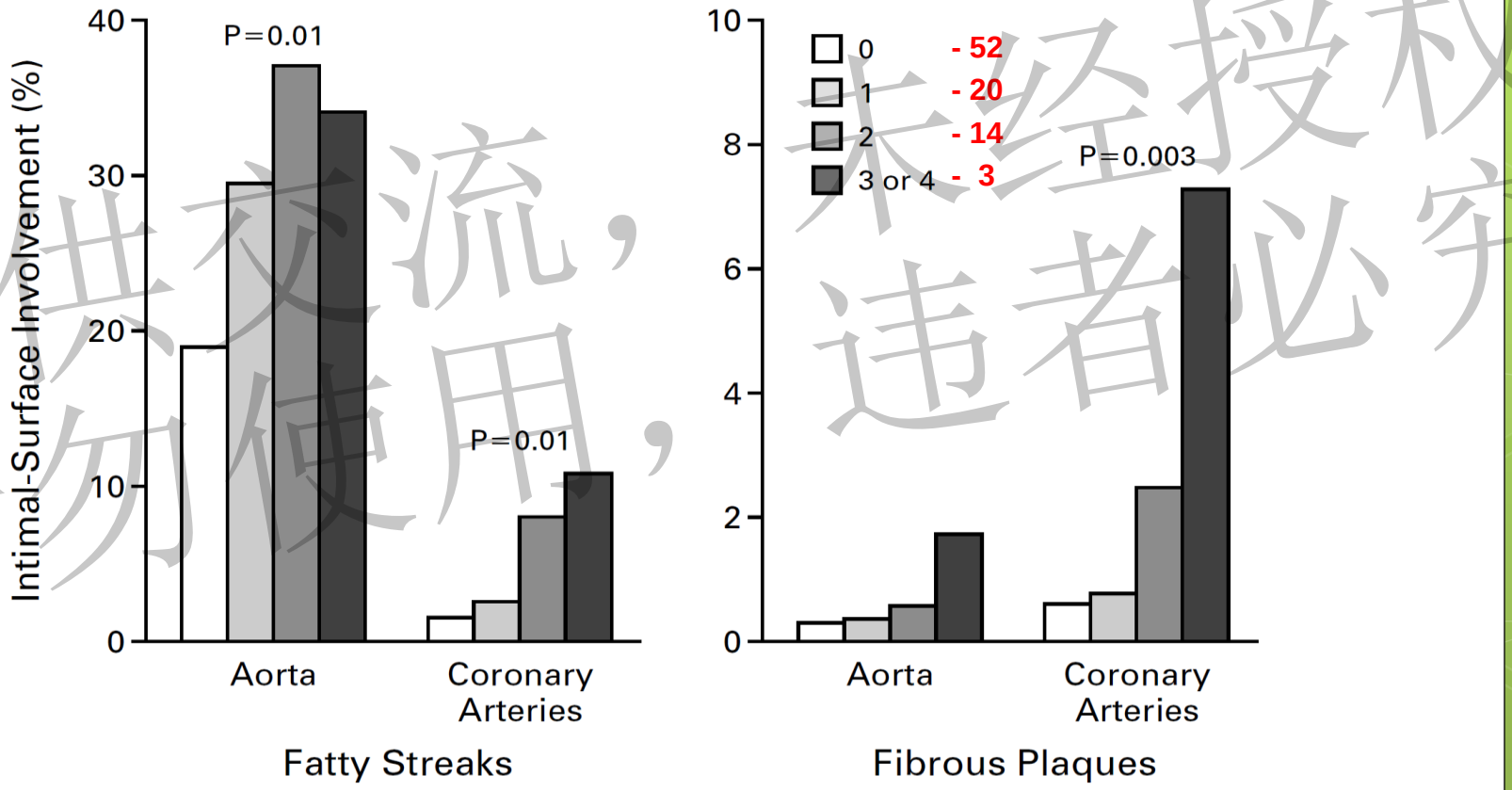
†P<0.01.

‡P<0.05.

§P<0.001.

N Engl J Med 1998;338:1650-6

Analysis of a subgroup of 93 subjects who had participated in the Bogalusa Heart Study and hence antemorteum risk factors known



Risk factors: BMI, SBP, TG and LDL-C >75th percentile for the study group

- **specific for study period, race, sex, and age**

N Engl J Med **1998**;338:1650-6

Risk Scores Predict Atherosclerotic Lesions in Young People

McMahan CA et al.
ARCH INTERN MED. 2005, 165:883-890

A Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study

Modifiable risks factors

- Smoking
- Blood pressure
- Non-HDL-C***
- HDL cholesterol
- Obesity
- Hyperglycaemia

Table 3. Risk Scores for Predicting Target Lesions in the Coronary Arteries and the Abdominal Aorta

Risk Factor	Points	
	Coronary Arteries	Abdominal Aorta
Age, y		
15-19*	0	0
20-24	5	5
25-29	10	10
30-34	15	15
Sex		
M*	0	0
F	−1	1
Non-HDL cholesterol, mg/dL		
<130*	0	0
130-159	2	1
160-189	4	2
190-219	6	3
≥220	8	4
HDL cholesterol, mg/dL		
<40	1	0
40-59*	0	0
≥60	−1	0
Smoking		
Nonsmoker*	0	0
Smoker	1	4
Blood pressure		
Normotensive*	0	0
Hypertensive	4	3
Obesity (BMI, kg/m^2)		
Men		
≤30*	0	0
>30	6	0
Women		
≤30*	0	0
>30	0	0
Hyperglycemia (glycohemoglobin, %)		
<8*	0	0
≥8	5	3

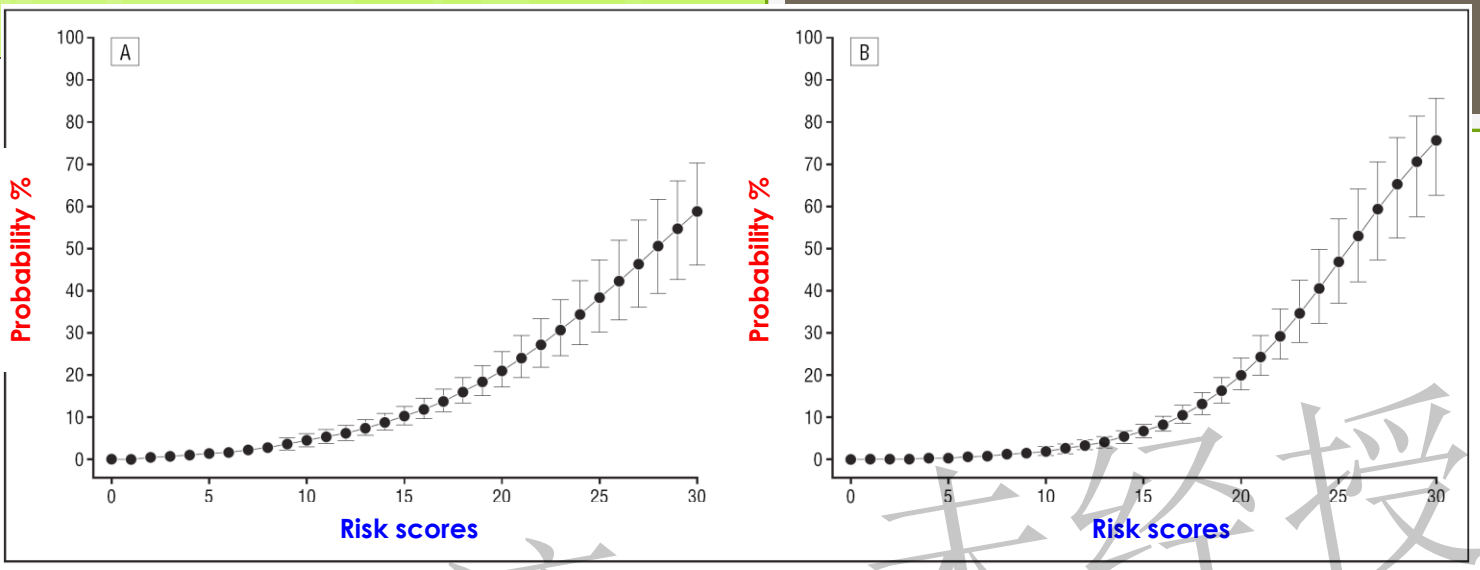


Figure 1. Estimated probability of target lesions in the coronary arteries (A) and the abdominal aorta (B) by risk score. Error bars represent 95% confidence intervals.

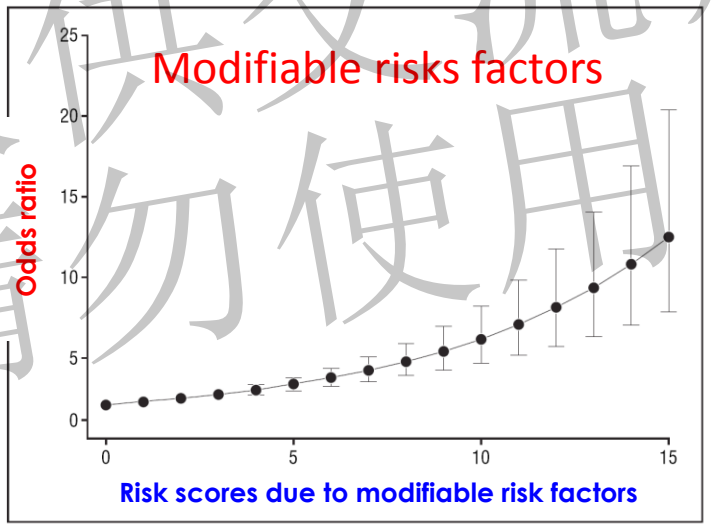


Figure 2. Estimated odds ratio of coronary artery target lesions relative to an individual of the same sex and 5-year age group without risk factors by risk score due to modifiable risk factors (non–high-density lipoprotein cholesterol, high-density lipoprotein cholesterol, smoking, hypertension, obesity, and hyperglycemia). Error bars represent 95% confidence intervals.

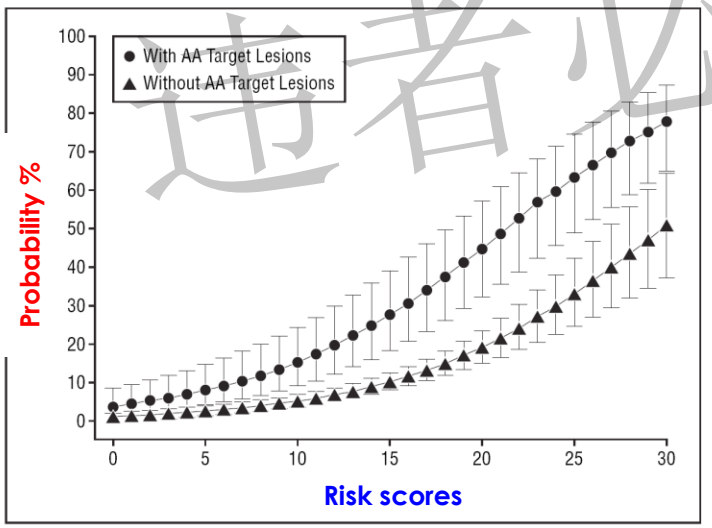


Figure 3. Estimated probability of coronary artery target lesions by risk score for individuals with and without abdominal aorta (AA) target lesions. Error bars represent 95% confidence intervals.

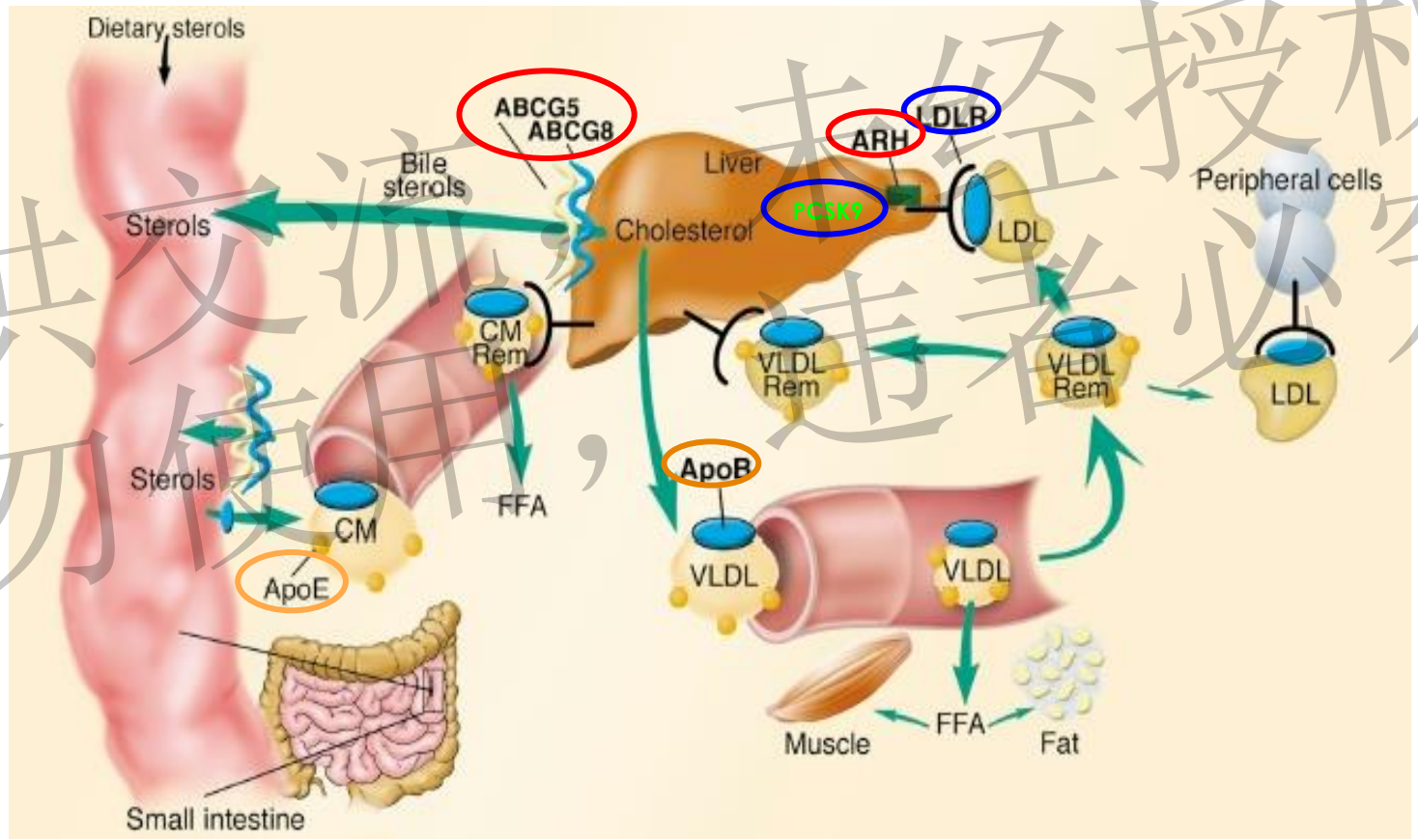
Monogenic causes of dyslipidaemia

Disorder	Mutant gene		Estimated population frequency	Lp pattern	Xanthoma	Premature vascular disease
Familial Hypercholesterolaemia (FH)	LDLR	AD	Heterozygote 1:500 Homozygote 1:10^6	IIa (IIb)	Tendon Xanthelasma	+
Familial defective ApoB (FDB)	Apo-B 100	AD	1:1,000	IIa	Tendon	+
AD Hypercholesterolaemia	PCSK9	AD	Unknown	IIa	Tendon	+
Sitosterolaemia	ABCG5 ABCG8	AR	1:5x10^4 ??	IIa	Tendon	+
Autosome recessive hypercholesterolaemia (ARH)	ARH	AR	Unknown	IIa	Tendon Xanthelasma	+
Type III hyperlipoproteinemia (dysbetalipoproteinemia)	Apo-E	AR	1:10,000	III	Plamar, Tuberous	+
Familial Combined Hyperlipidemia (FCHL)	Unknown	AD	1:100	IIb	-	+
Familial hypertriglyceridemia	Unknown	AD	Unknown	IV	-	+(?)
Familial LPL deficiency	LPL	AR	1:10^6	I, V	Eruptive	-
Familial Apo-CII deficiency	Apo-CII	AR	1:10^6	I, V	Eruptive (rare)	-

Monogenic causes of hypercholesterolaemia – related to key regulator of cholesterol metabolism

AD

AR



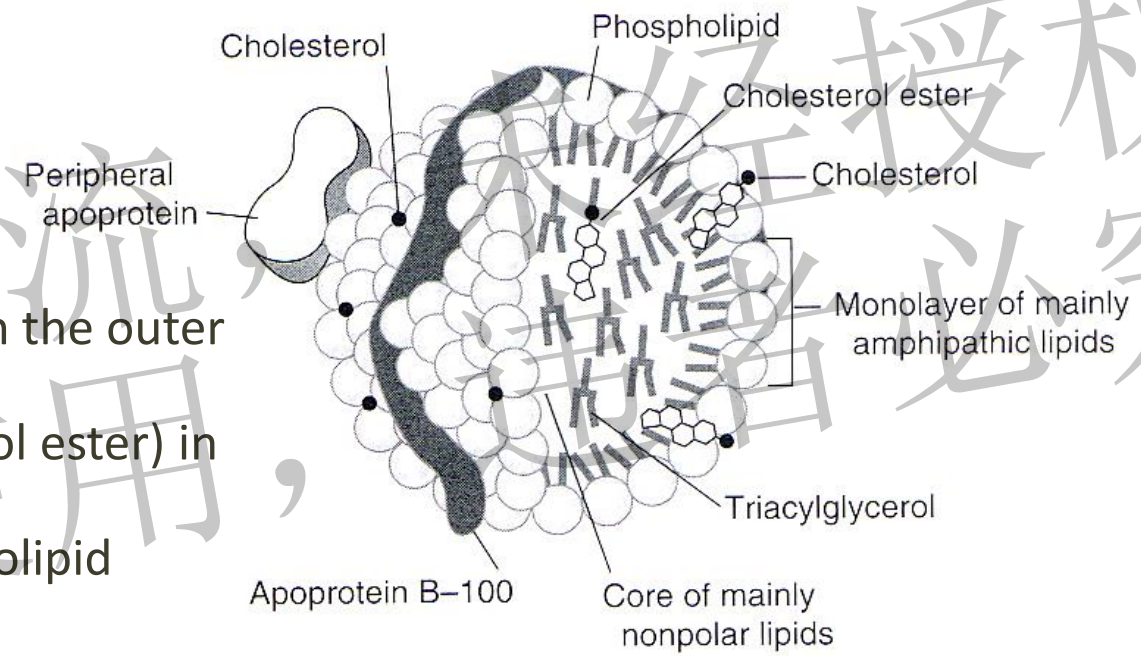
Causes of Secondary Dyslipidemia

- **Exogenous**
  - Alcohol
  - Drug therapy:
    - Corticosteroids
    - Isoretinoin
    - Beta-blockers
    - Some oral contraceptives
    - Select chemotherapeutic agents
    - Select antiretroviral agents
- **Endocrine/Metabolic**
  - Hypothyroidism/hypopituitarism
  - Diabetes mellitus type 1 and type 2
  - Pregnancy
  - Polycystic ovary syndrome
  - Lipodystrophy
  - Acute intermittent porphyria

Causes of Secondary Dyslipidemia

- **Renal**
  - Chronic renal disease
  - Hemolytic uremic syndrome
  - Nephrotic syndrome
- **Infectious**
  - Acute viral/bacterial infection*
  - Human immunodeficiency virus (HIV) infection
  - Hepatitis
- **Hepatic**
  - Obstructive liver disease/cholestatic conditions
  - Biliary cirrhosis
  - Alagille syndrome
- **Inflammatory**
  - Systemic lupus erythematosis
  - Juvenile rheumatoid arthritis
- **Storage**
  - Glycogen storage disease
  - Gaucher's disease
  - Cystine storage disease
  - Juvenile Tay-Sachs disease
  - Niemann-Pick disease
- **Other**
  - Kawasaki disease
  - Anorexia nervosa
  - Post solid organ transplantation
  - Childhood cancer survivor
  - Progeria
  - Idiopathic hypercalcemia
  - Klinefelter syndrome
  - Werner's syndrome

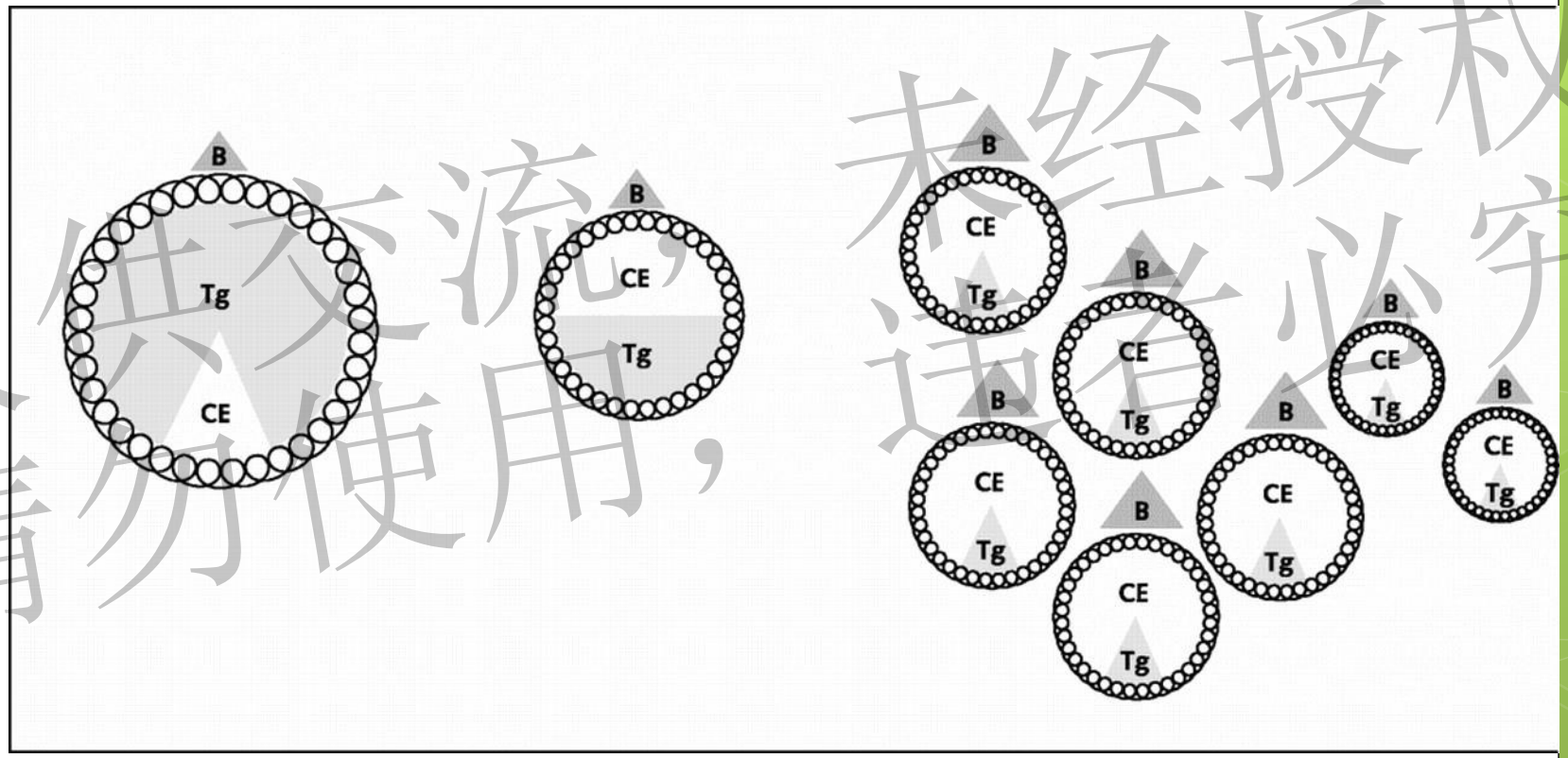
Lipids are predominantly transported as lipoprotein



- Free cholesterol – on the outer shell
- Esterified (cholesterol ester) in the lipoprotein core
- Wrapped by phospholipid membrane with apolipoproteins

- Actively exchanging various components between the different carrier lipoproteins – very dynamic

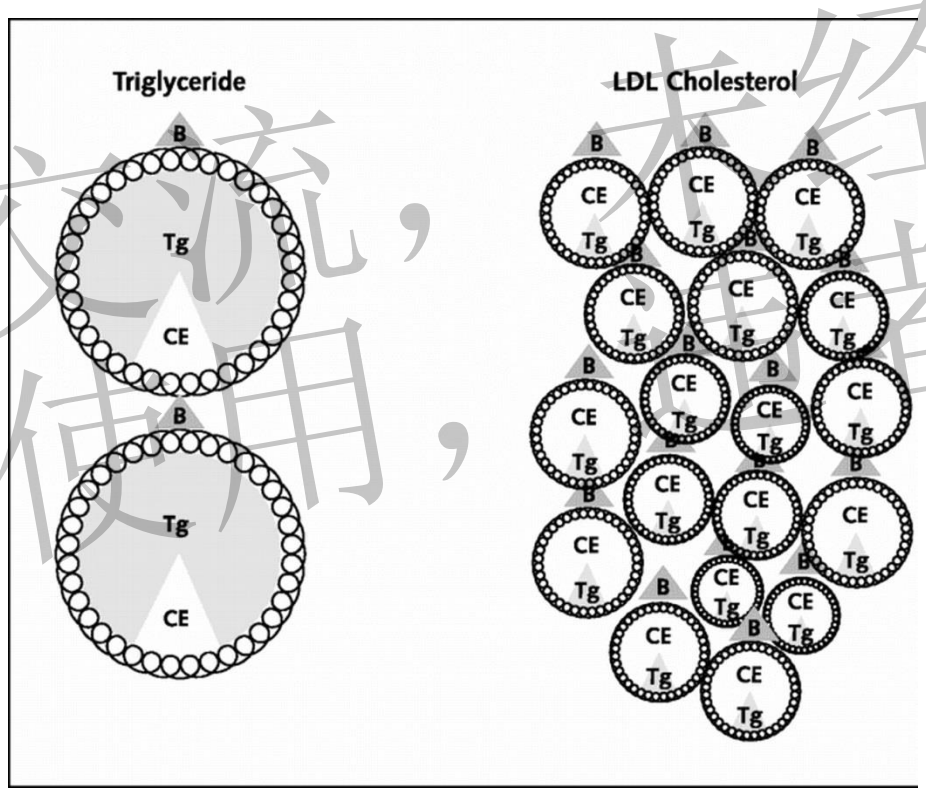
The relative number of very-low-density lipoprotein (VLDL) (left), intermediate-density lipoprotein (middle), and low-density lipoprotein (LDL) (right) particles



Sniderman A D et al. Ann Intern Med 2001;135:447-459

Annals of Internal Medicine

Differences between lipoprotein lipids and lipoprotein particles in a patient with a plasma triglyceride level of 3 mM (264 mg/dL) and a low-density lipoprotein (LDL) cholesterol level of 3 mM (116 mg/dL)



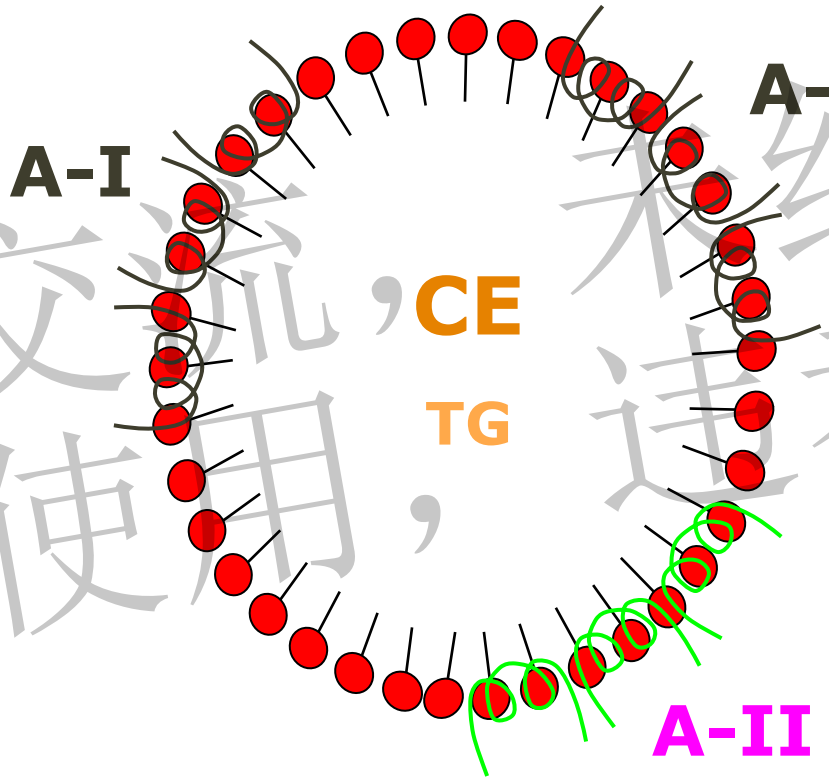
Sniderman A D et al. Ann Intern Med 2001;135:447-459

Annals of Internal Medicine

Apo B

- The concentration of apoB in plasma measures the total number of VLDL, intermediate-density lipoprotein (IDL), and LDL lipoprotein particles in plasma
- Lipoprotein(a) also contains one molecule of apoB
  - but characteristically does not contribute substantially to total apoB in hyperapoB
- When in excess, all apoB containing lipoproteins are considered atherogenic

Structure of HDL Particle



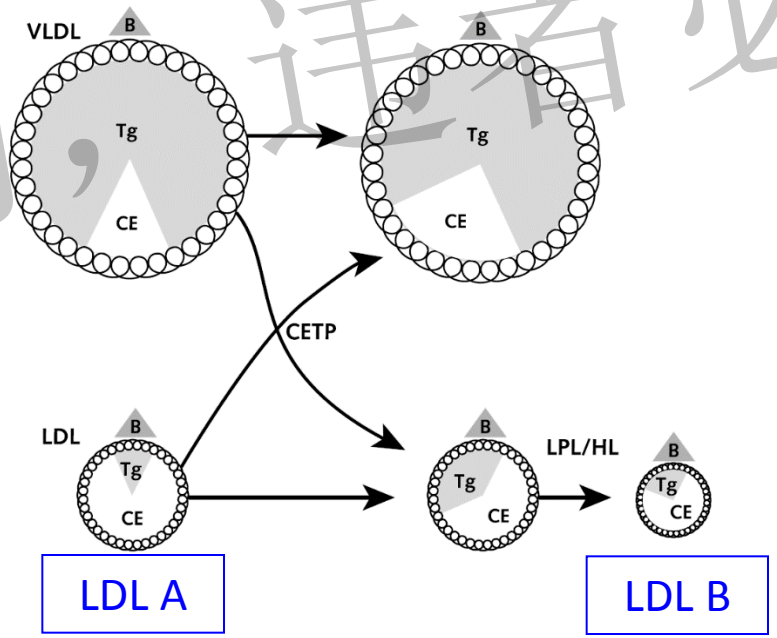
A-I, A-II	apolipoprotein A-I, A-II
CE	cholesteryl ester
TG	triglycerides

Apo A-1

- ApoA-1 is the major lipoprotein of HDL-C
- Both apoB and apoA-1 are not better than LDL-C and HDL-C in “tracking of dyslipidemia”
- Ratio of apoB/apoA-1 offers additional value in “selective screening”
  - Especially for youths with a family history of premature CVD in parents
  - This is likely because elevated apoB is often the first expression of **familial combined dyslipidemia** in adolescents and young adults – before the overt combined dyslipidemia
- Bogalusa study **did not** but Young Finns study **did** find both childhood apoB and A-1 are better predictors of cIMT and FMD in adults than LDL-C or HDL-C

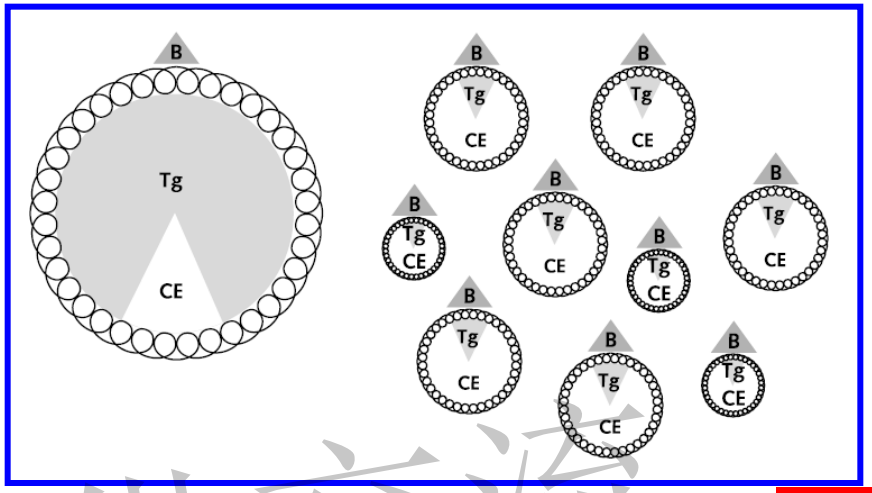
LDL-C

- LDL A - larger and more buoyant
- LDL B - smaller and denser
- Most LDL B particles are formed from LDL A particles

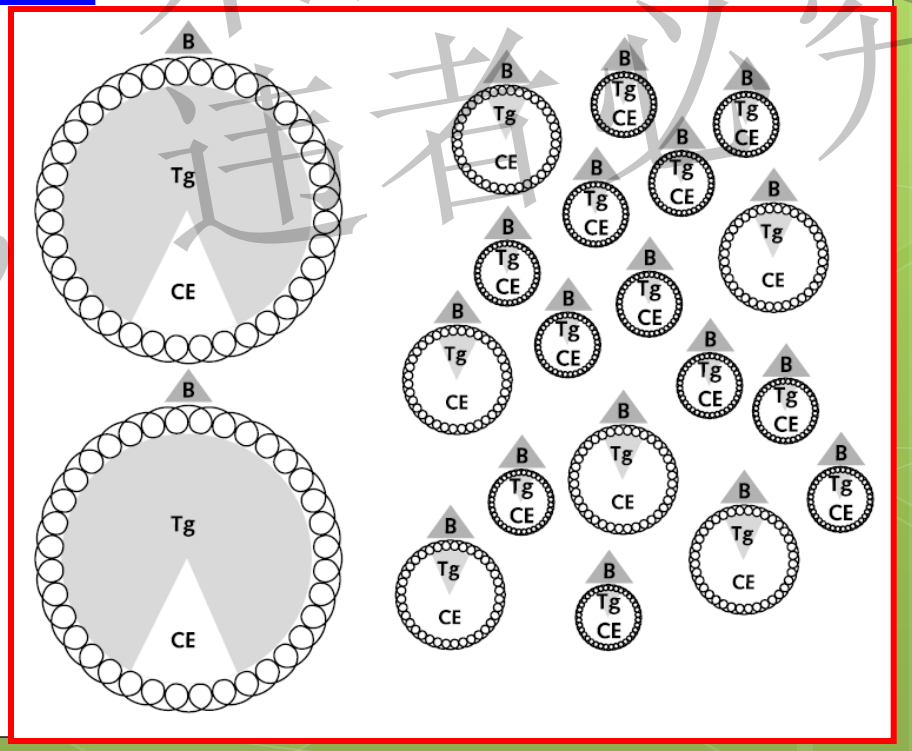


Hypertriglyceridemic hyperapoB

- The combination of
  - Hypertriglyceridemia
  - increased numbers of small, dense LDL particles
  - (often) low levels of HDL cholesterol
- More prevalent in
  - Type 2 diabetes mellitus
  - Insulin resistance
  - Pre-diabetes
  - Subjects with coronary disease



Normal



Hypertriglyceridemic hyperapoB

Analysis of lipids

- Friedewald formula:
  - LDL-C = TC – [HDL-C + (TG/5)]
  - TG/5 being an estimate of the VLDL-C component
  - Error 15-20%
  - *Fails completely when TG exceeds 400mg/dL*
- LDL direct – measures LDL by immunoseparation reagent

One way of defining the complex size variation of cholesterol-TG-lipoprotein

- Chylomicrons (Sf >400)
- $VLDL_1$ (Sf 60-400)
- $VLDL_2$ (Sf 20-60)
- LDL I 1.025-1.034 g/ml
- LDL II 1.034-1.044 g/ml
- LDL III 1.044-1.060 g/ml
- HDL_2 1.063-1.125 g/ml
- HDL_3 1.125-1.210 g/ml

Svedberg flotation unit (Sf)

Defining the abnormal ranges

- Age- and gender- specific lipoprotein threshold concentrations for adolescents

Month-to-month variability of lipids, lipoproteins, and apolipoproteins & the impact of acute infection in adolescents

- The 50th and 95th percentiles, respectively, for the coefficient of variation for each variable were as follows
  - Total cholesterol 7.3% and 13.6%
  - **Triglycerides 22% and 47.3%**
  - HDL-C 7.9% and 16.8%
  - LDL-C 12.1% and 25%
  - Apolipoprotein A1 6.3% and 15.2%
  - Apolipoprotein B 9.5% and 17.2%
  - Lipoprotein(a) 19.3% and 40%
- Recent infection significantly lowered HDL-C (4 mg/dL; *P* < .0001) & apolipoprotein A1 (7 mg/dL; *P* < .005)
- Clinicians evaluating lipids and lipoproteins serially should expect significant visit-to-visit variation in triglycerides and LDL-C values
- Assessment of HDL-C and apolipoprotein A1 should not be done within 2 weeks of an acute infection
- Apolipoproteins B and A1 have slightly less variability than their respective lipoprotein cholesterol values

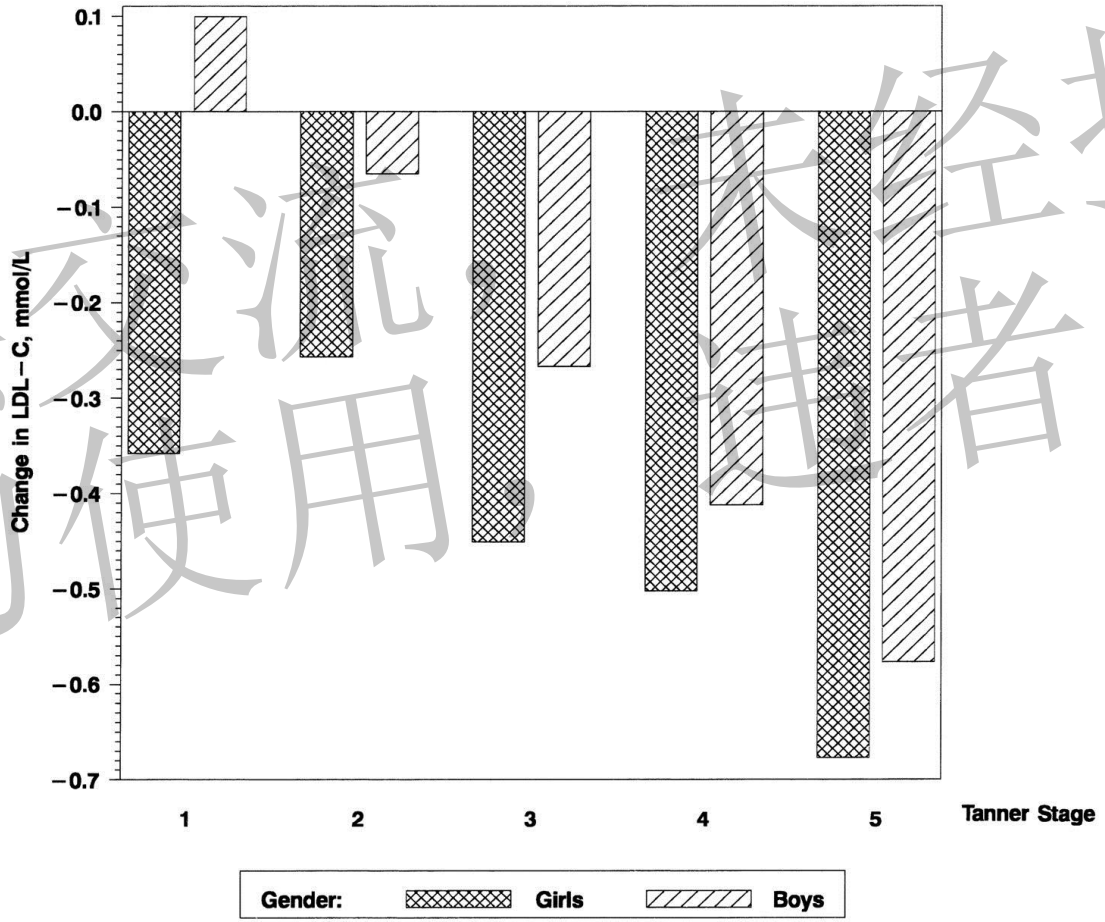
J Pediatr 1998;133:242-6

Changes and variability in high levels of LDL-C among children

- There can be large changes in extreme levels of LDL cholesterol because of **regression to the mean**, and practitioners should be aware that very high levels may decrease substantially in the absence of any intervention
- Careful documentation of persistently elevated levels is necessary before commencement of long term therapy

Pediatrics 2010, 126:266–273

Mean change in LDL-C (baseline to 3 years) by sex & Tanner stage



Kwiterovich, P. O. et al. Circulation 1997;96:2526-2533

Define the nature of dyslipidaemia – more elaborate biochemical tests

- Phytosterol profile
- VLDL
- Chylomicrons
- Apo-B
- Apo-A1
- Apo E

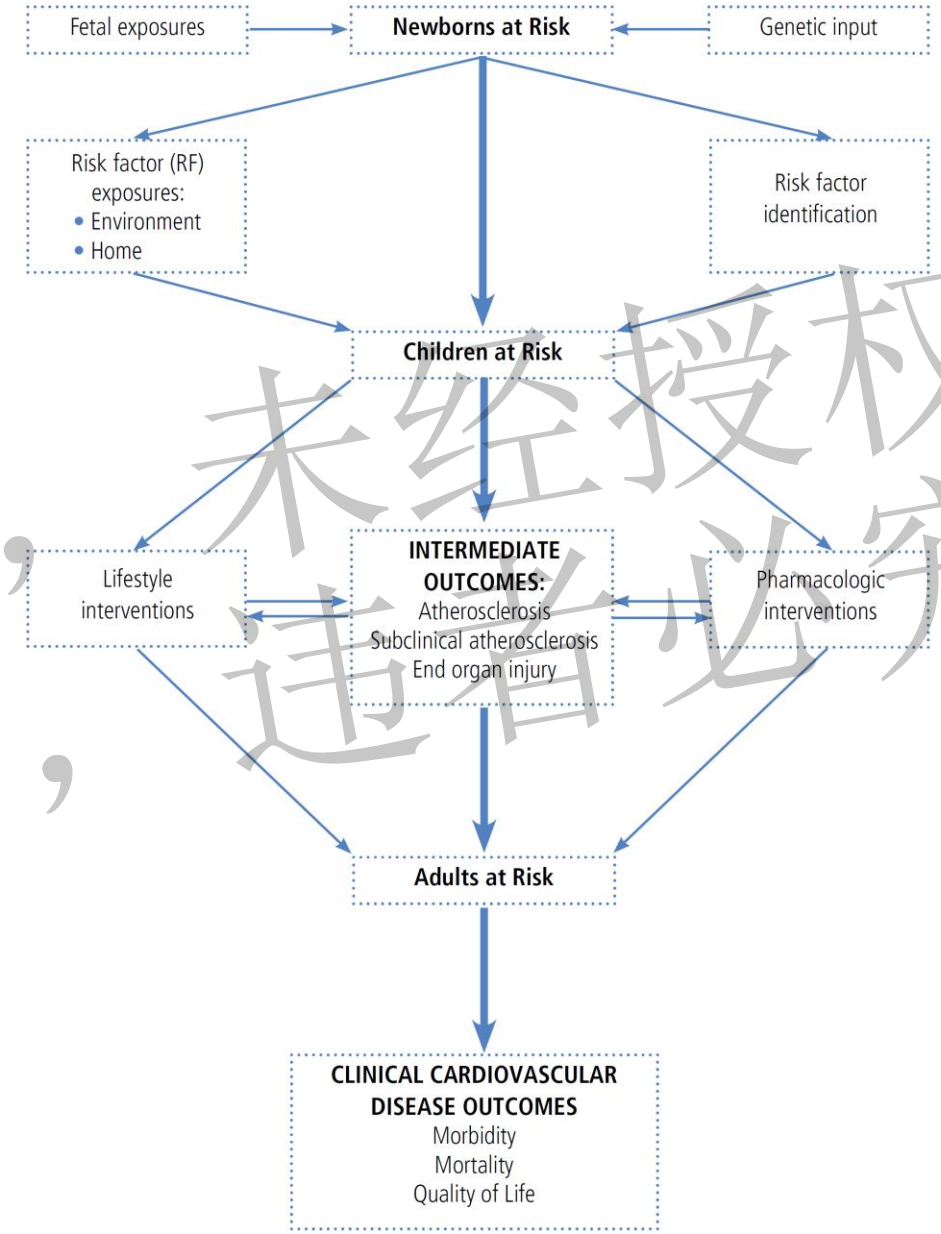
NB - Inspection of refrigerated plasma (for chylomicron and VLDL) – both rich in TG

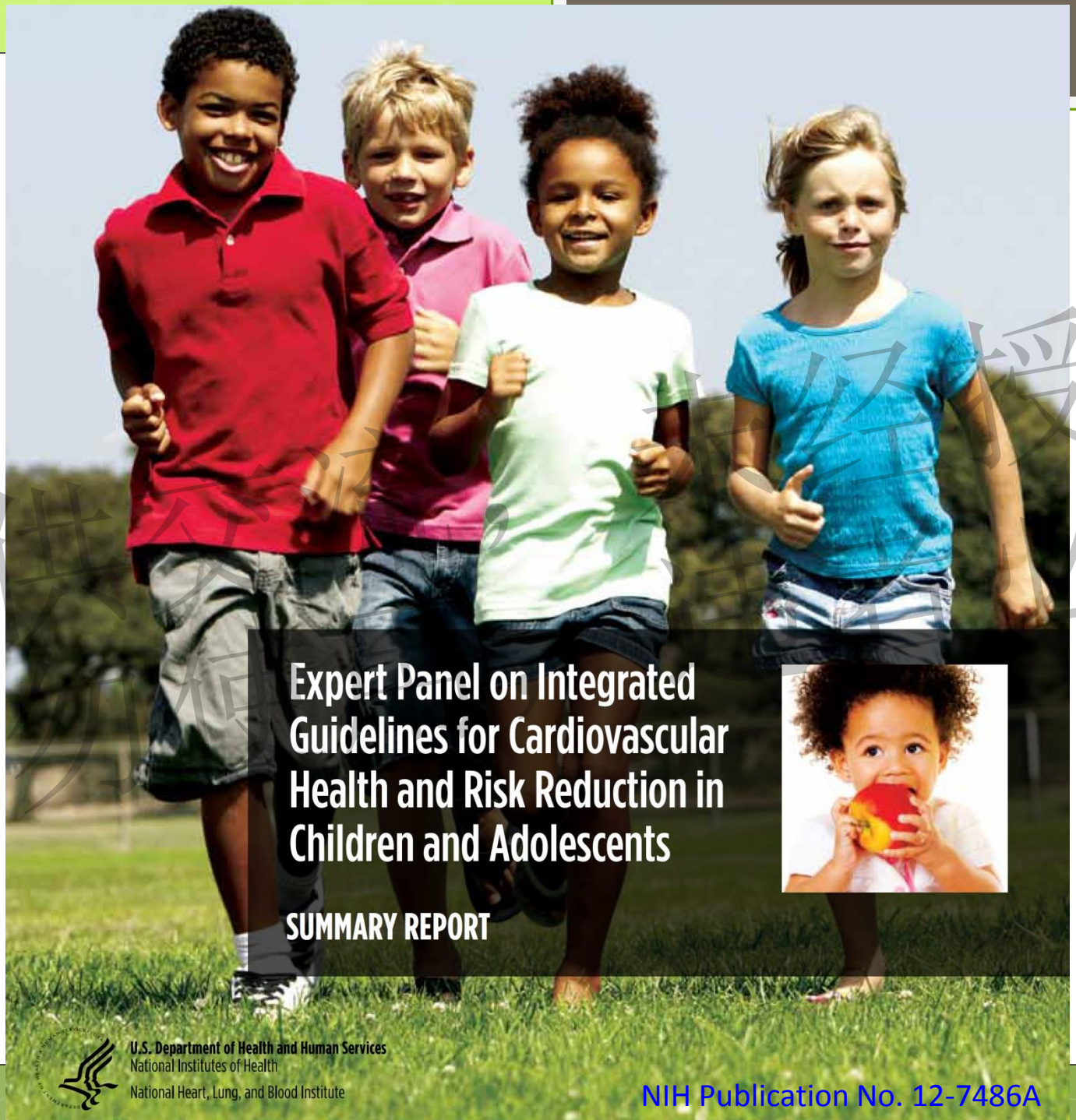
Beware of additional markers identified based on the ever-advancing understanding of dyslipidaemia

- Special details – size variation within the general classes of LDL and HDL
  - Small, dense LDL vs buoyant LDL
  - Pre-β-1 migrating HDL; small, dense HDL, HDL-2; HDL-3; α-HDL
- Oxidized LDL
- Remnant lipoproteins
- Lp(a)
- PCSK9
- LpX (lipoprotein X)

From before birth to adult life

Timeline for development of cardiovascular (CV) risk, atherosclerosis, and CV events as a continuum





NIH Publication No. 12-7486A October 2012

LIPID

AGE	Recommendations
Birth–12 m	No routine lipid screening
1–4 y	Obtain fasting lipid profile **only if** FHx (+), parent with dyslipidemia, any other RFs (+), or high-risk condition
5–8 y	Obtain fasting lipid profile **only if** FHx (+), parent with dyslipidemia, any other RFs (+), or high-risk condition
9–11 y	Obtain **universal lipid screen** with **nonfasting non-HDL** = TC – HDL, or **fasting lipid profile** → manage per lipid algorithms as needed
12–17 y	Obtain fasting lipid profile if **FHx newly (+),** parent with dyslipidemia, any other RFs (+), or high-risk condition; manage per lipid algorithms as needed
18–21 y	Measure **nonfasting non-HDL-C** or **fasting lipid profile in all x 1** → Review with patient; manage with lipid algorithms per ATP as needed

NIH Publication No. 12-7486A October 2012

Evidence Quality for Grades of Evidence

Grade	Evidence
A	Well-designed randomized controlled trials or diagnostic studies performed on a population similar to the Guidelines' target population
B	Randomized controlled trials or diagnostic studies with minor limitations; genetic natural history studies; overwhelmingly consistent evidence from observational studies
C	Observational studies (case-control and cohort design)
D	Expert opinion, case reports, or reasoning from first principles (bench research or animal studies)

NIH Publication No. 12-7486A October 2012

Guidelines' Definitions for Evidence–Based Statements

Statement Type	Definition	Implication
Strong recommendation	The benefits of the recommended approach clearly exceed the harm, and the quality of the supporting evidence is excellent (Grade A or B). In some clearly defined circumstances, strong recommendations may be made on the basis of lesser evidence (e.g., Grade C or D) when high-quality evidence is impossible to obtain and the anticipated benefits clearly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Recommendation	The benefits exceed the harms but the quality of the evidence is not as strong (Grade B or C). In some clearly defined circumstances, strong recommendations may be made on the basis of lesser evidence (e.g., Grade D) when high-quality evidence is impossible to obtain and the anticipated benefits clearly outweigh the harms.	Clinicians should generally follow a recommendation but remain alert to new information and sensitive to patient preferences
Optional	Either the quality of the evidence that exists is suspect (Grade D) or well-performed studies (Grade A, B, or C) show little clear advantage to one approach versus another.	Clinicians should be flexible in their decisionmaking regarding appropriate practice, although they may set boundaries on alternatives; patient preference should have a substantial influencing role.
No recommendation	There is both a lack of pertinent evidence (Grade D) and an unclear balance between benefits and harms.	Clinicians should be minimally constrained in their decision making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role.

NIH Publication No. 12-7486A October 2012

Integrated cardiovascular health schedule

Table 3–1. **INTEGRATED CARDIOVASCULAR HEALTH SCHEDULE**

Risk Factor	AGE					
	Birth–12 m	**1–4 y**	**5–8 y**	**9–11 y**	**12–17 y**	**18–21 y**
FAMILY HISTORY (FHx) OF EARLY CVD		At age 3 y, evaluate FHx for early CVD: parents, grandparents, aunts/uncles, M ≤ 55 y, F ≤ 65 y. Review with parents, refer prn. (+) FHx identifies children for intensive CVD RF attention.	Update at each nonurgent health encounter.	Reevaluate FHx for early CVD in parents, grandparents, aunts/uncles, M ≤ 55 y, F ≤ 65 y.	Update at each nonurgent health encounter.	Repeat FHx evaluation with patient.
TOBACCO EXPOSURE	Advise smoke-free home; offer smoking cessation assistance or referral to parents.	Continue active antismoking advice with parents. Offer smoking cessation assistance and referral as needed.	Begin active antismoking advice with child.	Assess smoking status of child. Active antismoking counseling or referral as needed.	Continue active antismoking counseling with patient. Offer smoking cessation assistance or referral as needed.	Reinforce strong antismoking message. Offer smoking cessation assistance or referral as needed.
NUTRITION/ DIET	Support breastfeeding as optimal to age 12 m if possible. Add formula if breastfeeding decreases or stops before age 12 m.	Age 12-24 m, may change to cow's milk with % fat per family & pediatric care provider. After age 2 y, fat-free milk for all; juice ≤ 4 oz/d; transition to CHILD 1 by age 2 y.	Reinforce CHILD 1 messages.	Reinforce CHILD 1messages as needed.	Obtain diet information from child and use to reinforce healthy diet and limitations and provide counseling as needed.	Review healthy diet with patient.
GROWTH, OVERWEIGHT/ OBESITY	Review FHx for obesity → Discuss wt for ht tracking, growth chart, and healthy diet.	Chart ht/wt/BMI → classify wt by BMI from age 2 y; review with parent.	Chart ht/wt/BMI and review with parent. BMI > 85th%ile, crossing %iles→ intensify diet/activity focus x 6m. If no change → RD referral, manage per obesity algorithms. BMI ≥ 95th%ile, manage per obesity algorithms.	Chart ht/wt/BMI and review with parent and child. BMI > 85th%ile, crossing %iles→ intensify diet/activity focus x 6m. If no change → RD referral, manage per obesity algorithms. BMI ≥ 95th%ile, manage per obesity algorithms	Chart ht/wt/BMI and review with child and parent. BMI > 85th%ile, crossing %iles→ intensify diet/activity focus x 6m. If no change → RD referral, manage per obesity algorithms. BMI ≥ 95th%ile, manage per obesity algorithms.	Review ht/wt/BMI and norms for health with patient. BMI > 85th%ile, crossing %iles →intensify diet/activity focus x 6 m. If no change → RD referral, manage per obesity algorithms. BMI ≥ 95th%ile, manage per obesity algorithms.
LIPIDS	No routine lipid screening.	Obtain fasting lipid profile only if FHx (+), parent with dyslipidemia, any other RFs (+), or high-risk condition.	Obtain fasting lipid profile only if FHx (+), parent with dyslipidemia, any other RFs (+), or high-risk condition.	Obtain universal lipid screen with nonfasting non-HDL = TC – HDL, or fasting lipid profile → manage per lipid algorithms as needed.	Obtain fasting lipid profile if FHx newly (+), parent with dyslipidemia, any other RFs (+), or high-risk condition; manage per lipid algorithms as needed.	Measure nonfasting non-HDL-C or fasting lipid profile in all x 1 → Review with patient; manage with lipid algorithms per *ATP* as needed.
BLOOD PRESSURE	Measure BP in infants with renal/ urologic/cardiac diagnosis or Hx of neonatal ICU.	Measure annual BP in all from age 3 y; chart for age/gender/ht %ile and review with parent.	Check BP annually and chart for age/gender/ht → Review with parent; work up and/or manage per BP algorithm as needed.	Check BP annually and chart for age/gender/ht → Review with parent, work up and/or manage per BP algorithm as needed.	Check BP annually and chart for age/gender/ht → Review with adolescent and parent, work up and/or manage per BP algorithm as needed.	Measure BP → Review with patient. Evaluate and treat as per *JNC* guidelines.
PHYSICAL ACTIVITY	Encourage parents to model routine activity. No screen time before age 2 y.	Encourage active play; limit sedentary/ screen time to ≤ 2 h/d. No TV in bedroom.	Recommend MVPA ≥ 1h/d; limit screen/sedentary time to ≤ 2 h/d.	Obtain activity Hx from child → recommend MVPA ≥ 1 h/d; screen/sedentary time ≤ 2 h/d.	Use activity Hx with adolescent to reinforce MVPA ≥ 1 h/d, leisure screen time ≤ 2 h/d.	Discuss lifelong activity, sedentary time limits with patient.
DIABETES				Measure fasting glucose per ADA guidelines, refer to endocrinologist as needed.	Measure fasting glucose per ADA guidelines, refer to endocrinologist as needed.	Obtain fasting glucose if indicated, refer to endocrinologist as needed.

Abbreviations: m = month(s); y = year(s); FHx = family history; M = male; F = female; RF = risk factor; % = percent; BMI = body mass index; %ile = percentile; ADA = American Diabetes Association; MVPA = moderate-to-vigorous physical activity; *ATP = Adult Treatment Panel III (Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults)*; CHILD 1= **C**ardiovascular **H**ealth **I**ntegrated **L**ifestyle **D**iet; *JNC = The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure;* BP = blood pressure; h/d = hours per day

The Full and Summary Report of the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents may also be found on the NHLBI Web site at: http://www.nhlbi.nih.gov/

NIH Publication No. 12-7486A October 2012

Lipid screening

- Birth to 2 years – no screening
- 2 to 8 years – no routine screening
  - FLP for certain conditions
- 9 - 11 years - **universal screening**
- 12 - 16 years – no routine screening
- 17 - 21 years - **universal screening once** in this time period

9–11 y — **Universal Screening** — Grade B

I
- Non-FLP: Calculate non-HDL-C:
  Non-HDL-C = TC – HDL-C*

Strongly recommend

Non-HDL ≥ 145 mg/dL, HDL < 40 mg/dL
→ FLP × 2, Lipid algorithms below**

OR

II
- FLP:

LDL-C ≥ 130 mg/dL, non-HDL-C ≥ 145 mg/dL
HDL-C < 40 mg/dL, TG ≥ 100 mg/dL if < 10 years; ≥ 130 mg/dL if ≥ 10 years
→ Repeat FLP after 2 weeks but within 3 months → lipid algorithms below**

* Disregard TG and LDL-C in nonfasting sample.

** Use Table 9–1 for interpretation of results; use lipid algorithms in Figures 9–1 and 9–2 for management of results.

17–21 y **Universal screening once in this time period:** Grade B *Recommend*

Non-FLP: Calculate non-HDL-C:
Non-HDL-C = TC – HDL-C*

17–19 y: Non-HDL-C ≥ 145 mg/dL, HDL-C < 40 mg/dL
→ FLP × 2,*** lipid algorithm below (Figure 9–1)
OR
FLP:
LDL-C ≥ 130 mg/dL, non-HDL-C ≥ 145 mg/dL
HDL-C < 40 mg/dL, TG ≥ 130 mg/dL → Repeat FLP after 2 weeks but within 3 months → lipid algorithms in Figures 9–1 and 9–2

20–21 y: Non-HDL-C ≥ 190 mg/dL, HDL-C < 40 mg/dL**
→ FLP × 2,*** average results → *Adult Treatment Panel III (ATP III)* management algorithm
OR
FLP:
LDL-C ≥ 160 mg/dL, non-HDL-C ≥ 190 mg/dL
HDL-C < 40 mg/dL, TG ≥ 150 mg/dL → Repeat FLP after 2 weeks but within 3 months, average results → *ATP III* management algorithm

* Use Table 9–1 for interpretation of results of 7– to 19–year olds and lipid algorithms in Figures 9–1 and 9–2 for management. Use Table 9–2 for interpretation of results of 20– to 21–year olds and *ATP III* algorithms for management.

** Disregard TG and LDL-C in nonfasting sample.

*** Interval between FLP measurements: after 2 weeks but within 3 months.

Lipid screening –
Universal Screening at 9-11 and 17-21 years old

- First time to recommend that non-fasting Lipid Profile (non-FLP) could be used for screening and
  - Focus on non-HDL-C only
  - Ignoring TG and LDL-C
- Fasting LP (FLP) remains an option
- Grade B; Strongly recommended

Use of non-HDL-C as screening tool

- Non-HDL–C has been identified as a significant predictor of the presence of atherosclerosis, as powerful as any other lipoprotein cholesterol measure in children and adolescents.
- For both children and adults, non-HDL–C appears to be more predictive of persistent dyslipidemia, and therefore atherosclerosis and future events, than TC, LDL–C, or HDL–C alone.
- A major advantage is that non-HDL–C can be accurately calculated in a nonfasting state and is therefore very practical to obtain in clinical practice
- The evidence supports use of non-HDL–C as a screening tool for identification of a dyslipidemic state in childhood

Non-HDL-C

- In adults, non-HDL-C is a better independent predictor of CVD than LDL-C
- Childhood non-HDL is a better predictor than LDL-C
  - Adult dyslipidemia
  - Non-lipid CVD risk factor
- In the Bogalusa longitudinal cohort of 1163 children followed up from 4-5 years old to 27 years later
  - odd ratios of developing dyslipidemia is
    - 4.49 for non-HDL-C versus 3.46 for LDL-C
  - Both high non-HDL-C and LDL-C are associated with
    - Increased obesity, high LDL-C and high TG
  - Only high non-HDL is associated with
    - Low HDL-C, hyperinsulinemia and hyperglycemia (marginally)

Non-HDL-C [continued]

- In the Bogalusa study, non-HDL-C is a significant predictor of subclinical atherosclerosis as defined as higher cIMT in adults
  - Other being LDL-C, TC/HDL-C, apoB and apoB/apoA-1
  - Odd ratios being highest for **LDL-C and non-HDL-C**
- In PDAY study both **non-HDL-C and HDL-C** are the best lipid predictors of pathologic atherosclerosis

Risk Scores Predict Atherosclerotic Lesions in Young People

McMahan CA et al.
ARCH INTERN MED. 2005; 165:883-890

A Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study

Modifiable risks factors

- Smoking
- Blood pressure
- Non-HDL-C***
- HDL cholesterol
- Obesity
- Hyperglycaemia

Table 3. Risk Scores for Predicting Target Lesions in the Coronary Arteries and the Abdominal Aorta

Risk Factor	Points	
	Coronary Arteries	Abdominal Aorta
Age, y		
15-19*	0	0
20-24	5	5
25-29	10	10
30-34	15	15
Sex		
M*	0	0
F	−1	1
Non-HDL cholesterol, mg/dL		
<130*	0	0
130-159	2	1
160-189	4	2
190-219	6	3
≥220	8	4
HDL cholesterol, mg/dL		
<40	1	0
40-59*	0	0
≥60	−1	0
Smoking		
Nonsmoker*	0	0
Smoker	1	4
Blood pressure		
Normotensive*	0	0
Hypertensive	4	3
Obesity (BMI, kg/m^2)		
Men		
≤30*	0	0
>30	6	0
Women		
≤30*	0	0
>30	0	0
Hyperglycemia (glycohemoglobin, %)		
<8*	0	0
≥8	5	3

Birth–2 y	No lipid screening	Grade C *Recommend*
2–8 y	No routine lipid screening	Grade B *Recommend*
	Measure fasting lipid profile (FLP) × 2*, average results** if:	
	• Parent, grandparent, aunt/uncle, or sibling with myocardial infarction (MI), angina, stroke, coronary artery bypass graft (CABG)/stent/angioplasty at < 55 years in males, < 65 years in females	Grade B *Strongly recommend*
	• Parent with TC ≥ 240 mg/dL or known dyslipidemia	Grade B *Strongly recommend*
	• Child has diabetes, hypertension, BMI ≥ 95th%ile or smokes cigarettes	Grade B *Strongly recommend*
	• Child has a moderate- or high-risk medical condition (Table 9–7)	Grade B *Strongly recommend*

* Interval between FLP measurements: after 2 weeks but within 3 months.

** Use Table 9–1 for interpretation of results; use lipid algorithms in Figures 9–1 and 9–2 for management of results.

12–16 y	No routine screening*	Grade B *Recommend*
	Measure FLP × 2**, average results, if new knowledge of:	
	• Parent, grandparent, aunt/uncle or sibling with MI, angina, stroke, CABG/stent/ angioplasty, sudden death at < 55 years in males, < 65 years in females	Grade B *Strongly recommend*
	• Parent with TC ≥ 240 mg/dL or known dyslipidemia	Grade B *Strongly recommend*
	• Patient has diabetes, hypertension, BMI ≥ 85th%ile or smokes cigarettes	Grade B *Strongly recommend*
	• Patient has a moderate- or high-risk medical condition (Table 9–7)	Grade B *Strongly recommend*

* Lipid screening is not recommended for those ages 12-16 years because of significantly decreased sensitivity and specificity for predicting adult LDL-C levels and significantly increased false-negative results in this age group. Selective screening is recommended for those with the clinical indications outlined.

** Interval between FLP measurements: after 2 weeks but within 3 months.

For the age periods when **universal screening is not recommended**

- Selective lipid screening based on
  - Family history
  - Personal CV risk factors
  - Existing high or moderate CV risk medical conditions

Family history for Dyslipidemia Algorithms

(+) Family history:

- Myocardial infarction
- Angina (need treatment)
- Coronary artery bypass graft/stent/angioplasty
- Sudden cardiac death

In parent, grandparent, aunt, or uncle, siblings

- male < 55 y, female < 65 y

Use of Family History in Cardiovascular Health Promotion - Evidence–Based Recommendations

Birth - 17 y

Take detailed family history (FHx) of CVD* at initial encounter and/or at 3y, 9-11y & 18y	Grade B Recommend
If (+) FHx identified, evaluate patient for other CV risk factors, including dyslipidemia, hypertension, diabetes, obesity, history of smoking, and sedentary lifestyle	Grade B Recommend
If (+) FHx and/or CV risk factors identified, evaluate family, especially parents, for CV risk factors	Grade B Recommend
Update FHx at each non-urgent health encounter	Grade D Recommend
Use FHx to stratify risk for CVD risk as risk profile evolves	Grade D Recommend

Supportive actions:

Educate parents about the importance of FHx in estimating future health risks for all family members

NIH Publication No. 12-7486A October 2012

Use of Family History in Cardiovascular Health Promotion - Evidence–Based Recommendations

18 - 21 y

- Review FHx of heart disease with young adult patient
- **Grade B Strongly recommend**
- Supportive actions:
  - Educate patient about family/personal risk for early heart disease including need for evaluation for all CV risk factors

Risk Factor (RF) Definitions for Dyslipidemia Algorithms

- **High Level Risk Factors**
  - Hypertension requiring drug therapy (BP ≥ 99th centile + 5 mmHg)
  - BMI ≥ 97th centile
  - Current cigarette smoker
  - Presence of high risk conditions
    - Diabetes mellitus, type 1 and type 2
    - Chronic renal disease (stage 3 & 4)/end-stage renal disease (stage 5)/ postrenal transplant
    - Postorthotopic heart transplant
    - Kawasaki disease with current aneurysms

Risk Factor (RF) Definitions for Dyslipidemia Algorithms

- **Moderate-Level RFs**
  - Hypertension not requiring drug therapy
  - BMI ≥ 95th%ile, < 97th%ile
  - HDL-C < 40 mg/dL
  - Presence of moderate risk conditions
    - Kawasaki disease with regressed coronary aneurysms
    - Chronic inflammatory disease (systemic lupus erythematosis, juvenile rheumatoid arthritis)
    - Human immunodeficiency virus infection (HIV)
    - Nephrotic syndrome

Acceptable, borderline high, and high plasma lipid, lipoprotein, and apolipoprotein concentrations (mg/dl) for children and adolescents

Category	Acceptable	Borderline High	High
TC	< 170 (4.4mM)	170–199	>200 (5.2mM)
LDL-C	< 110 (2.8mM)	110–129	>130 (3.4mM)
Non-HDL-C	< 120 (3.1mM)	120–144	>145 (3.8mM)
ApoB	< 90	90–109	>110
TG			
0-9 years	< 75 (0.85mM)	75–99	>100 (1.1mM)
10-19 years	< 90 (1mM)	90–129	>130 (1.47mM)

Category	Acceptable	Borderline Low	Low
HDL-C	>45 (1.2mM)	40–45	< 40 (1mM)
ApoA-1	>120	115–120	<115

Recommended cutpoints for lipid and lipoprotein levels (mg/dl) in young adults

Category	Acceptable	Borderline High	High
TC	<190 (4.9mM)	190–224	225 (5.8mM)
LDL-C	<120 (3.1mM)	120–159	160 (4.1mM)
Non-HDL-C	<150 (3.9mM)	150 –189	190 (4.9mM)
TG	<115 (1.3mM)	115–149	150 (1.7mM)

Category	Acceptable	Borderline Low	Low
HDL-C	>45 (1.2mM)	40–45	< 40 (1.0mM)

Dyslipidemia algorithm: Target-LDL-C

Fasting lipid profile (FLP) x 2;
average results

TG ≥ 5.6mM
→Consult lipid specialist

LDL-C ≥ 6.5mM
→Consult lipid specialist

LDL-C ≥ 3.5 to <6.5mM →TARGET LDL-C

TG ≥ 1.1 to <5.6mM [<10 y] OR TG ≥ 1.5 to <5.6mM [10-19 y] → TARGET TG

- **Exclude secondary causes**
- **Evaluate for risk factors**
- **Start CHILD1→CHILD2-LDL + lifestyle change x 6 months**
- ***LDL-C >4.9mM - + other RFs, trial of CHILD2 may be abbreviated**

FLP

LDL-C < 3.4 mM
Continue CHILD2-LDL
Repeat FLP q12m

LDL-C ≥ 3.4 to <4.9mM
FHx –ve; no other RF

Continue CHILD2-LDL
FU q6m FLP
Update FHx/RFs

LDL-C ≥ 4.9mM

→ Statin therapy

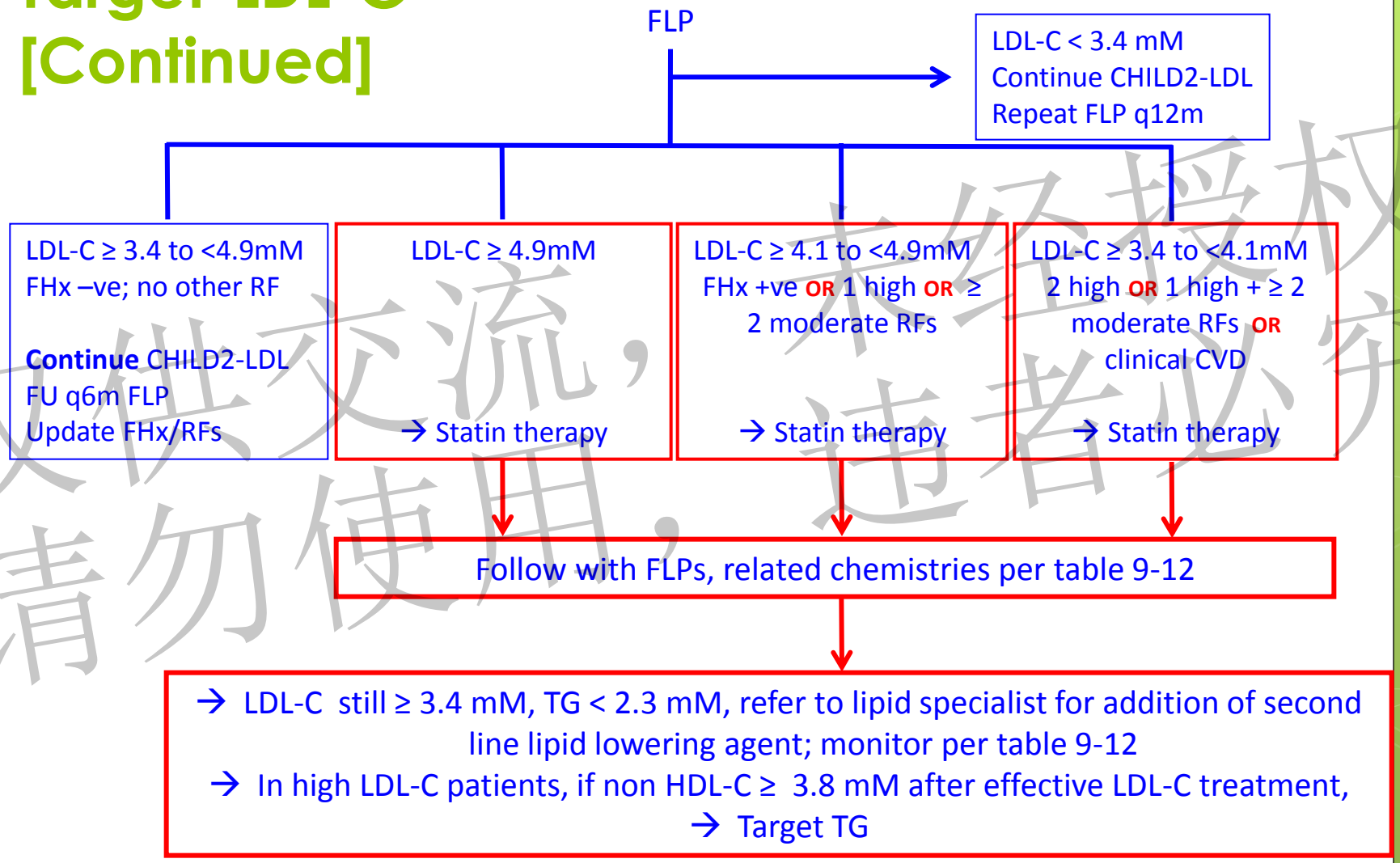
LDL-C ≥ 4.1 to <4.9mM
FHx +ve **OR** 1 high **OR** ≥ 2 moderate RFs

→ Statin therapy

LDL-C ≥ 3.4 to <4.1mM
2 high **OR** 1 high + ≥ 2 moderate RFs **OR** clinical CVD

→ Statin therapy

Dyslipidemia algorithm: Target-LDL-C [Continued]



Dyslipidemia algorithm: Target-TG

Fasting lipid profile (FLP) x 2; average results

TG ≥ 5.6mM
→Consult lipid specialist

LDL-C ≥ 6.5mM
→Consult lipid specialist

TG ≥ 1.1 to <5.6mM [<10 y] → TARGET TG
TG ≥ 1.5 to <5.6mM [10-19 y] → TARGET TG

LDL-C ≥ 3.5 to <6.5mM →TARGET LDL-C

Start CHILD1→CHILD2-TG + lifestyle modification with weight loss goals as needed x 6 months

FLP

TG <1.1 mM, [<10 y]
<1.5 mM, [10-19 y]

→ **Continue** CHILD2-TG + lifestyle change
→ Reassess q12m

TG <1.1 mM, <2.3 mM [<10 y]
<1.5 mM , <2.3 mM [10-19 y]

→ Intensify CHILD2-TG + weight loss
→ Increase dietary fish content **
→ Repeat FLP in 6 m

TG ≥ 2.3 mM – 5.64mM
→ If LDL-C achieved and non-HDL-C ≥ 2.3 mM → lipid specialist for drug therapy [statin ± fibrate ± nicotinic acid]
→ Consider omega-3 fish oil therapy

Cardiovascular Health Integrated Lifestyle Diet - **CHILD 1**

- CHILD 1 is the first stage in dietary change for children **that may ultimately require more intensive dietary change**
  - with
    - identified dyslipidemia
    - overweight and obesity
    - risk factor clustering, and
    - high-risk medical conditions
- CHILD 1 is also the recommended diet for children
  - with a positive family history of early CV disease, dyslipidemia, obesity, primary hypertension, diabetes, or exposure to smoking in the home

CHILD 1 is the recommended first step diet for all children and adolescents at elevated cardiovascular risk.

Grades reflect the findings of the evidence review.
Recommendation levels reflect the consensus opinion of the Expert Panel.
Supportive actions represent expert consensus suggestions from the Expert Panel provided to support implementation of the recommendations; they are not graded.

Birth–6 m	Infants should be exclusively breastfed (no supplemental formula or other foods) until age 6 m.*	Grade B *Strongly recommend*
	* Infants that cannot be fed directly at the breast should be fed expressed milk. Infants for whom expressed milk is not available should be fed iron-fortified infant formula.	
6–12 m	Continue breastfeeding* until at least age 12 m while gradually adding solids; transition to iron-fortified formula until 12 m if reducing breastfeeding.	Grade B *Strongly recommend*
	Fat intake in infants less than 12 months of age should not be restricted without medical indication.	Grade D *Recommend*
	Limit other drinks to 100% fruit juice ≤ 4 oz/d; No sweetened beverages; encourage water.	Grade D *Recommend*
	* Infants that cannot be fed directly at the breast should be fed expressed milk. Infants for whom expressed milk is not available should be fed iron-fortified infant formula.	
12–24 m	Transition to reduced-fat* (2% to fat-free) unflavored cow's milk** (see *Supportive Actions* bullet 1)	Grade B *Recommend*
	Limit/avoid sugar-sweetened beverage intake; encourage water	Grade B *Strongly recommend*
	Transition to table food with:	
	• Total fat 30% of daily kcal/EER***	Grade B *Recommend*
	• Saturated fat 8-10% of daily kcal/EER	Grade B *Recommend*
	• Avoid *trans* fat as much as possible	Grade D *Strongly recommend*
	• Monounsaturated and polyunsaturated fat up to 20% of daily kcal/EER	Grade D *Recommend*
	• Cholesterol < 300 mg/d	Grade B *Strongly recommend*
	Supportive actions: • The fat content of cow's milk to introduce at age 12-24 m should be decided together by parents and health care providers based on the child's growth, appetite, intake of other nutrient dense foods, intake of other sources of fat, and potential risk for obesity and CVD • 100% fruit juice (from a cup) no more than 4 oz/d • Limit sodium intake • Consider DASH-type diet rich in fruits, vegetables, whole grains, low-fat/fat-free milk and milk products; lower in sugar (Table 5–2)	

* Toddlers 12-24 m of age with a family history of obesity, heart disease, or high cholesterol, should discuss transition to reduced-fat milk with pediatric care provider after 12 months of age.
** Continued breastfeeding is still appropriate and nutritionally superior to cow's milk. Milk reduced in fat should be used only in the context of an overall diet that supplies 30% of calories from fat.
*** EER = Estimated Energy Requirements/d for age/gender (Table 5–3)

2–10 y	Primary beverage: Fat-free unflavored milk	Grade A *Strongly recommend*
	Limit/avoid sugar-sweetened beverages; encourage water.	Grade B *Recommend*
	Fat content:	
	• Total fat 25-30% of daily kcal/EER**	Grade A *Strongly recommend*
	• Saturated fat 8-10% of daily kcal/EER	Grade A *Strongly recommend*
	• Avoid *trans* fat as much as possible	Grade D *Recommend*
	• Monounsaturated and polyunsaturated fat up to 20% of daily kcal/EER	Grade D *Recommend*
	• Cholesterol < 300 mg/d	Grade A *Strongly recommend*
	Encourage high dietary fiber intake from foods*	Grade B *Recommend*
	Supportive actions: • Teach portions based on EER for age/sex/activity (Table 5–3) • Encourage moderately increased energy intake during periods of rapid growth and/or regular moderate-to-vigorous physical activity • Encourage dietary fiber from foods: Age plus 5 g/d* • Limit naturally sweetened juice (no added sugar) to 4 oz/d • Limit sodium intake • Support DASH-style eating plan as outlined below (Table 5–3)	
	* Naturally fiber-rich foods are recommended (fruits, vegetables, whole grains); fiber supplements are not advised Limit refined carbohydrates (sugars, white rice, and white bread) ** EER = Estimated Energy Requirements/d for age/gender (Table 5–3)	
11–21 y	Primary beverage: Fat-free unflavored milk	Grade A *Strongly recommend*
	Limit/avoid sugar-sweetened beverages; encourage water	Grade B *Recommend*
	Fat content:	
	• Total fat 25-30% of daily kcal/EER**	Grade A *Strongly recommend*
	• Saturated fat 8-10% of daily kcal/EER	Grade A *Strongly recommend*
	• Avoid *trans* fat as much as possible	Grade D *Recommend*
	• Monounsaturated and polyunsaturated fat up to 20% of daily kcal/EER	Grade D *Recommend*
	• Cholesterol < 300 mg/d	Grade A *Strongly recommend*
	Encourage high dietary fiber intake from foods*	Grade B *Recommend*
	Supportive actions: • Teach portions based on EER for age/sex/activity (Table 5–3) • Encourage moderately increased energy intake during periods of rapid growth and/or regular moderate-to-vigorous physical activity • Advocate dietary fiber: Goal of 14 g/1,000 kcal * • Limit naturally sweetened juice (no added sugar) to 4-6 oz/d • Limit sodium intake • Encourage healthy eating habits: Breakfast every day, eating meals as a family, limiting fast food meals • Support DASH-style eating plan as outlined below (Table 5–2)	
	* Naturally fiber-rich foods are recommended (fruits, vegetables, whole grains); fiber supplements are not advised. Limit refined carbohydrates (sugars, white rice, and white bread) ** EER = Estimated Energy Requirements/d for age/gender (Table 5–3)	

Cardiovascular Health Integrated Lifestyle Diet (CHILD) – 2 diet

for management of elevated TG

Elevated TG or non-HDL-C: CHILD 2–TG

2–21 y	Refer to a registered dietitian for family medical nutrition therapy:*	Grade B *Strongly recommend*
	• 25-30% of calories from fat, ≤ 7% from saturated fat, ~10% from monounsaturated fat; < 200 mg/d of cholesterol; avoid *trans* fat as much as possible	Grade A *Recommend*

	• Decrease sugar intake:
	  ▪ Replace simple with complex carbohydrates
	  ▪ No sugar-sweetened beverages
		Grade B
		Recommend

	• Increase dietary fish to increase omega-3 fatty acids**	Grade D *Recommend*

* If child is obese, nutrition therapy should include calorie restriction, and increased activity (beyond that recommended for all children) should be prescribed. See Section 10. Overweight and Obesity for additional age-specific recommendations.

** The Food and Drug Administration (FDA) and the Environmental Protection Agency are advising women of childbearing age who may become pregnant, pregnant women, nursing mothers, and young children to avoid some types of fish and shellfish and eat fish and shellfish that are low in mercury. For more information, call the FDA's food information line toll free at 1–888–SAFEFOOD or visit www.fda.gov/Food/FoodSafety/Product-specificinformation/Seafood/FoodbornePathogensContaminants/Methylmercury/ucm115644.htm

Cardiovascular Health Integrated Lifestyle Diet (CHILD) – 2 diet

for management of elevated LDL-C

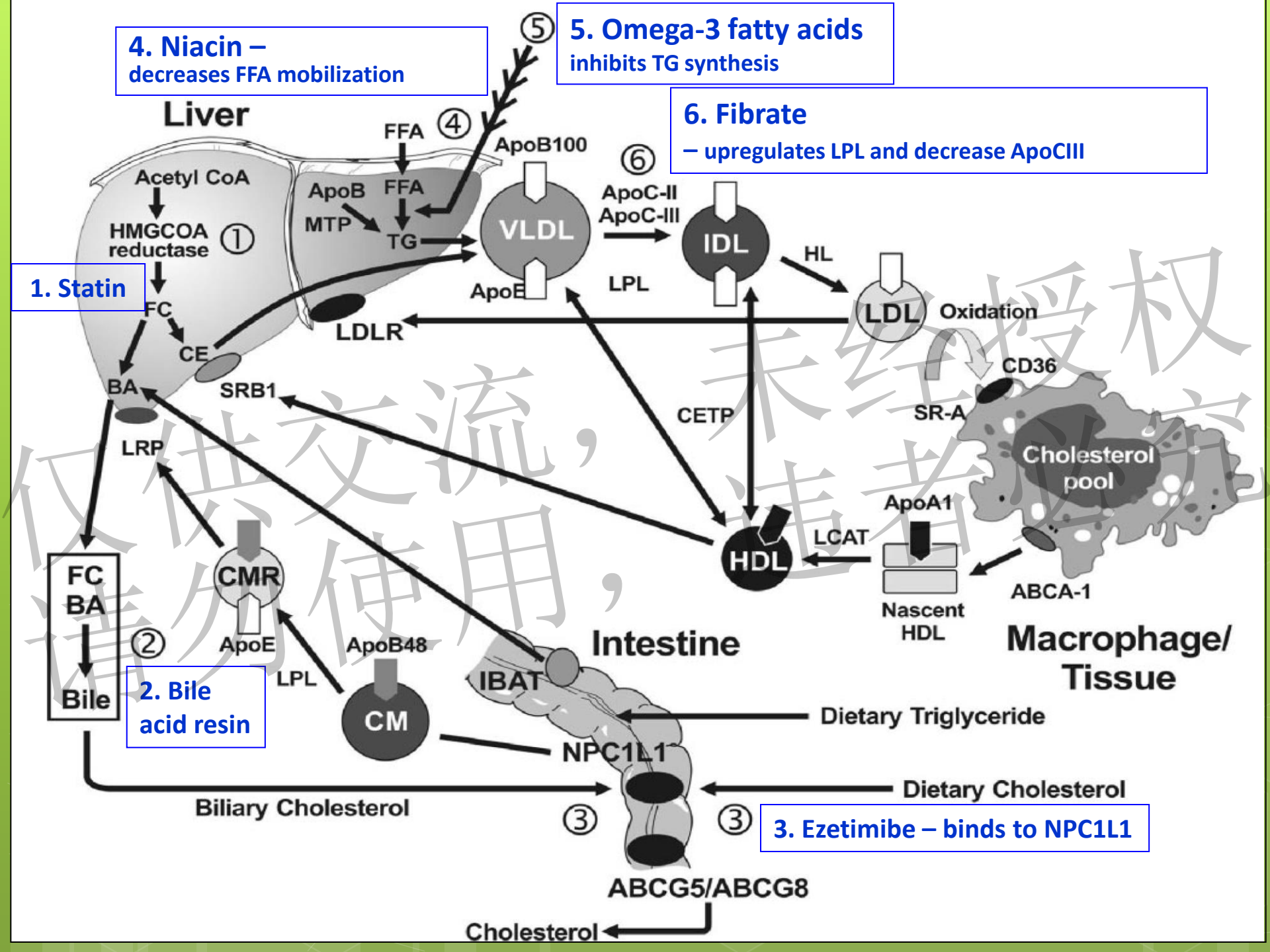
Elevated LDL-C: CHILD 2–LDL

2–21 y	Refer to a registered dietitian for family medical nutrition therapy:	Grade B *Strongly recommend*
	• 25-30% of calories from fat, ≤ 7% from saturated fat, ~10% from monounsaturated fat; < 200 mg/d of cholesterol; avoid *trans* fat as much as possible.	Grade A *Recommend*

Supportive Actions:

- Plant sterol esters and/or plant stanol esters* up to 2 g/d as replacement for usual fat sources can be used after age 2 years in children with familial hypercholesterolemia.
- Plant stanol esters as part of a regular diet are marketed directly to the public. Short-term studies show no harmful effects in healthy children.
- The water-soluble fiber psyllium can be added to a low-fat, low saturated fat diet as cereal enriched with psyllium at a dose of 6 g/d for children 2-12 years, and 12 g/d for those ≥ 12 years.
- As in all children, 1 hour/day (h/d) of moderate-to-vigorous physical activity and < 2 h/d of sedentary screen time are recommended.

* Can be found added to some foods, such as some margarines.


4. Niacin –
decreases FFA mobilization
5. Omega-3 fatty acids
inhibits TG synthesis
6. Fibrate
– upregulates LPL and decrease ApoCIII
Liver
FFA
④
ApoB100
⑤
⑥
Acetyl CoA
ApoB
FFA
MTP
TG
VLDL
ApoC-II
ApoC-III
IDL
HL
HMGCOA
reductase
①
1. Statin
FC
CE
ApoE
LPL
LDL
Oxidation
LDLR
BA
SRB1
CD36
SR-A
CETP
LRP
Cholesterol
pool
ApoA1
HDL
LCAT
FC
BA
Bile
②
CMR
ApoE
ABCA-1
Nascent
HDL
Macrophage/
Tissue
2. Bile
acid resin
LPL
ApoB48
Intestine
IBAT
Dietary Triglyceride
CM
NPC1L1
Dietary Cholesterol
Biliary Cholesterol
③
③
3. Ezetimibe – binds to NPC1L1
ABCG5/ABCG8
Cholesterol

Pharmacologic Treatment of Dyslipidemia

- Consideration of drug therapy based on the average of ≥ 2 fasting lipid profiles obtained at least 2 weeks but no more than 3 months apart
- If child is obese, nutrition therapy should include calorie restriction and increased activity beyond that recommended for all children according to additional age-specific recommendations
- When medication is recommended, this should always be in the context of the complete cardiovascular risk profile of the patient and in consultation with the patient and the family

Ways to circumvent the lack of "long-term" study directly demonstrating the improved CVD outcome from lowering LDL-C

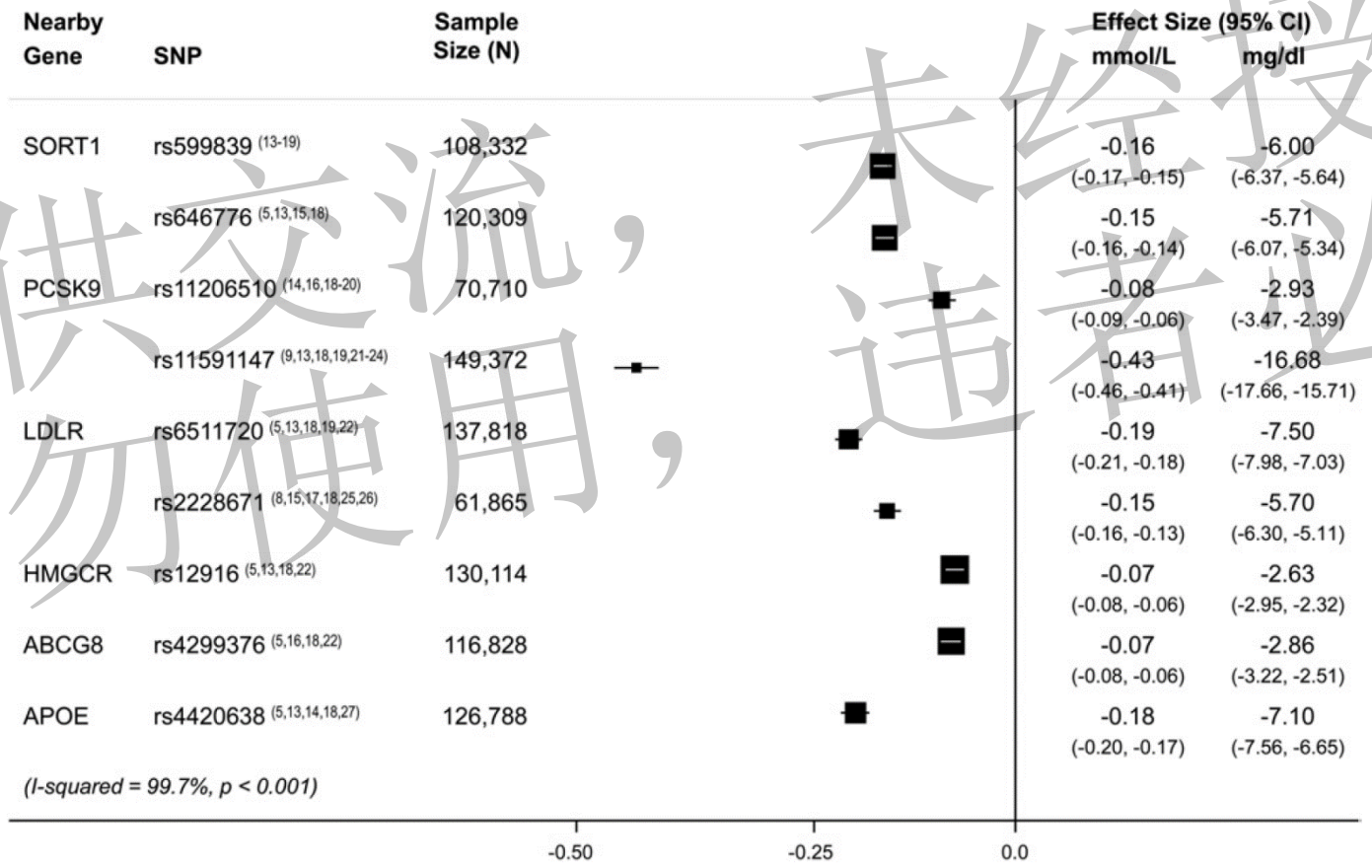
- Surrogate intermediate endpoint
  - Carotid intimal thickness (cIMT)
  - Vascular function -
  - (FMD) in the brachial artery
  - Coronary artery calcium (CAC)
- Mendelian randomization studies

Evidence from Key Mendelian randomization studies

Mutation	LDL cholesterol reduction	mg/dL	mM	Coronary heart disease risk
APOC-III	↓ 16%	↓ 23.4	↓ 0.6	↓ 40%
NPC1L1	-	↓ 12	↓ 0.31	↓ 53%
PCSK9				
Blacks	↓ 28%	↓ 40	↓ 1.0	↓ 88%
Whites	↓ 15%	↓ 20	↓ 0.5	↓ 47%

J Clinical Lipidology 2015, 9: S1–S4

Long-Term Reduction in LDL Cholesterol



JACC Vol. 60, No. 25, 2012

Effect of Long-Term Exposure to Lower Low-Density Lipoprotein Cholesterol Beginning Early in Life on the Risk of Coronary Heart Disease - A Mendelian Randomization Analysis

- All 9 polymorphisms were associated with a highly consistent reduction in the risk of CHD per unit lower LDL-C, with no evidence of heterogeneity of effect (I^2 = 0.0%)
- In a meta-analysis combining nonoverlapping data from 312,321 participants, naturally random allocation to long-term exposure to lower LDL-C was associated with a 54.5% (95% confidence interval: 48.8% to 59.5%) reduction in the risk of CHD for each mmol/l (38.7 mg/dl) lower LDL-C
- This represents a 3-fold greater reduction in the risk of CHD per unit lower LDL-C than that observed during treatment with a statin started later in life

J Am Coll Cardiol 2012, 60:2631–9

Pharmacologic Treatment of Dyslipidemia

Birth–10 y

- Pharmacologic treatment is limited to those with
  - severe primary hyperlipidemia (homozygous familial hypercholesterolemia, primary hypertriglyceridemia with TG ≥ 500 mg/dL - 5.65mM) or
  - **a high-risk condition** (Tables 9–6 and 9–7) or
  - evident cardiovascular disease [CVD]
- All under the care of a lipid specialist
- Grade C ; Recommend

Pharmacologic Treatment of Dyslipidemia – LDL-C 11-21 y

If average LDL-C ≥ 6.5 mM, consult lipid specialist	Grade B Strongly recommend
If average LDL-C ≥ 3.4-6.5 mM, or non-HDL ≥ 3.8 mM ● Refer to dietitian for medical nutrition therapy with Cardiovascular Health Integrated Lifestyle Diet **(CHILD 1)** → **CHILD 2-LDL × 6 months → repeat fasting lipid panel**	Grade A Strongly recommend
● Repeat fasting lipid panel :	
→ LDL-C < 3.4 mM, continue CHILD 2- LDL, reevaluate in 12 months	Grade A Strongly recommend
→ LDL-C ≥ 4.9 mM, consider initiation of **statin** therapy	Grade A Strongly recommend
→ LDL-C ≥ 3.4 – 4.9 mM, FHx (-), no other RF or RC, continue CHILD 2-LDL, reevaluate q 6 months	Grade B Recommend
→ LDL-C = 4.1 - 4.9 mM + FHx positive **OR** ≥ 1 high-level RF/RC **OR** ≥ 2 moderate-level RFs/RCs, consider **statin** therapy	Grade B Recommend
→ LDL-C ≥ 3.4 – 4.1 mM + ≥ 2 high-level RFs/RCs **OR** 1 high-level + 2 moderate-level RFs/RCs, consider **statin** therapy	Grade B Recommend

Pharmacologic Treatment of Dyslipidemia – Triglyceride 11-21 y

Detailed FHx and RF/RC assessment required before initiation of drug therapy High- and moderate-level RFs/RCs	Grade C Strongly recommend
If average TG ≥ 5.6 mM, consult lipid specialist	Grade B Recommend
If average TG ≥ 1.13 mM & < 5.6 mM in a child < 10 years ≥ 1.47 mM & < 5.6 mM in a child age 10-19 years ●Refer to dietitian for medical nutrition therapy with CHILD 1 → CHILD 2-TG × 6 months	Grade B Strongly recommend
● **Repeat fasting lipid profile:**	
→ TG < 1.13 (1.47) mM, ●continue CHILD 2-TG, monitor q 6–12 months	Grade B Strongly recommend
→ TG > 1.13 (1.47) mM, ●reconsult dietitian for intensified CHILD 2-TG diet counseling	Grade C Recommend
→ TG ≥ 2.26-5.6 mM, non-HDL ≥ 3.8mM, ● consider fish oil +/- consult lipid specialist	Grade D Recommend

OTHER AGENTS

Study	Medication	Subjects/ Gender/ Condition	Daily Dose	Effect on Lipid Profile			
				TC	LDL–C	HDL–C	TG
Wheeler et al.[150] RCT 26 weeks **1985**	Bezafibrate	14/both/FH (TC > 269 mg/dL, nl TG + FHx of FH or premature CAD; ages 4–15 years)	10–20 mg	-22%	NC	+15%	-23%
Colletti et al.[149] Open-label 1–19 months **1993**	Niacin	21/both/FH (mean LDL = 243 ± 45 mg/dL on low-fat diet; mean TG = 87 ± 39 mg/dL; ages 4–14 years)	500–2,200 mg	-13%	-17%	+4%	+13%
McCrindle et al.[148] RCT cross-over 2 × 18 weeks **2002**	Pravastatin and Colestipol	36/both/FH/FCHL (LDL > 160 mg/dL + FHx of FH or premature CAD; TG > 177 mg/dL in 10/36; ages 10–18 years)	Pravastatin, 10 mg (with Colestipol, 5g)	-13%	-17%	+4%	+8%
Van der Graaf et al.[154] RCT 6 and 27 weeks; Open-label to 53 weeks **2008**	Simvastatin and Ezetimibe	248/both/FH (LDL > 159 mg/dL + genotype-confirmed FH or + parental genotype-confirmed FH or + parental LDL > 210 mg/dL or + tendinous xanthomas or LDL > 189 mg/dL + FHx of hypercholesterolemia; ages 10–17 years)	Simvastatin 10–40 mg with Ezetimibe 10 mg	- 38%	- 49%	+7%	-17%
Addendum: *Goldberg et al.* [157] *Omega-3 fatty acid review in adults; no RCTs in children* **2005**	*Omega-3 fish oils** (1 gram/ capsule)*		*1–4 g/d*	NC	*+17–31%*	*+6–17%*	*-30–40%*

HMG COA REDUCTASE INHIBITORS (STATINS) (continued)

Study	Medication	Subjects/ Gender/ Condition	Daily Dose	Effect on Lipid Profile			
				TC	LDL–C	HDL–C	TG
Wiegman et al.[21] RCT 2 years **2004**	Pravastatin	214/both/FH (LDL–C ≥ 155 mg/dL and TG ≤ 350 mg/dL; diet × 3 months; ages 8–18 years)	20–40 mg	-19%	-24%	+6%	-17%
Rodenburg et al.[22] Open-label 2-year RCT; 4.5 year open-label follow-up **2007**	Pravastatin	186/both/FH (LDL–C ≥ 154 mg/dL and TG < 154 mg/dL; 3 months on diet; ages 8–18 years)	20 mg (ages < 14 years) or 40 mg (ages >14 years)	-23%	-29%	+3%	-2%
de Jongh et al.[145] RCT 48 weeks **2002**	Simvastatin	173/both/FH (LDL–C:158–397 mg/dL; ages 10–17 years)	10–40 mg	-31%	-41%	+3%	-9%
de Jongh et al.[23] RCT 28 weeks **2002**	Simvastatin	50/both/FH (LDL–C above 95th percentile, FHx hyperlipidemia, or LDL receptor mutation; ages 9–18 years)	40 mg	-30%	-40%	+5%	-17%
Avis et al.[146] RCT 12 weeks; then, 40 week open-label follow-up **2010**	Rosuvastatin	177/both/FH (LDL–C ≥ 190 mg/dL or LDL–C > 160 mg/dL plus (+)FHx of early CVD or ≥ 2 other RFs for CVD)	5 mg 10 mg 20 mg	-30% -34% -39%	-38% -45% -50%	+4% +10% +9%	-13% -15% -16%

HMG COA REDUCTASE INHIBITORS (STATINS)

Study	Medication	Subjects/ Gender/ Condition	Daily Dose	Effect on Lipid Profile			
				TC	LDL–C	HDL–C	TG
McCrindle et al.[139] RCT Open-label 26 weeks **2003**	Atorvastatin	187/both/FH/Severe hyperlipidemia (LDL–C ≥ 190 mg/dL or ≥ 160 mg/dL with FHx; and TG < 400 mg/dL; ages 10–17 years)	10–20 mg	-30%	-40%	+6%	-13%
Van der Graaf et al.[140] Open-label 2 years **2006**	Fluvastatin	85/both/FH (LDL–C ≥ 190 mg/dL or LDL–C ≥ 160 mg/dL and 1+ risk factor or LDL receptor mutation; ages 10–16 years)	80 mg	-27%	-34%	+5%	-5%
Lambert et al.[141] RCT 8 weeks **1996**	Lovastatin	69/male/FH (LDL–C > 95th percentile, FHx atherosclerosis and hyperlipidemia; on diet; mean age 13 years)	10 mg 20 mg 30 mg 40 mg	-17% -19% -21% -29%	-21% -24% -27% -36%	+9% +2% +11% +3%	-18% +9% +3% -9%
Stein et al.[142] RCT 48 weeks **1999**	Lovastatin	132/male/FH (LDL 189–503 mg/dL + FHx of high LDL; or 220–503 mg/dL + FHx CAD death; AHA diet 4+ months; ages 10–17 years)	10 mg 20 mg 40 mg	-13% -19% -21%	-17% -24% -27%	+4% +4% +5%	+4% +8% +6%
Clauss et al.[143] RCT 24 weeks **2005**	Lovastatin	54/female/FH (FHx FH; LDL 160–400 mg/dL and TG < 350 mg/dL; 4-week diet placebo run-in and 20-week tx; ages 10–17 years, postmenarchal)	40 mg	-22%	-27%	+3%	-23%
Knipscheer et al.[144] RCT 12 weeks **1996**	Pravastatin	72/both/FH (FHx hypercholesterol or premature atherosclerosis; LDL > 95th percentile; diet × 8 weeks; ages 8–16 years)	5 mg 10 mg 20 mg	-18% -17% -25%	-23% -24% -33%	+4% +6% +11%	+2% +7% +3%

BILE ACID BINDING RESINS

Study	Medication	Subjects/ Gender/ Condition	Daily Dose	Effect on Lipid Profile			
				TC	LDL–C	HDL–C	TG
Tonstad et al.[99] RCT 1 year **1996**	Cholestyramine	72/both/FH (LDL ≥ 190 mg/dL without FHx premature CVD or LDL ≥ 160 with FHx after 1-year diet; ages 6–11 years)	8 g	-12%	-17%	+8%	NA
McCrindle et al.[146] RCT crossover 2 × 8 weeks **1997**	Cholestyramine	40/both/FH (1 parent with FH; LDL–C ≥ 131 mg/dL; on diet; ages 10–18 years)	8 g	-7 to -11%	-10 to -15%	+2 to +4%	+6 to +9%
Tonstad et al.[147] RCT 8 weeks; Open-label 44–52 weeks **1996**	Colestipol	66/both/FH (TC ≥ 239 mg/dL and TG ≤ 115 mg/dL; ages 10–16 years)	2–12 g	-17%	-20%	-7%	-13%
McCrindle et al.[148] RCT crossover 2 × 18 weeks **2002**	Colestipol	36/both/FH/FCHL (LDL ≥ 160 mg/dL after 6 months diet counseling; ages 8–18 years)	10 g	- 7%	-10%	+2%	+12%
Stein et al.[149] **1993**	Colesevelam	191/both/ FH (LDL ≥ 190mg/dL or LDL ≥ plus 2 additional RFs after 6 months diet counseling; ages 10–17 years)	1.875 g 3.75 g	-3% -7%	-6% -13%	+5% +8%	+6% +5%

Ezetimibe Treatment of Pediatric Patients with hypercholesterolemia

- 36 identified patients treated with ezetimibe for 105 days (range, 32-175 days)
  - 26 suggestive of familial hypercholesterolemia (FH)
  - 10 suggestive of familial combined hyperlipidemia (FCHL)
- In patients with FH
  - TC decreased from 7.3 to 5.7 mmol/L (22%, $P < .0001$)
  - LDL-C decreased from 5.3 to 3.9 mmol/L (26.2%, $P < .0001$)
- In patients with FCHL
  - TC decreased from 6.4 to 5.6 mM (13%, $P < .002$)
  - LDL-C decreased from 4.7 to 3.8 mM (19%, $P < .005$).
- There was no significant change in TG or HDL-C
- No adverse effects attributable to ezetimibe for as long as 3.5 years
- At a mean of 13.6 months (range, 1-44 months) after the initiation of ezetimibe, LDL-C levels remained decreased at 4.0 ± 0.6 mM

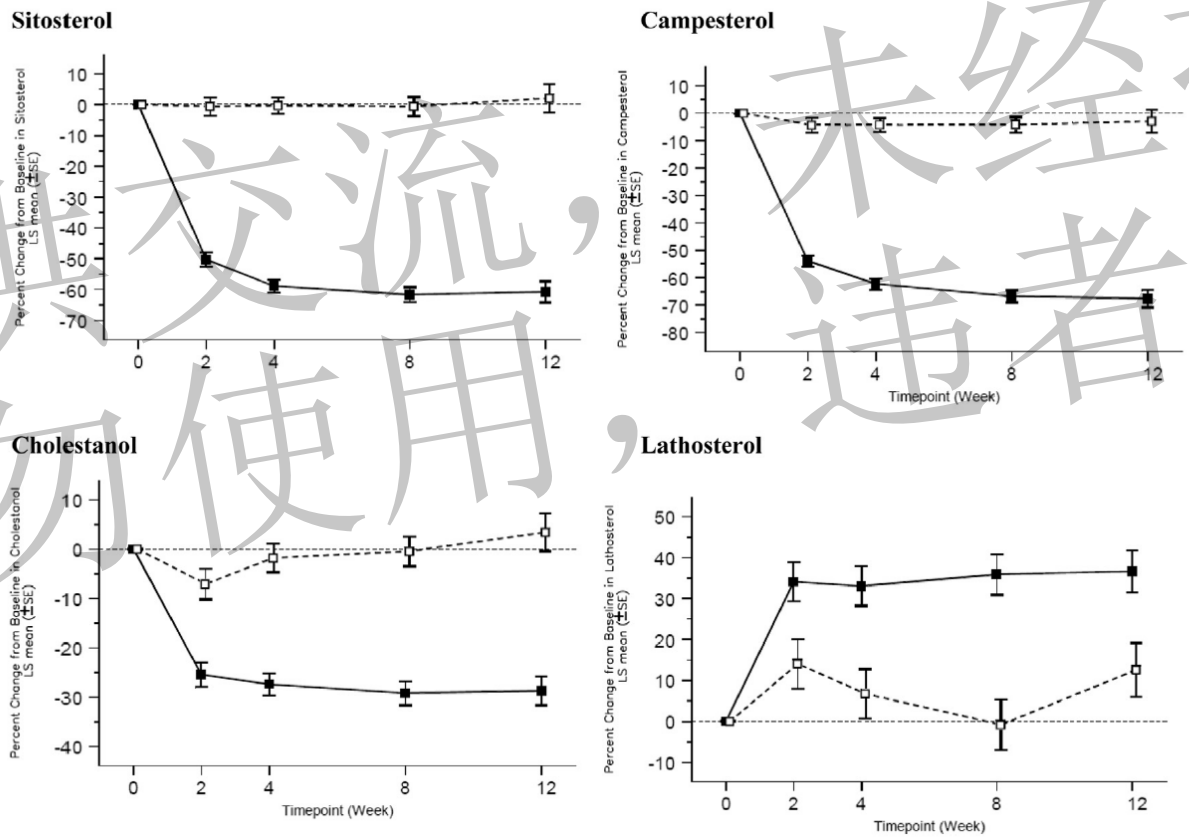
J Pediatr 2009;154:869-72

Efficacy and Safety of Ezetimibe Monotherapy in Children with Heterozygous Familial or Nonfamilial Hypercholesterolemia

- Mean age was 8.2 (SD1.7; range 6-11) years
- 57% were girls, 80% were white
- Mean baseline LDL-C was 228 mg/dL (5.9 mmol/L)
- 90% (84) had HeFH, 10% (9) had nonFH
- After 12 weeks, ezetimibe significantly reduced
  - LDL-C by 27% after adjustment for placebo ($P < .001$) and produced significant reductions in total cholesterol (21%),
  - Non-HDL cholesterol (26%),
  - Apolipoprotein B (20%) ($P < .001$ for all).
  - LDL-C lowering response in sex, race, baseline lipids, and HeFH/nonFH subgroups was generally consistent with overall study results.
- Ezetimibe was well tolerated, with a safety profile similar to studies in older children, adolescents, and adults.

J Pediatr 2015,166:1377-84

Efficacy and Safety of Ezetimibe Monotherapy in Children



Percent change from baseline sterol over time

J Pediatr 2015,166:1377-84

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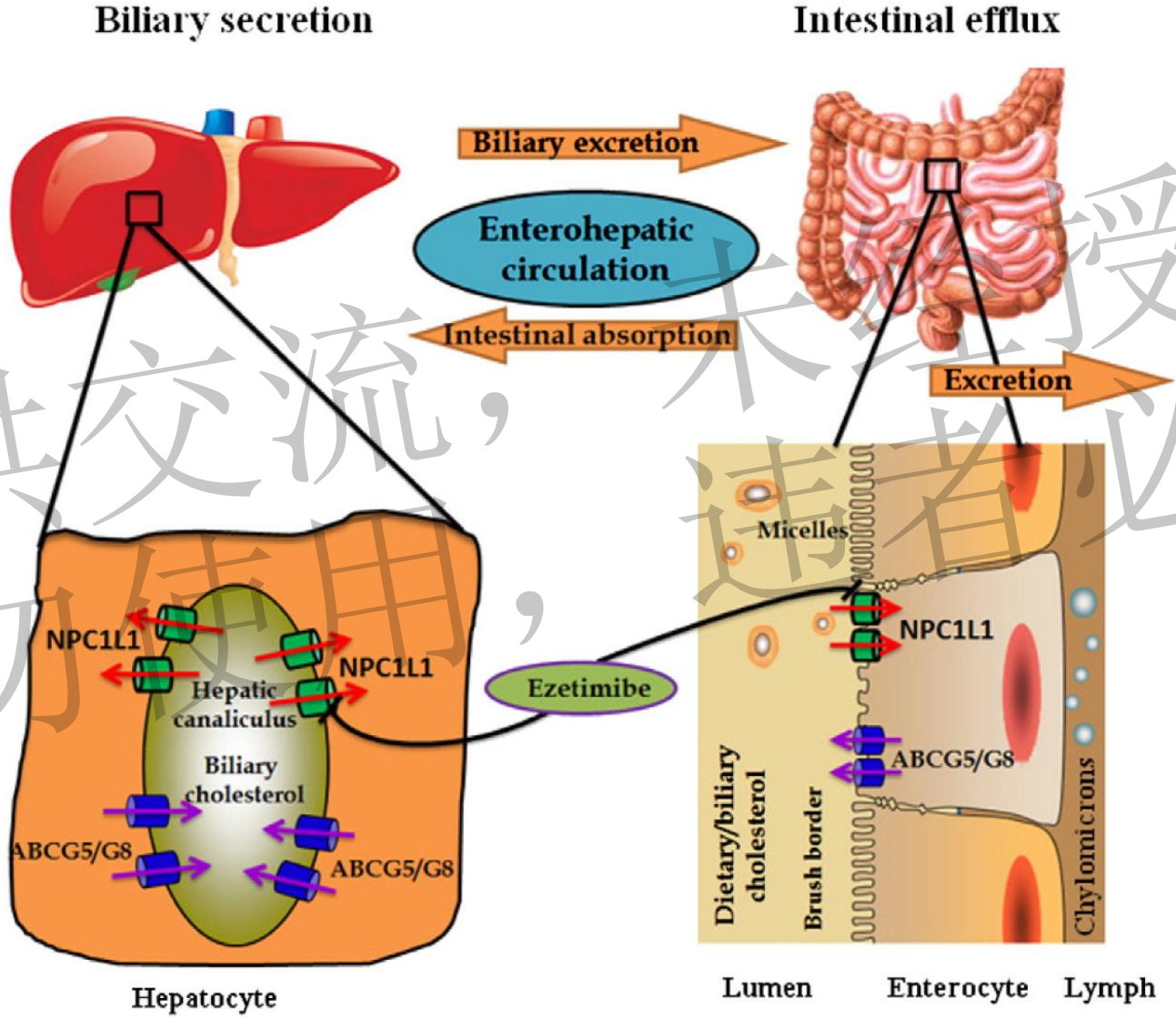


Recommendations for Use of HMG–CoA reductase Inhibitors (Statins) in Children and Adolescents

- Patient selection

1. Use algorithm and risk factor categories to select statin therapy for patients.
2. Include preferences of patient and family in decision making
3. In general, do not start treatment with statins before age 10 years (patients with high-risk family history, high-risk conditions, or multiple risk factors might be considered for medication initiation at age 10 years or younger.)
4. Precaution/contraindication with potentially interactive medications (cyclosporine, niacin, fibric acid derivatives, erythromycin, azole antifungals, nefazodone, many HIV protease inhibitors). **Check for potential interaction with all current medications at baseline**
5. Conduct baseline hepatic panel and creatine kinase (CK) before initiating treatment

Statins in Children and Adolescents
- Initiation and titration

1. Choice of particular statin is a matter of preference. Clinicians are encouraged to develop familiarity and experience with one of the statins, including dosage regimen and potential drug-drug interactions
2. Start with the lowest dose once daily, usually at bedtime. Atorvastatin and rosuvastatin can be taken in the morning or evening because of their long half-lives
3. Measure baseline CK, alanine aminotransferase (ALT), and aspartate aminotransferase (AST)

Statins in Children and Adolescents - Initiation and titration

4. Instruct the patient to report all potential adverse effects,
   - especially muscle cramps, weakness, asthenia, and
   - more diffuse symptoms suggestive of myopathy.
5. Advise female patients about concerns with pregnancy and the need for appropriate contraception
6. Advise about potential future medication interactions, especially cyclosporine, niacin, fibric acid derivatives, erythromycin, azole antifungals, nefazodone, and HIV protease inhibitors
   - **Check for potential interaction whenever any new medication is initiated**

Statins in Children and Adolescents - Initiation and titration

7. Whenever potential myopathy symptoms present, stop medication and assess CK; determine relation to recent physical activity
   - The threshold for worrisome level of CK is 10 times above the upper limit of reported normal, considering the impact of physical activity
   - Monitor the patient for resolution of myopathy symptoms and any associated increase in CK
   - Consideration can be given to restarting the medication once symptoms and laboratory abnormalities have resolved

Statins in Children and Adolescents - Initiation and titration

8. After 4 weeks, measure fasting lipid profile (FLP), ALT, and AST and compare with laboratory-specific reported normal values.
   - The threshold for worrisome levels of ALT or AST is ≥ 3 times the upper limit of reported normal
   - Target levels for LDL-C: Minimal < 3.4 mM; Ideal < 2.8mM
9. If target LDL-C levels are achieved and there are no potential myopathy symptoms or laboratory abnormalities, continue therapy and recheck FLP, ALT, and AST in 8 weeks and then 3 months
10. If laboratory abnormalities are noted or symptoms are reported, temporarily withhold the medication and repeat the blood work in 2 weeks. When abnormalities resolve, the medication may be restarted with close monitoring

Statins in Children and Adolescents - Initiation and titration

11. If target LDL-C levels are not achieved, increase the dose by one increment (usually 10 mg) and repeat the blood work in 4 weeks
    - If target LDL-C levels are still not achieved, dose may be further increased by one increment or another agent (bile acid sequestrant or cholesterol absorption inhibitor) may be added under the direction of a lipid specialist

Statins in Children and Adolescents - Maintenance monitoring

1. Monitor growth (height, weight, and BMI relative to normal growth charts), sexual maturation, and development.
2. Whenever potential myopathy symptoms present, stop medication and assess CK.
3. Monitor fasting lipoprotein profile, ALT, and AST every 3-4 months in the first year, every 6 months in the second year and beyond, and whenever clinically indicated.
4. Monitor and encourage compliance with lipid-lowering dietary and medication therapy. Serially assess and counsel for other risk factors, such as weight gain, smoking, and inactivity.
5. Counsel adolescent females about statin contraindications in pregnancy and the need for abstinence or use of appropriate contraceptive measures. Use of oral contraceptives is not contraindicated if medically appropriate. Seek referral to an adolescent medicine or gynecologic specialist as appropriate.

Statins Linked to Raised Risk of Type 2 Diabetes

- Statin therapy is associated with a slightly increased risk of development of diabetes, but the risk is low both in absolute terms and when compared with the reduction in coronary events
- Clinical practice in patients with moderate or high cardiovascular risk or existing cardiovascular disease should not change
- Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion

Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials

- 13 statin trials with 91,140 participants,
  - 4278 (2226 assigned statins and 2052 assigned control treatment) developed diabetes during a mean of 4 years
- Statin therapy was associated with
  - a 9% increased risk for incident diabetes (odds ratio [OR] 1.09; 95% CI 1·02–1·17)
- Risk of development of diabetes with statins
  - highest in trials with older participants
  - not related to BMI or LDL-C
- Treatment of 255 (95% CI 150–852) patients with statins for 4 years resulted in one extra case of diabetes.

Lancet 2010; 375: 735–42

Statins and risk for new-onset DM - A real-world cohort study using a clinical research database

Incidence of NODM according to statin exposure.

Drug	Incidence, per 1000 PY	Study population, PY
Atorvastatin	4.196	8342
Fluvastatin	4.176	718
Pitavastatin	1.321	757
Pravastatin	4.716	3181
Rosuvastatin	4.770	2935
Simvastatin	6.131	2773
Statin-exposed	6.000	13,669
Matched nonexposed	3.244	55,183

NODM = new-onset diabetes mellitus, PY = patient-years.

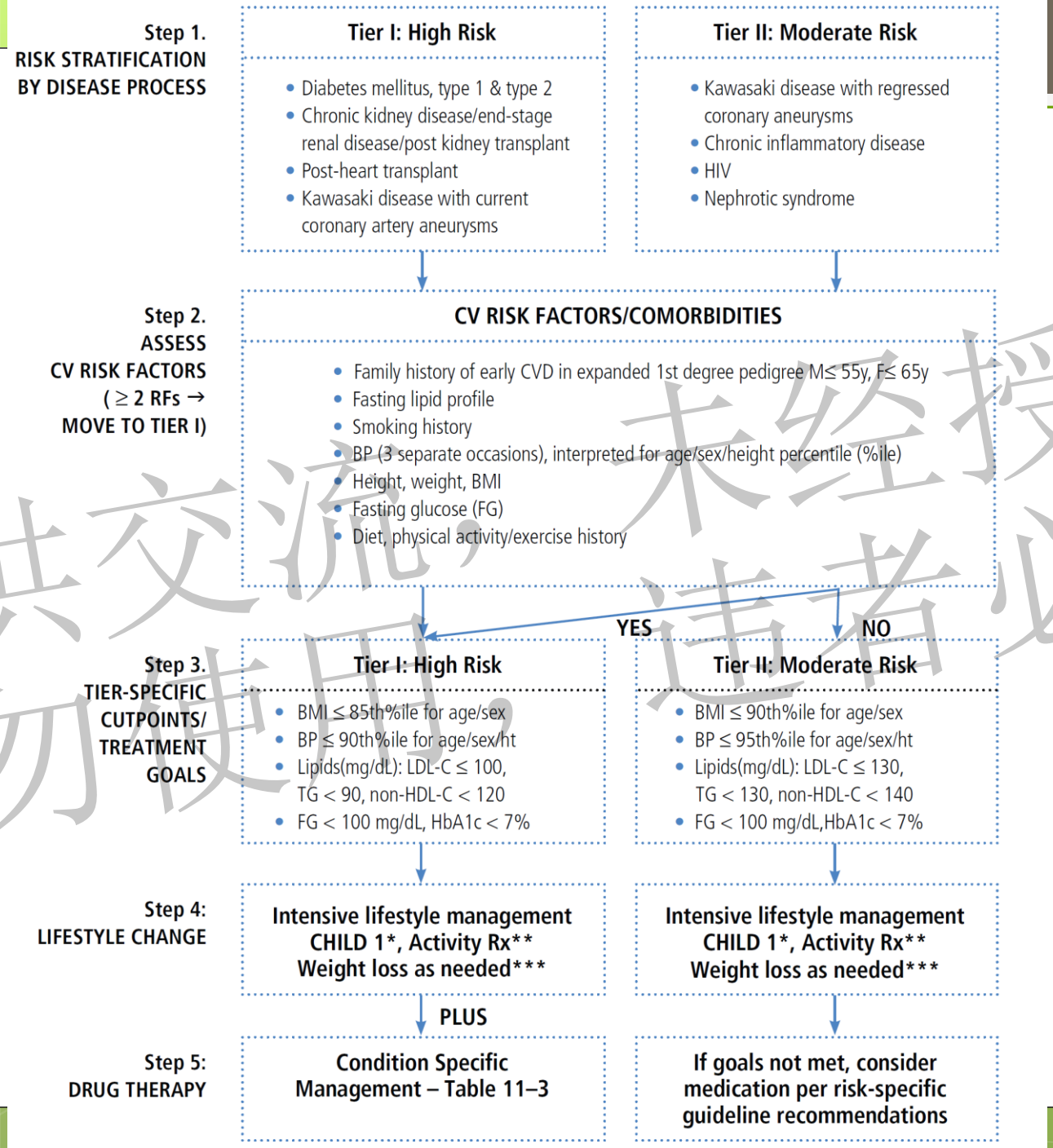
Korean study

Medicine 2016, 95:46

Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: a 6 year follow-up study of the METSIM cohort

- Participants on statin treatment (N=2,142) had a 46% increased risk of type 2 diabetes (adj HR 1.46)
- The risk was dose dependent for simvastatin and atorvastatin
- Statin treatment significantly increased 2 h glucose (2hPG) and glucose AUC of an OGTT at follow-up, with a nominally significant increase in fasting plasma glucose (FPG)
- Insulin sensitivity was decreased by 24% and insulin secretion by 12% in individuals on statin treatment (at FPG and 2hPG <5.0 mmol/l) compared with individuals without statin treatment ($p<0.01$).
- Decreases in insulin sensitivity and insulin secretion were dose dependent for simvastatin and atorvastatin

Diabetologia 2015, 58:1109–1117



Take the management of a child with diabetes mellitus through this journey

Step 1: Tier I

Step 2: Assess all cardiovascular risk factors

Step 3: Define the tier-specific treatment goals/cutpoints

Step 4: Initiate therapeutic lifestyle change

PLUS

Step 5: Condition specific management including medication for the corresponding risk factor

Condition specific management – diabetes mellitus

- For T1DM, intensive glucose management per endocrinologist with frequent glucose monitoring/insulin titration to maintain optimal plasma glucose and HbA1c for age
- For T2DM, intensive weight management and glucose control, in consultation with an endocrinologist as needed to maintain optimal plasma glucose and HbA1c for age
- Assess body mass index (BMI), fasting lipids: Step 4 lifestyle management of weight, lipids for 6 months
- If LDL goals not achieved, consider statin therapy if age ≥10 years to achieve Tier I treatment goals for LDL-C
- Initial BP ≥ 90th%ile: Step 4 lifestyle management plus no added salt, increased activity for 6 months
- If BP consistently ≥95th%ile for age/sex/height: initiate angiotensin-converting enzyme inhibitor therapy with BP goal < 90th%ile for sex/height, or < 120/80, whichever is lower

Take the management of a child with chronic inflammatory disease through this journey

Step 1: Risk stratification: Moderate risk = Tier II

Step 2: Assess all cardiovascular risk factors –

- If there are ≥ 2 comorbidities, move to Tier I for subsequent management
- If not, stay on tier II

Step 3: Tier-specific treatment goals/cutpoints defined

Step 4: Initial therapy:

- For Tier I, initial management is therapeutic lifestyle change **PLUS** **Step 5:** disease-specific management
- For Tier II, initial management is therapeutic lifestyle change.

Step 5: For Tier II, if goals are not met, consider medication per risk factor specific recommendations in these guidelines