

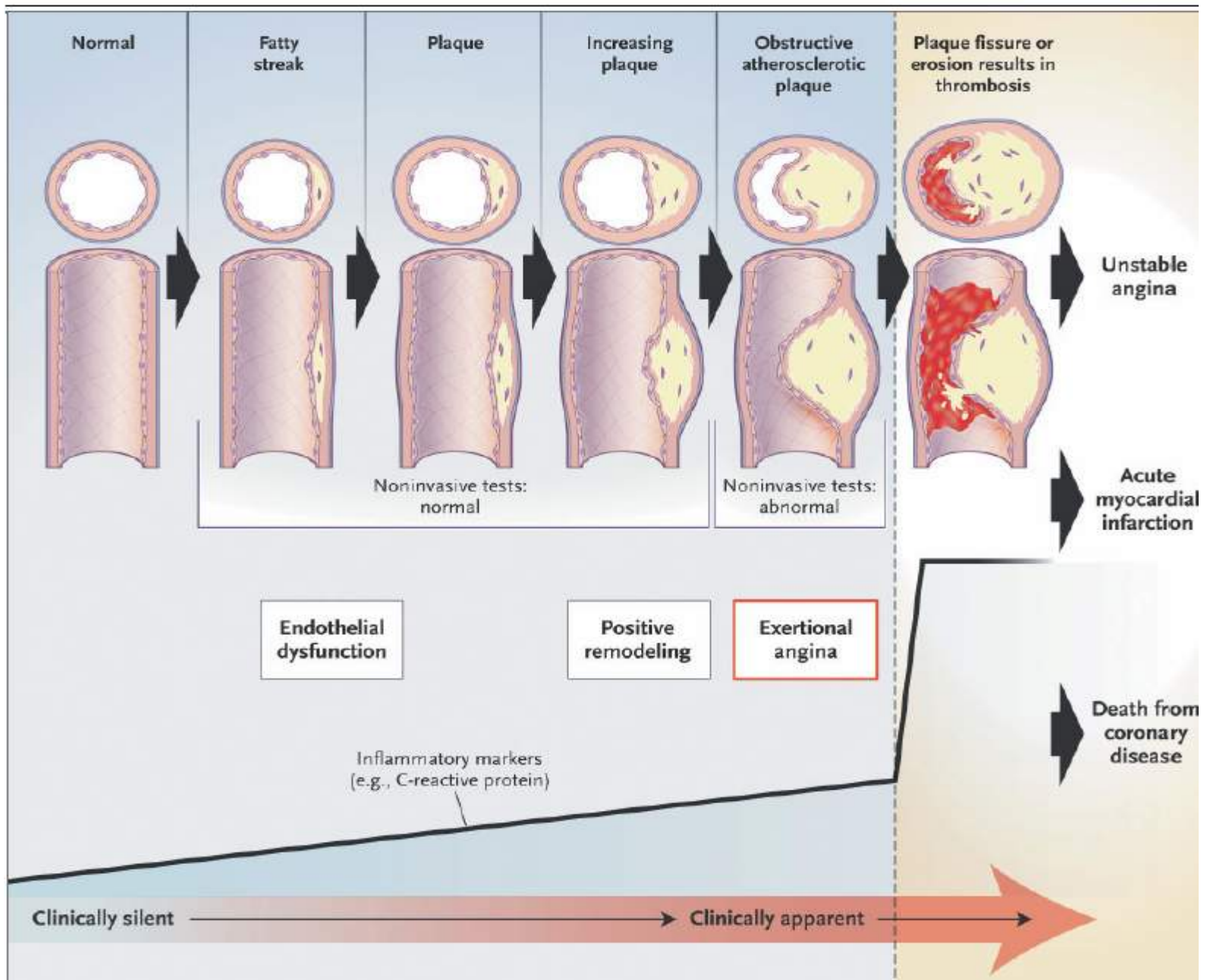
# היפרכולסטרולמיה בילדים

פרופ' רענן שמיר, המכון לגסטרואנטרולוגיה,  
תזונה, ומחלות כבד, מרכז שניידר לרפואת  
ילדים

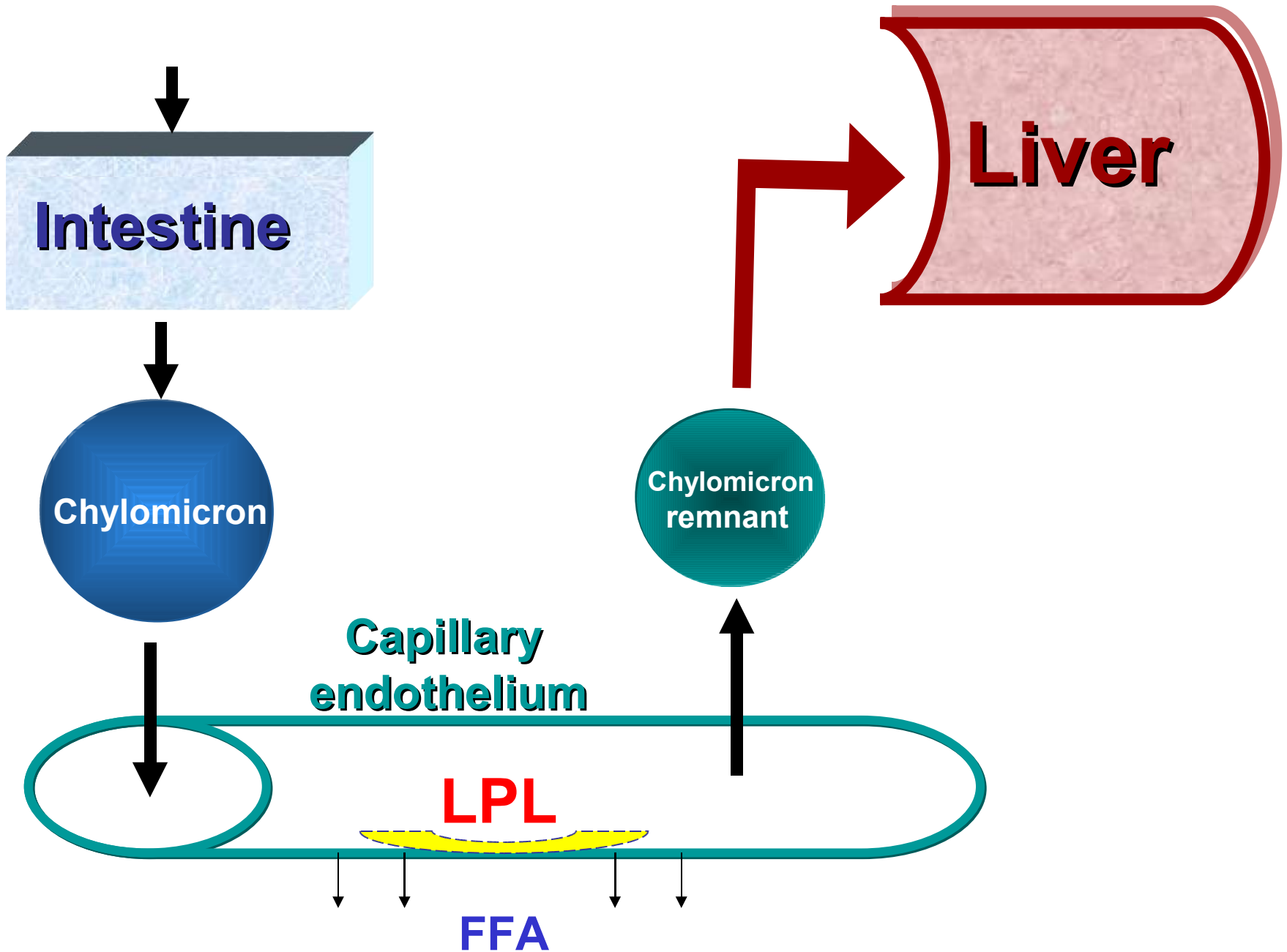
כנס מחוז הצפון

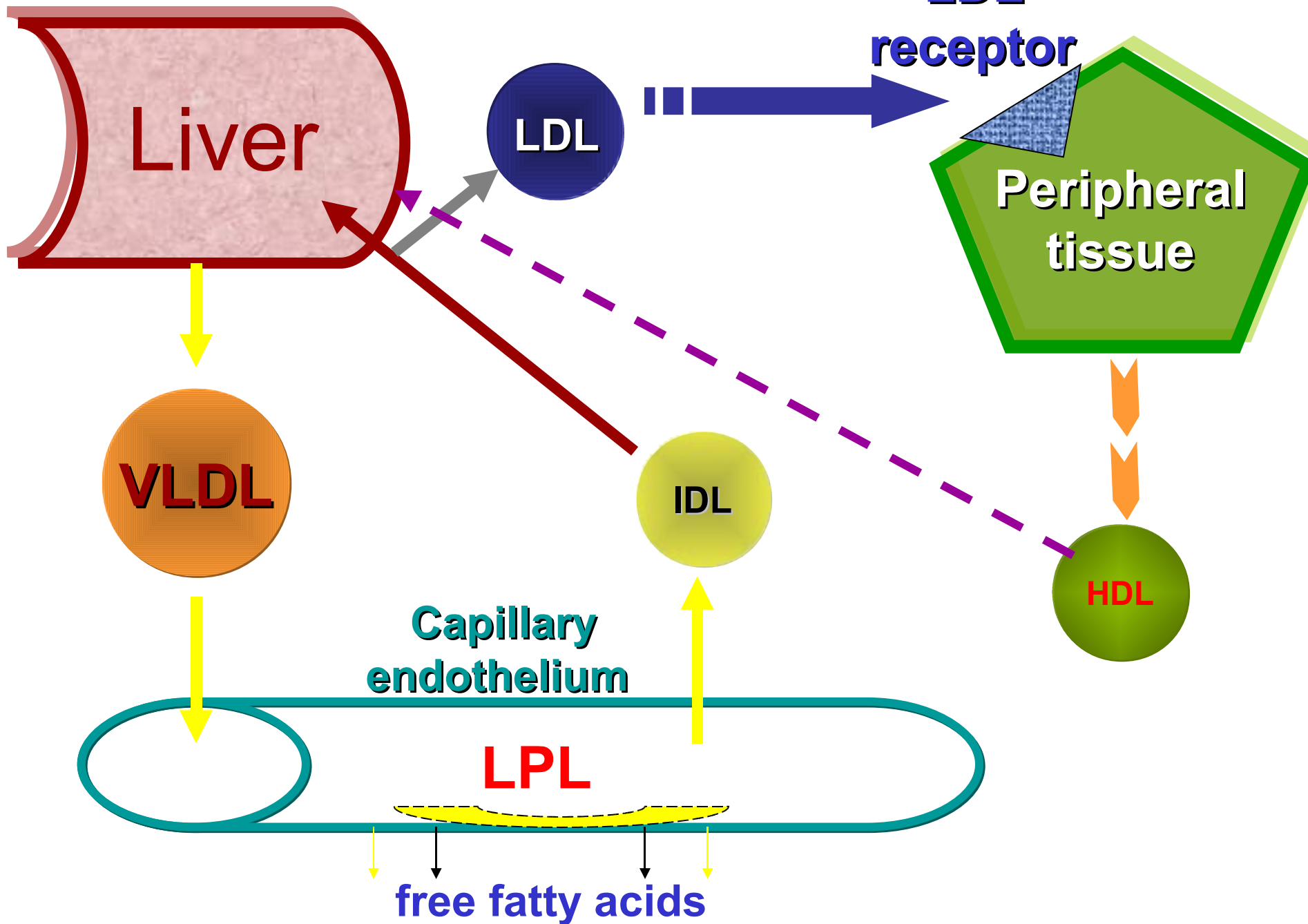
לזכרו של ד"ר חנוך האגר ז"ל

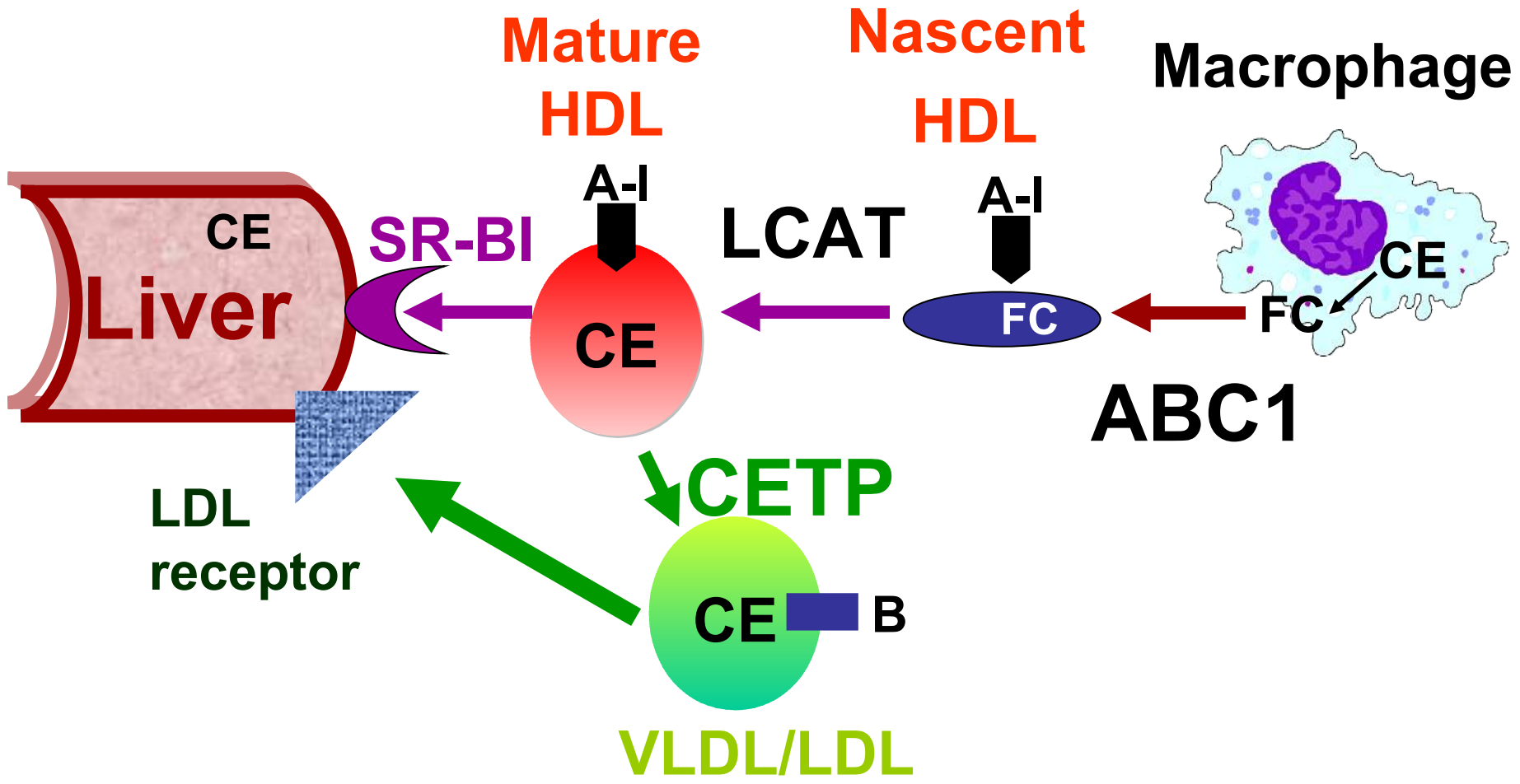
טבריה, 19 למרץ 2008



*From Abrams J. N Engl J Med 2005*





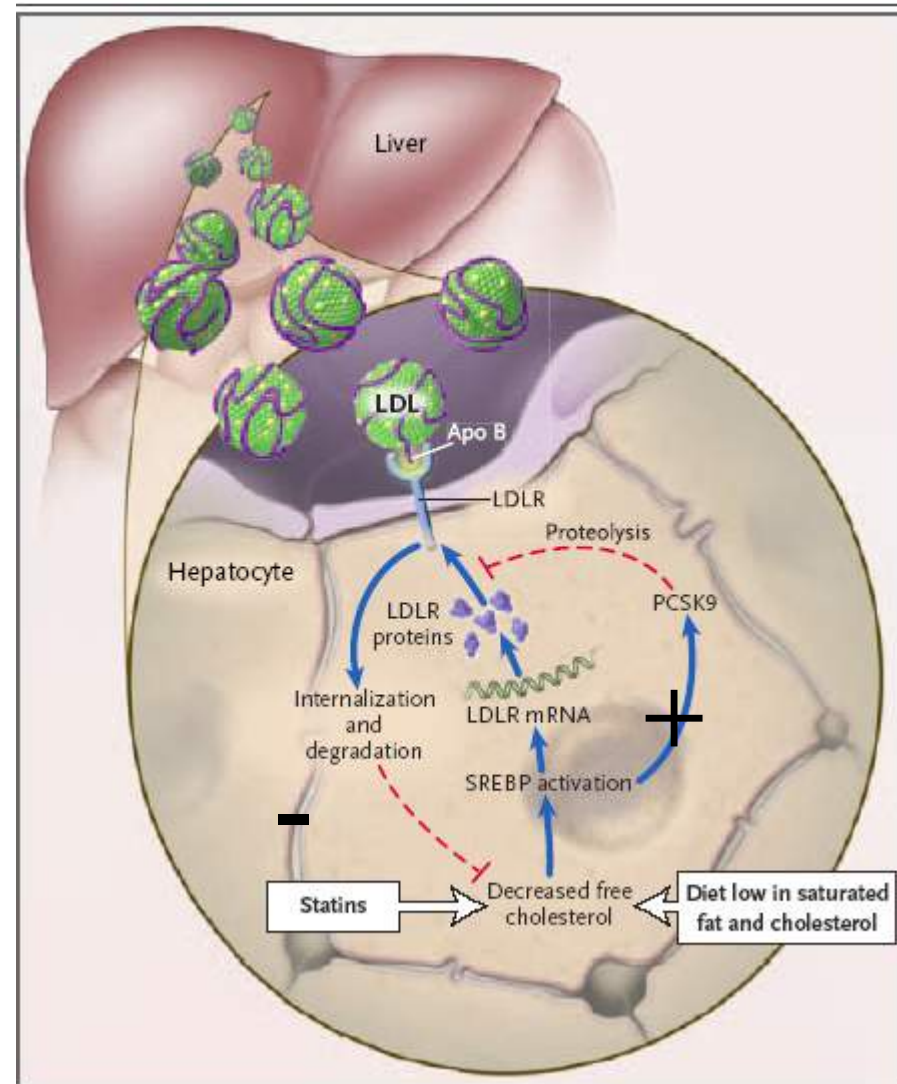


# Monogenic disorders resulting in high LDL-C levels

- **FH**
  - Marks D, et al. *Atherosclerosis* 2003;168:1-14
- **FCHL**
  - Cortner J, et al. *J Pediatr* 1990;116:514-19
- **Familial ligand-defective apoB100**
  - Viola S, et al. *JPGN* 2001;33:122-6
- **NARC-1 (PCSK9) mutations**
  - Cohen JC, et al. *N Engl J Med* 2006;354:1264-72
- **ARH (autosomal recessive hyperchol.)**
  - Garcia CK, et al. *Science* 2001;292:1310-2

# NARC-1 (PCSK9) mutations

- ✓ PCSK9 is a protease that regulates levels of LDL receptors.
- ✓ Mutations that increase its activity will result in reduced LDLR and increased LDL-C serum levels



*From Tall AR, N Engl J Med 2006;354:1310-2*

## Remnant (apo E2) hyperlipidemia



## Homozygous FH



# Pathological evidence relating atherosclerosis and childhood hyperlipidemia

- Korean War

*Enos WF, et al. JAMA 1953;152:1090-3*

- PDAY study

*JAMA 1990;264:3018-24*

*Circulation. 2000;102:374-379*

- Bogalusa Cohort

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

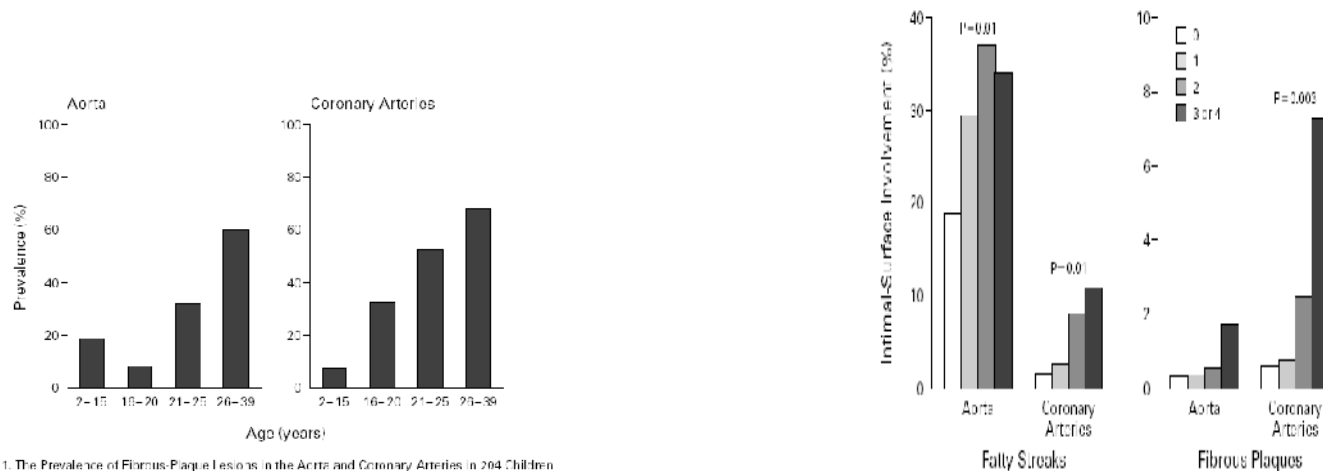


Figure 1. The Prevalence of Fibrous Plaque Lesions in the Aorta and Coronary Arteries in 204 Children and Young Adults, According to Age. There is a consistent trend toward a greater prevalence of coronary-artery lesions with increasing age ( $P=0.001$ ).

# שאלה 1

עדויות שהתהליך הטרשתי מתחיל בגיל הילדות  
כוללות:

עדויות קליניות

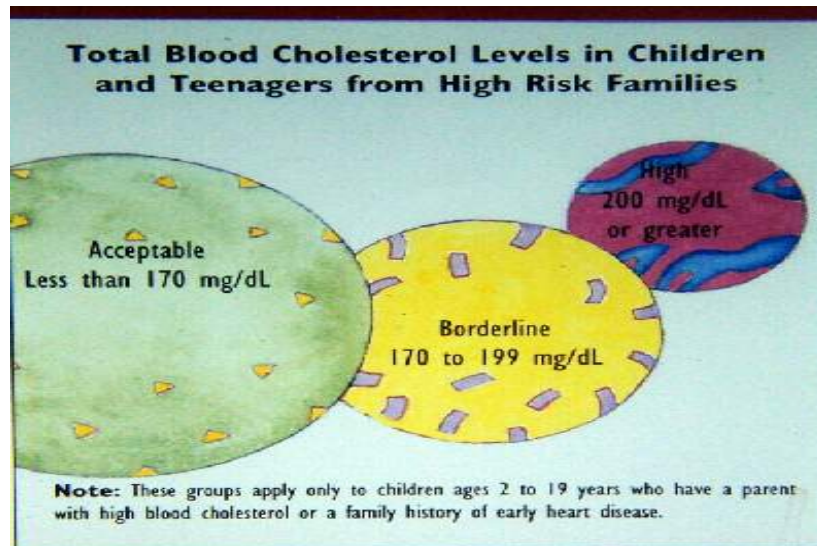
עדויות אפידמיולוגיות

עדויות פתולוגיות

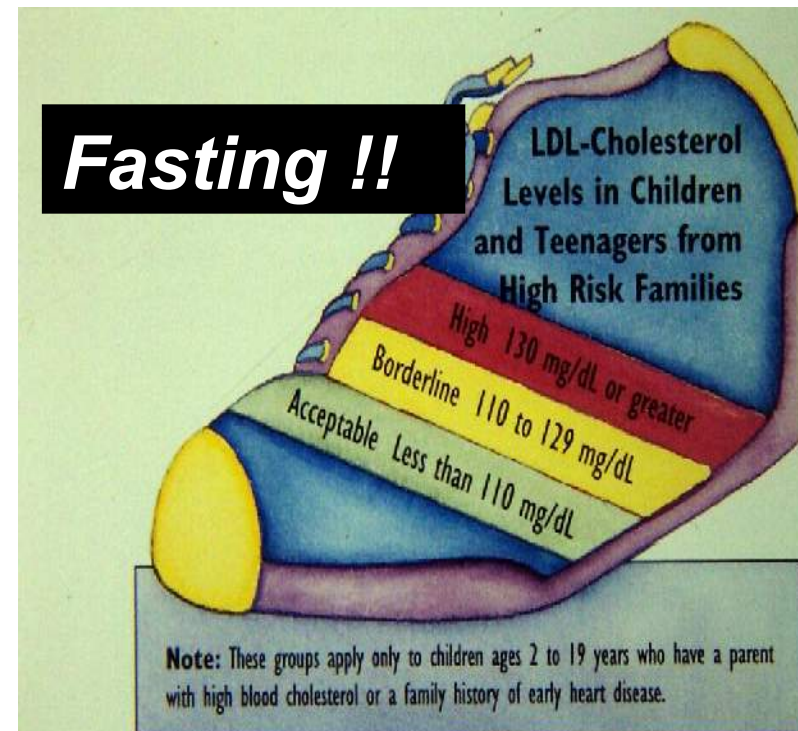
כל התשובות הנכונות

# ?What is elevated cholesterol

- NCEP guidelines are based on cholesterol distribution among American children in the Lipid Research Clinics Prevalence study
- 75<sup>th</sup> percentile was set as borderline and 95<sup>th</sup> percentile as high



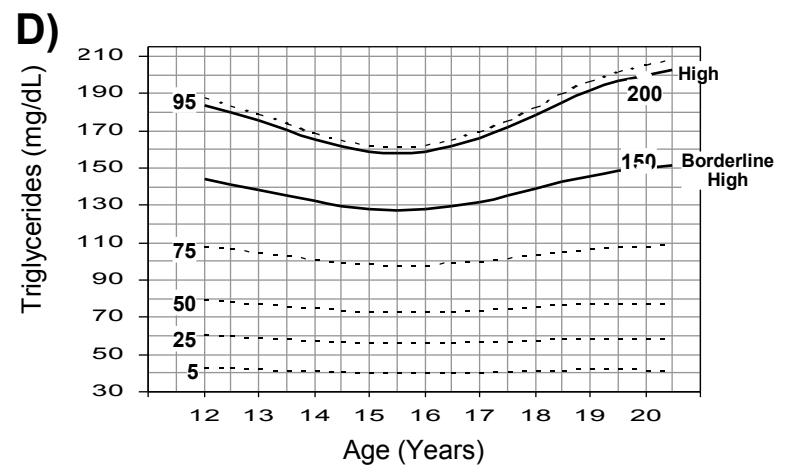
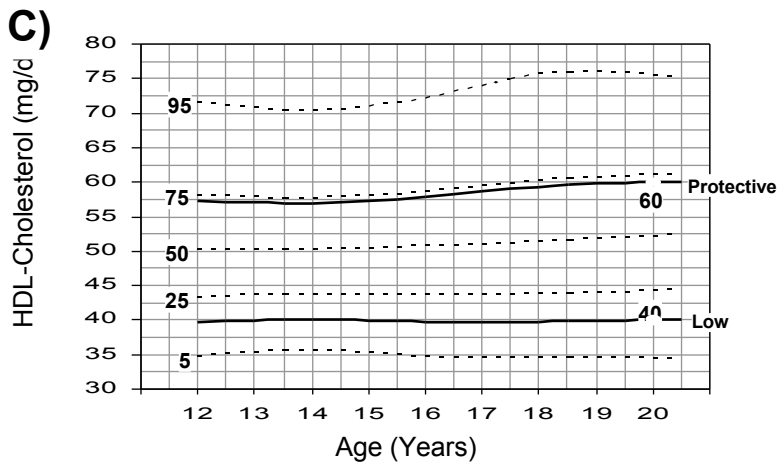
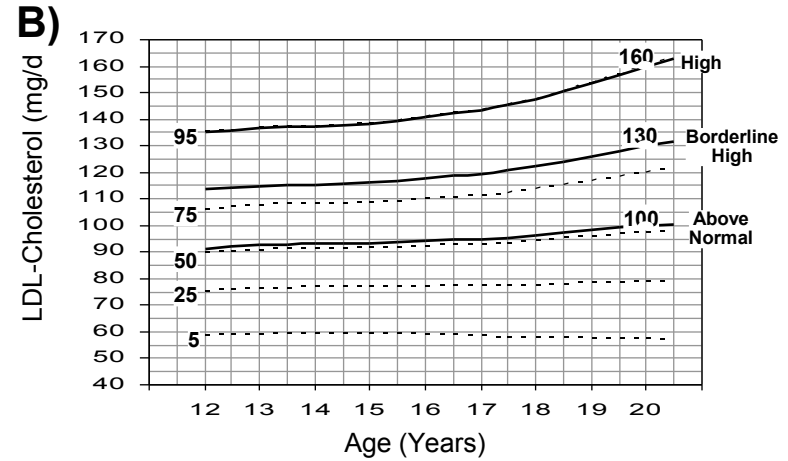
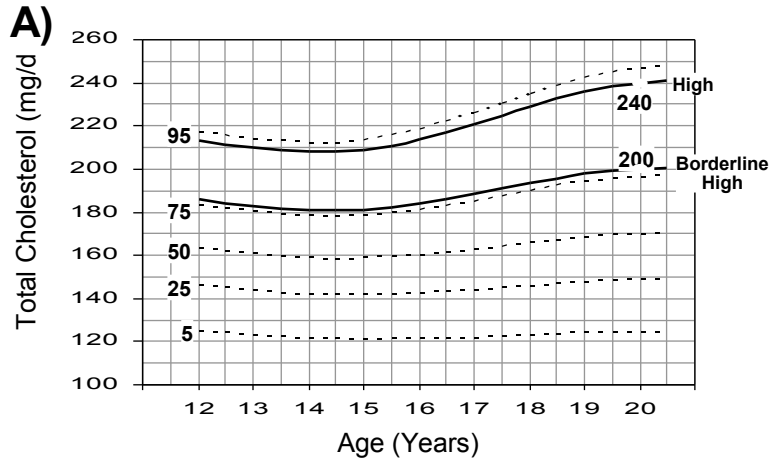
**X 2 measurements !!**



# Distribution of Lipoproteins by Age and Gender in Adolescents

Courtney J. Jolliffe, MSc; Ian Janssen, PhD

**Circulation 2006;114:1056-62**



**Females 12-20 years**

# Practical approach to screening, evaluation and follow up for hyperlipidemia

## Screening for childhood hypercholesterolemia

- current pediatric recommendations are to selectively screen children older than two years of age with:
  - ✓ a positive family history of hypercholesterolemia and/or early CHD
  - ✓ Presence of other conditions commonly associated with increased risk of CHD, such as smoking, diabetes, obesity and hypertension are also reasons for checking cholesterol levels.

# Recommendations for populations at risk

*Circulation, November 2006*

## *Disease stratification by risk*

	Risk Category	Rationale	Disease Process/Condition
Tier I	High risk	Manifest CAD <30 years of age: Clinical evidence	Homozygous familial hypercholesterolemia (FH) Diabetes mellitus, type 1 Chronic kidney disease (CKD)/end-stage renal disease (ESRD) Post-orthostatic heart transplantation (OHT) Kawasaki disease with current coronary aneurysms
Tier II	Moderate risk	Accelerated atherosclerosis: Pathophysiological evidence	Heterozygous FH Kawasaki disease with regressed coronary aneurysms Diabetes mellitus, type 2 Chronic inflammatory disease
Tier III	At risk	High-risk setting for accelerated atherosclerosis: Epidemiological evidence	Post-cancer-treatment survivors Congenital heart disease Kawasaki disease without detected coronary involvement

# שאלה מספר 2

סריקה (סקרינינג) לכולסטרול בדם צריכה להיעשות:

בילדים מעל גיל שנתיים עם סיפור משפחתי של PCAD

רק במבוגרים מעל גיל 25 עם סיפור משפחתי של  
PCAD

בילדים עם סיפור משפחתי של PCAD, בשנת החיים  
הראשונה

בכל הילדים לפני גיל ביה"ס

# Treatment of hypercholesterolemia

- Dietary therapy is the primary approach to treating children and adolescents with elevated blood cholesterol

ESPGHAN recommendations (JPGN 1994)

NCEP guidelines (Pediatrics 1992)

## Current AHA guidelines for primary prevention of atherosclerotic CVD beginning in childhood.

**Circulation 2005;112:2061-75**

- After 2 years of age, limit foods high in saturated fat (< 10% of calories), cholesterol (<300 mg/day), and trans fatty acids
- *However, emphasis different from the past Step I and II diet include:*
  - Allowance of a more liberal intake of unsaturated fat and focus on ensuring adequate intake of w-3 fatty acids.
  - Participation in regular moderate to vigorous physical activity most days of the week for at least 1 hour/day
  - Limit video screen time to < 2 hours/day

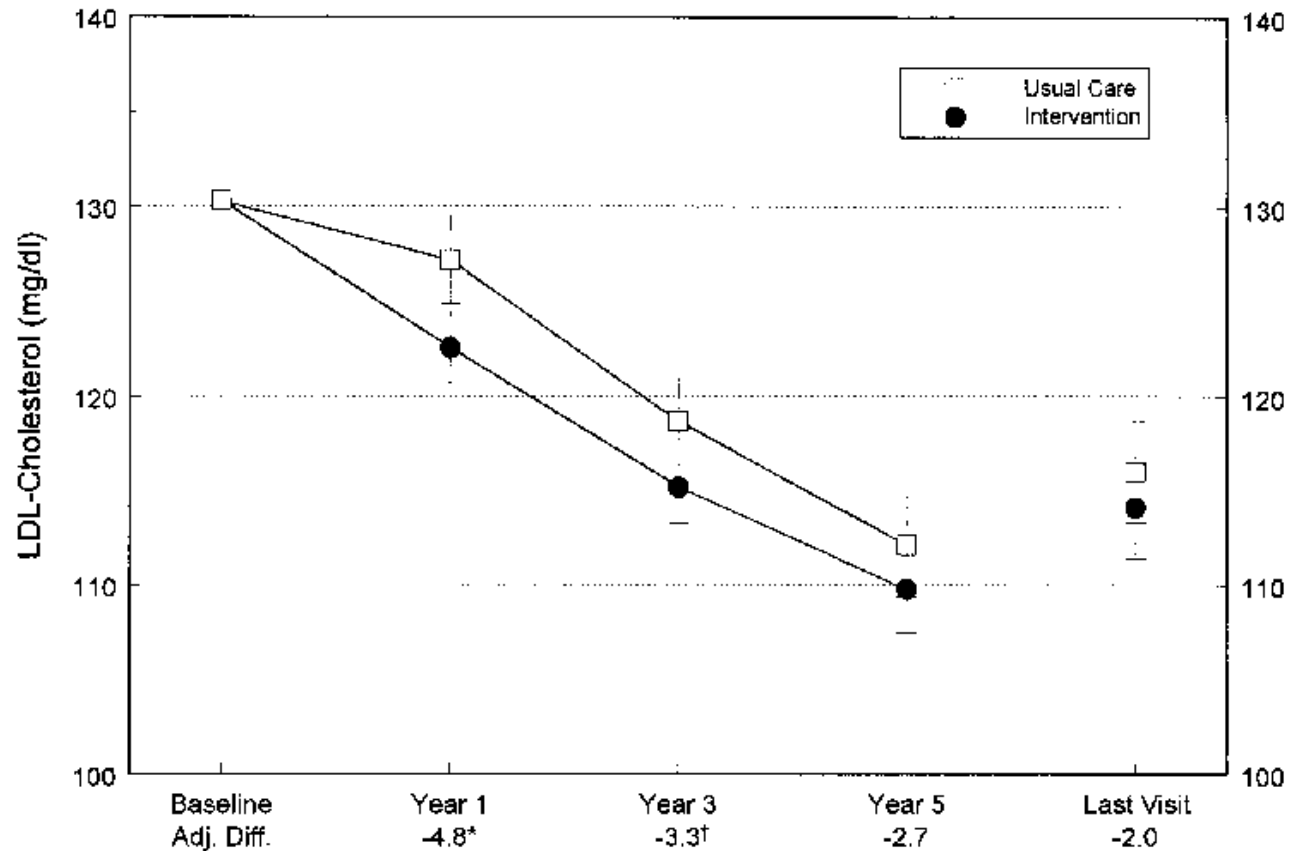
# DISC STUDY

JAMA 1995;273:1429-35

Pediatrics 1997;100:51-9

Pediatrics 2001;107:256-64

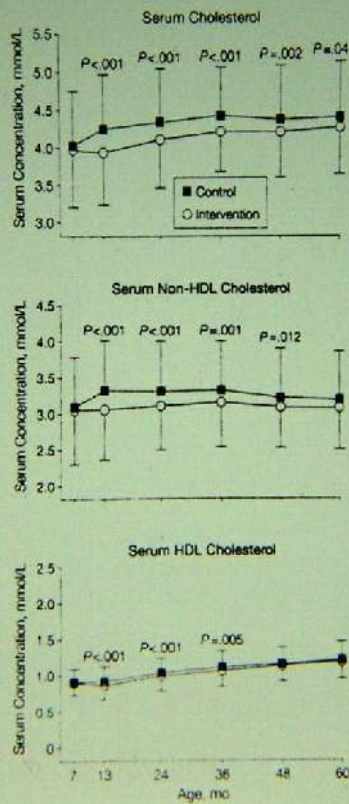
## Lipoproteins



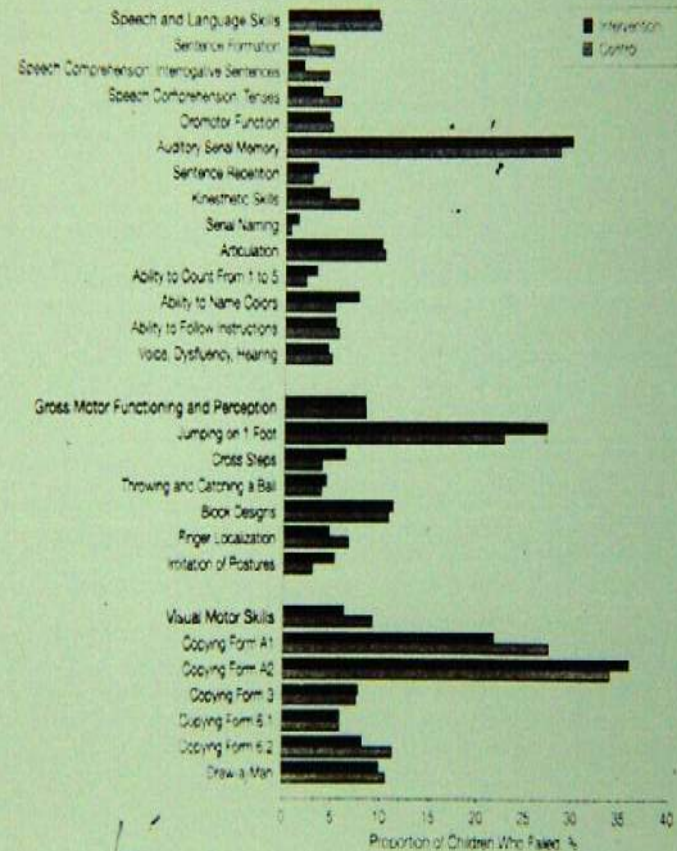
# STRIP Study

*JAMA 2000;284:993-1000*

**Figure 2.** Mean Serum Cholesterol, Non-HDL Cholesterol and HDL Cholesterol Concentrations of Children in the Intervention and Control Groups

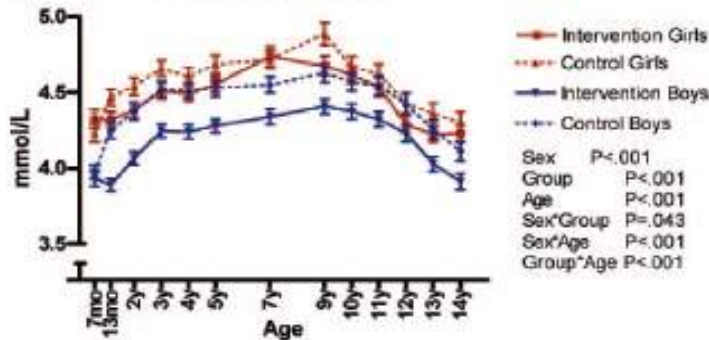


**Figure 3.** Results of Neurodevelopmental Tests of Children in the Intervention and Control Groups at Age 5 Years

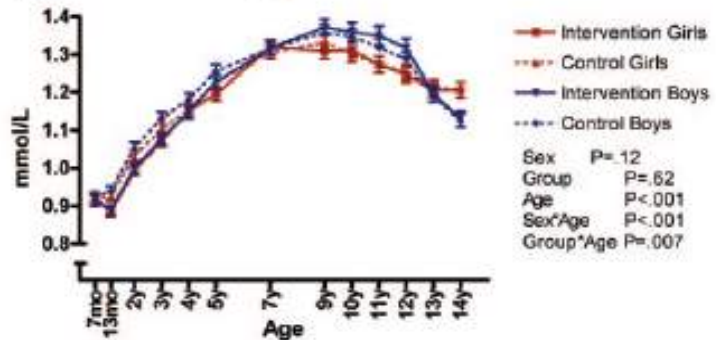


# Niinikoski H, et al. *Circulation* 2007 (14 years of dietary counseling in the STRIP study)

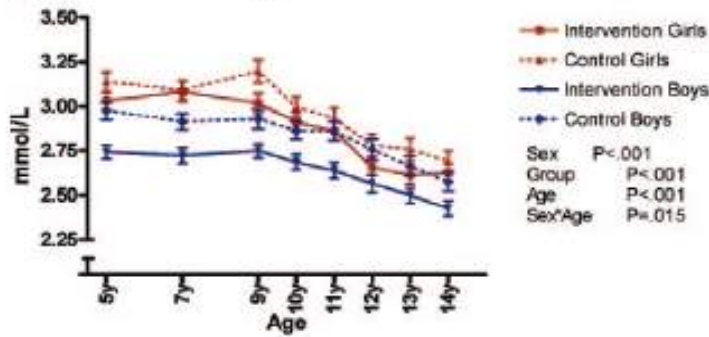
**A Serum Cholesterol**



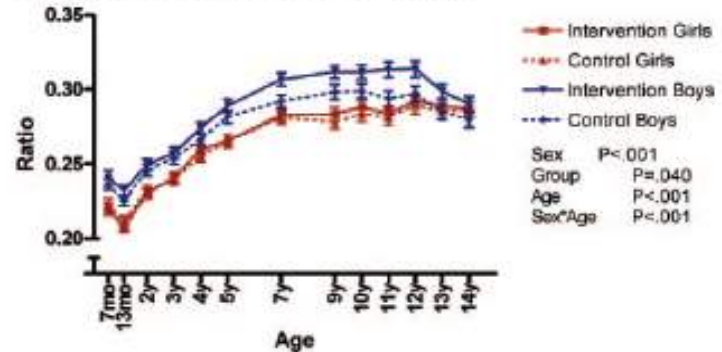
**B HDL**



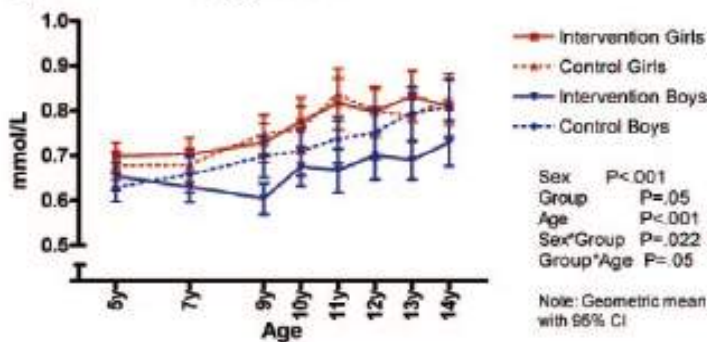
**C LDL**



**D HDL to Serum Cholesterol Ratio**



**E Triglycerides**



# שאלה מספר 3

טיפול תזונתי בהיפרכולסטרולמיה כולל:

1. דיאטה דלה בשומנים בלתי רוויים
2. דיאטה עשירה בשומנים מוקשים
3. דיאטה דלת חלבון
4. דיאטה דלה בשומנים רוויים

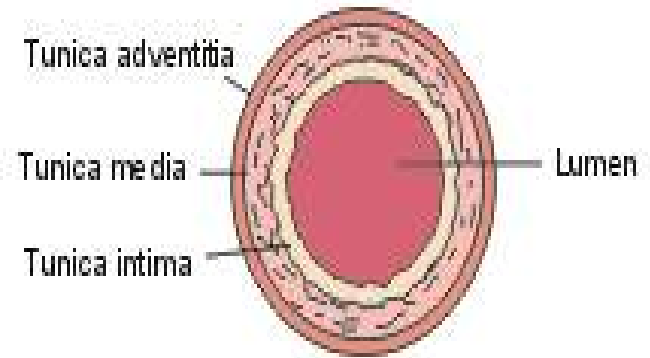
# Evaluation of hyperlipidemia

## Lipid clinic

- Comprehensive family pedigree and risk factors' assessment
- Lipoprotein profile of all immediate family members
- Blood chemistry and thyroid function
- Three day diet record
- Nutritional evaluation
- Base line non-invasive assessment of vascular changes

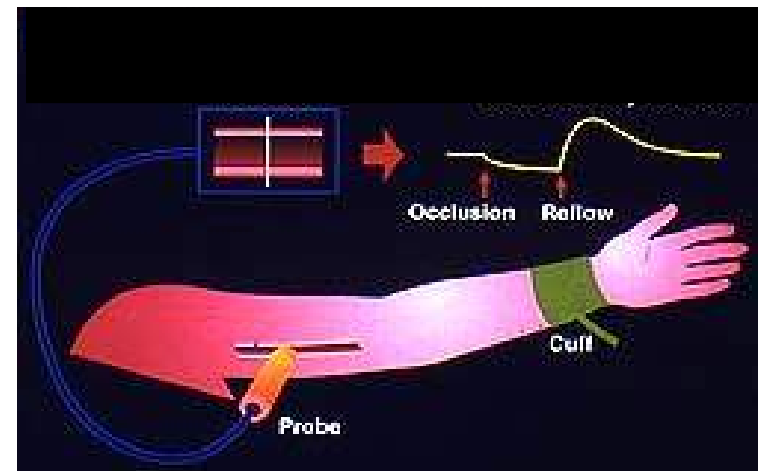
# Base line non-invasive assessment of vascular changes

Pediatrics 2006;118:1683-91



- FMD

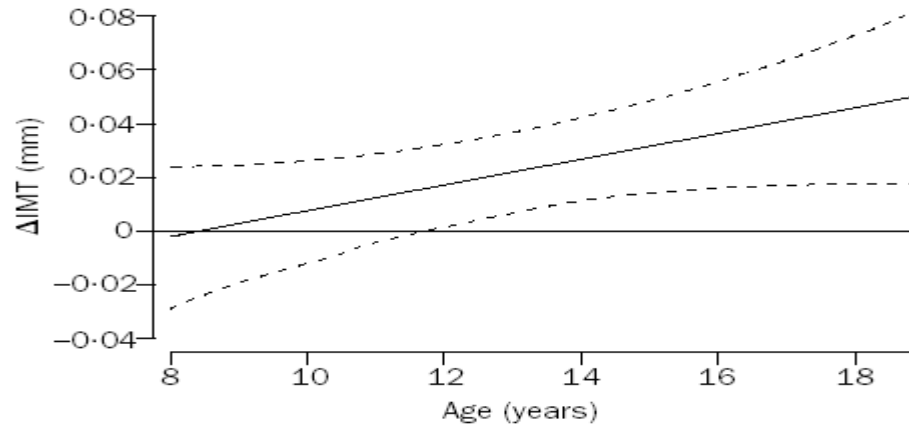
- Arterial distensibility



## Arterial intima-media thickness in children heterozygous for familial hypercholesterolaemia

Albert Wiegman, Eric de Groot, Barbara A Hutten, Jessica Rodenburg, Johan Gort, Henk D Bakker, Eric J G Sijbrands, John J P Kastelein

Lancet 2004; 363: 369-70  
See Commentary page 342

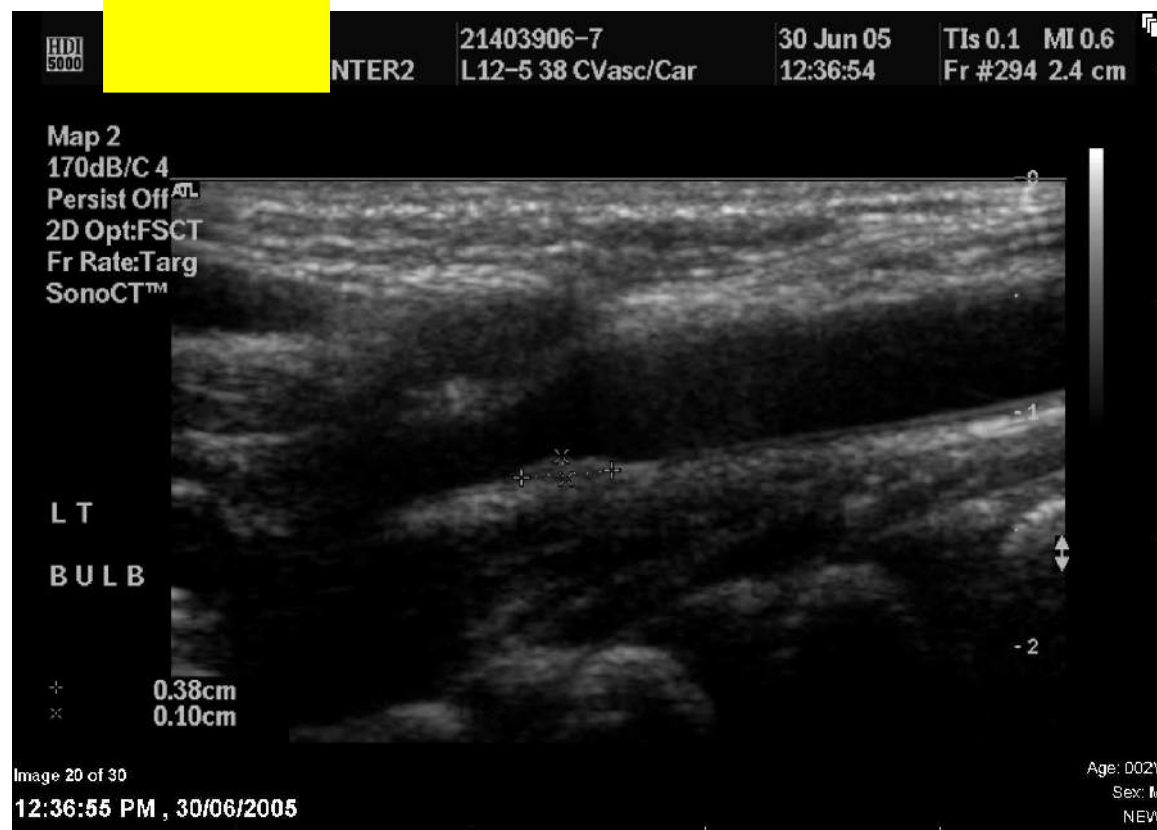


**Difference in mean carotid intima-media thickness (IMT) and 95% CI between children with familial hypercholesterolaemia and unaffected siblings (n=281) plotted against age, taking account of family relations**

Mean=thick line. 95% CI=dashed lines.

- Multivariate analysis showed LDL cholesterol, age, and sex to be strong and independent predictors of IMT

# CIMT in homozygous FH



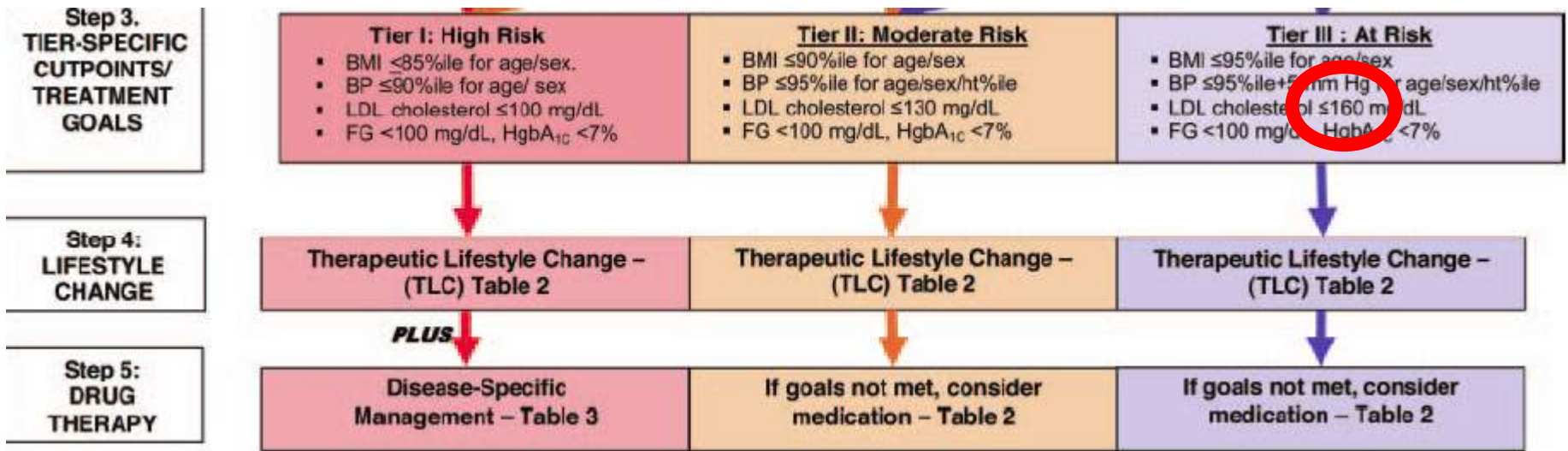
# Treatment of hyperlipidemia

## Lipid clinic

- Dietary manipulation
- Exercise
- Achieve ideal body weight
  - Monitor growth
  - Observe for excessive restrictions
- Eliminate other risk factors
- Six month trial period

# High risk pediatric populations: risk stratification and treatment

*Circulation, November 2006*



# Drug Therapy

- **Bile acid sequestrants**  
(Cholestyramine and colestipol)
- **Statins**  
(Simvastatin, pravastatin, atorvastatin, Rosuvastatin)
- **Ezetimibe**

# Simovil treatment in children with FH

de Jongh S, et al. Efficacy and safety of statin therapy in children with FH. *Circulation* ;2002;106:2231-7

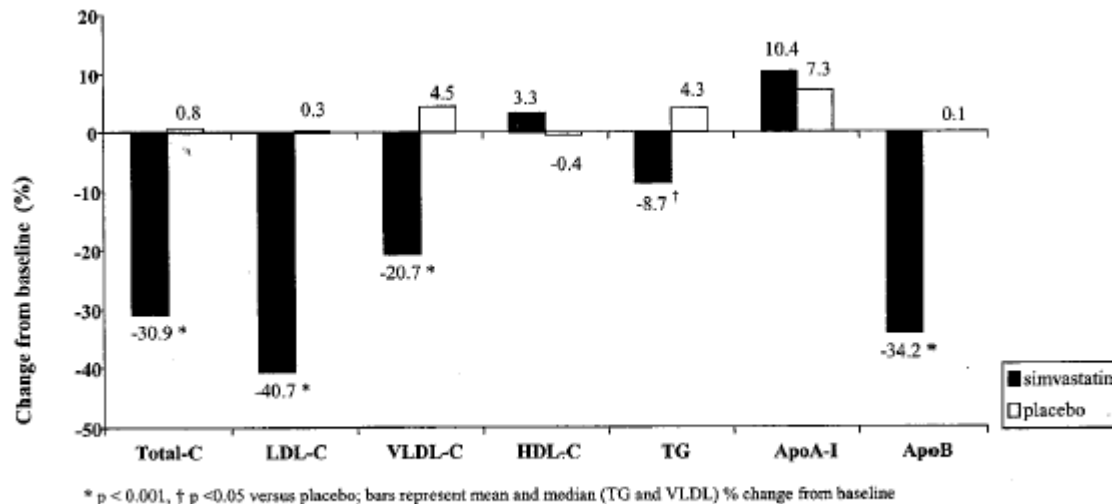
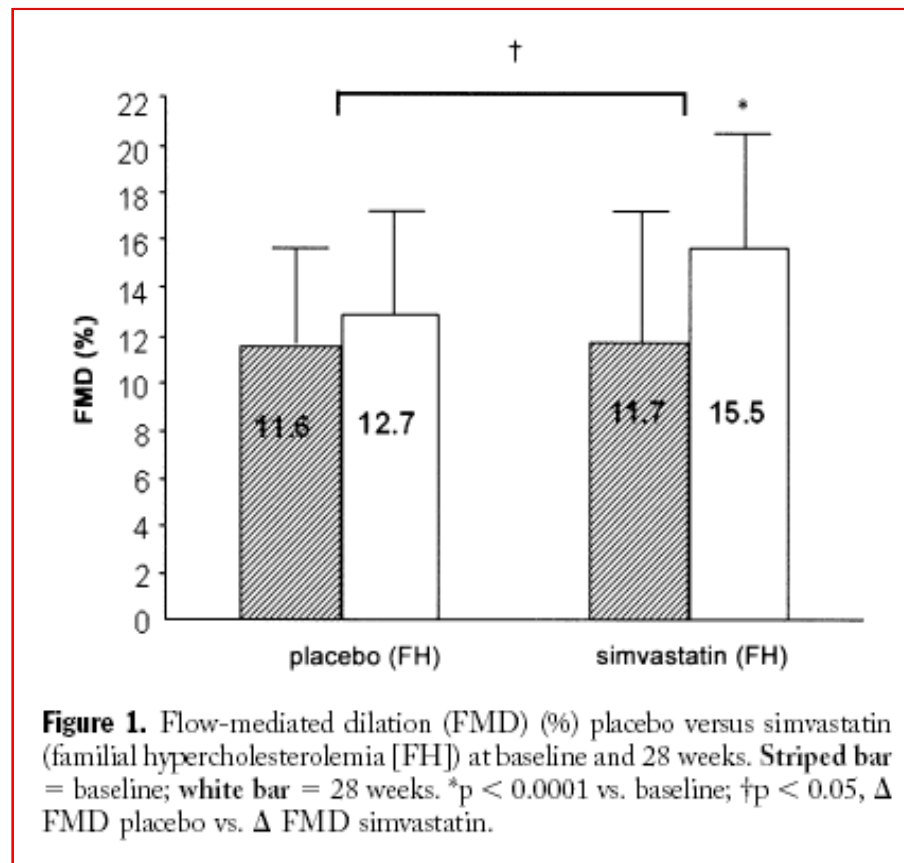


Figure 2. Effect of 48 weeks of simvastatin (40 mg) or placebo therapy on lipids and lipoproteins of heFH children.

# de Jongh S, et al. Early statin therapy restores endothelial function in children with familial hypercholesterolemia.

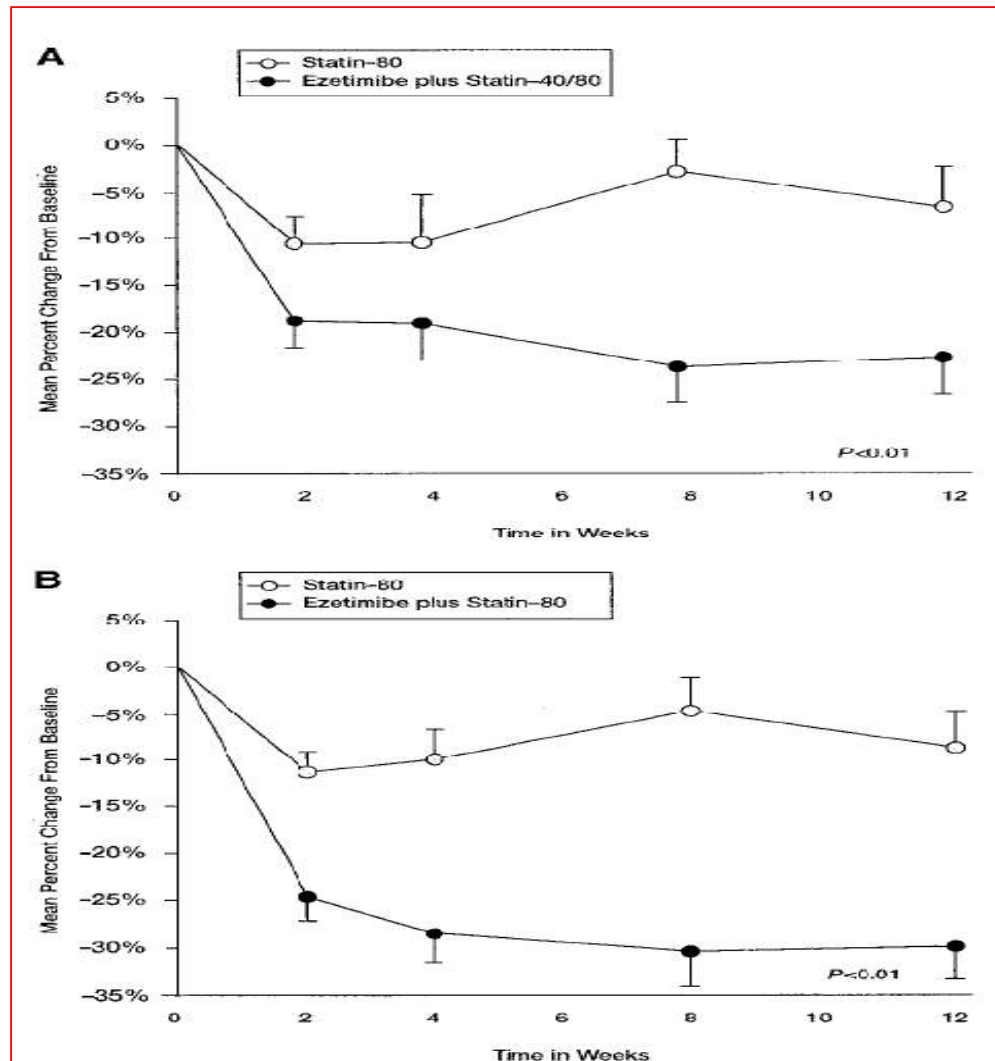
J Am Coll Cardiol 2002;40:2117-21



# Ezetimibe

- Ezetimibe is a compound of the 2-azetidione class that has been shown to decrease cholesterol absorption in animals (up to 96%)
- Acts at the brush border of the small intestine and inhibits the uptake of cholesterol into the enterocyte without affecting TG or fat soluble vitamins absorption

Gagne C, et al. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. *Circulation* 2002;105:2469-75



# When should we start treatment ?

✓ PCSK9 loss of function mutations  $\longrightarrow$  28%  $\downarrow$  in LDL-C  $\longrightarrow$  88%  $\downarrow$  risk of CHD

*Cohen JC, et al. N Engl 2006;354:1264-72*

✓ 5 years of statin treatment (adults)  $\longrightarrow$  80mg%  $\downarrow$  in LDL-C  $\longrightarrow$  40%  $\downarrow$  risk of CHD

*Brown MS, Goldstein J. Science 2006;311:1721-3*

✓ 4.5 y of statins in FH children  $\longrightarrow$  30%  $\downarrow$  in LDL-C  $\longrightarrow$  0.003  $\uparrow$  mm CIMT for year of statin postponed

*Rodenburg J, et al. Circulation 2007;116:64-8*

independent predictors of final CIMT on multy-variant analysis:  
age at statin start, male sex, statin tx duration, initial CIMT

# Monitoring and follow up for drug therapy

## AHA. Circulation 2007

- Treatment is a commitment for life...
- Monitor growth and development (Tanner)
- Monitor fasting lipoproteins, CPK, ALT, AST every 3-6 months
- Monitor and encourage lipid lowering dietary and drug therapy. Assess other risk factors (weight gain, smoking, physical inactivity)
- Counsel adolescent female on statin contraindication during pregnancy and appropriate contraceptive use.

**Thank you**



**for your kind attention**

**Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents. A Scientific Statement From the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, With the Council on Cardiovascular Nursing**

**TABLE 3. Recommendations for the Use of HMG CoA Reductase Inhibitors (Statins) in Children and Adolescents With Hyperlipidemia**

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**Patient selection**

1. Begin with the present criteria of the expert panel of the NCEP for drug initiation.
2. The age and LDL level at which statin therapy is initiated may be influenced by the presence, magnitude, and number of other cardiovascular risk factors, as well as by the presence of cutaneous xanthomas.
3. Include the preferences of patient and family in the decision making.
4. In general, do not start before 10 y of age in boys and preferably after onset of menses in girls. Patients should ideally be at Tanner stage II or higher.
5. Ensure that there are no contraindications for statin therapy (eg, important hepatic disease).

*Circulation, April 2007*

# **Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents. A Scientific Statement From the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, With the Council on Cardiovascular Nursing**

## **Initiation and titration**

1. The choice of the particular statin is a matter of preference.
2. Start with the lowest dose given once daily, usually at bedtime. Measure baseline CK, ALT, and AST.
3. Instruct the patient to report all potential adverse effects, especially myopathy (muscle cramps, weakness, asthenia, and more diffuse symptoms), immediately. If myopathy is present, its relation to recent physical activity should be assessed, the medication stopped, and CK assessed. The patient should be monitored for resolution of the myopathy and any associated increases in CK. Consideration can be given to restarting the medication once symptoms and laboratory abnormalities have resolved.
4. Advise female patients about concerns with regard to pregnancy and the need for appropriate contraception if warranted.
5. Advise about drug interactions, especially cyclosporine, fibric acid derivatives, niacin, erythromycin, azole antifungals, nefazodone, and many HIV protease inhibitors.
6. After 4 wk, measure fasting lipoprotein profile, CK, ALT, and AST and compare with laboratory-specific reported normal values.  
The threshold for worrisome level of CK is 10 times above the upper limit of reported normal; consider impact of physical activity.  
The threshold for worrisome level of ALT or AST is 3 times above the upper limit of reported normal.  
Target levels for LDL: minimal, <3.35 mmol/L (130 mg/dL); ideal, <2.85 mmol/L (110 mg/dL)
7. If target LDL levels are achieved and there are no laboratory abnormalities, continue therapy and recheck in 8 wk and then 3 mo.
8. If laboratory abnormalities are noted or symptoms are reported, temporarily withhold the drug and repeat the blood work in ~2 wk. When abnormalities return to normal, the drug may be restarted with close monitoring.
9. If target LDL levels are not achieved, double the dose, and repeat the blood work in 4 wk. Continue stepped titration up to the maximum recommended dose until target LDL levels are achieved or there is evidence of toxicity.

*Circulation, April 2007*

# Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents. A Scientific Statement From the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, With the Council on Cardiovascular Nursing

**TABLE 1. Drugs for Managing Hyperlipidemia**

Type of Drug	Mechanism of Action	Major Effects	Example(s)	Adverse Reactions
HMG CoA reductase inhibitors (statins)	Inhibits cholesterol synthesis in hepatic cells, resulting in upregulation of hepatic LDL receptors	Lowers LDL cholesterol and triglyceride, raises HDL-C	Atorvastatin, lovastatin, pravastatin, simvastatin, fluvastatin, rosuvastatin	Raised hepatic enzymes, raised CPK, myopathy possibly progressing to rhabdomyolysis
Bile acid-binding resins	Binds intestinal bile acids interrupting enterohepatic recirculation, which in turn results in LDL receptor upregulation	Lowers LDL-C, raises triglycerides	Cholestyramine, colestipol, colesevelam	Limited to gastrointestinal tract: gas, bloating, constipation, cramps
Fibric acid derivatives	Probably inhibits hepatic synthesis of VLDL	Mainly lowers triglycerides and raises HDL-C, with less effect on LDL-C	Gemfibrozil, fenofibrate	Dyspepsia, constipation, myositis, anemia
Nicotinic acid (extended release)	Upregulates hepatic LDL receptors	Lowers triglycerides and LDL-C	Niacin	Flushing, hepatic toxicity
Cholesterol absorption inhibitors	Inhibits intestinal absorption of cholesterol and plant sterols	Lowers LDL-C	Ezetimibe	Myopathy, gastrointestinal upset

HDL-C indicates HDL cholesterol; LDL-C, LDL cholesterol; and CPK, creatine phosphokinase.

*Circulation, April 2007*