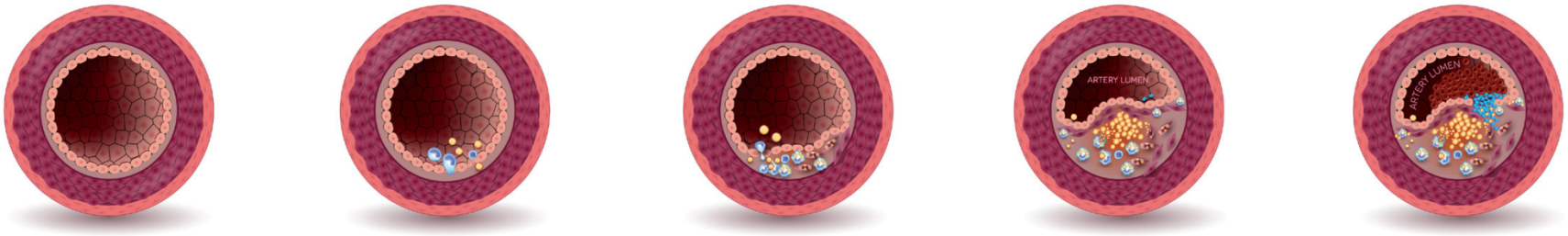


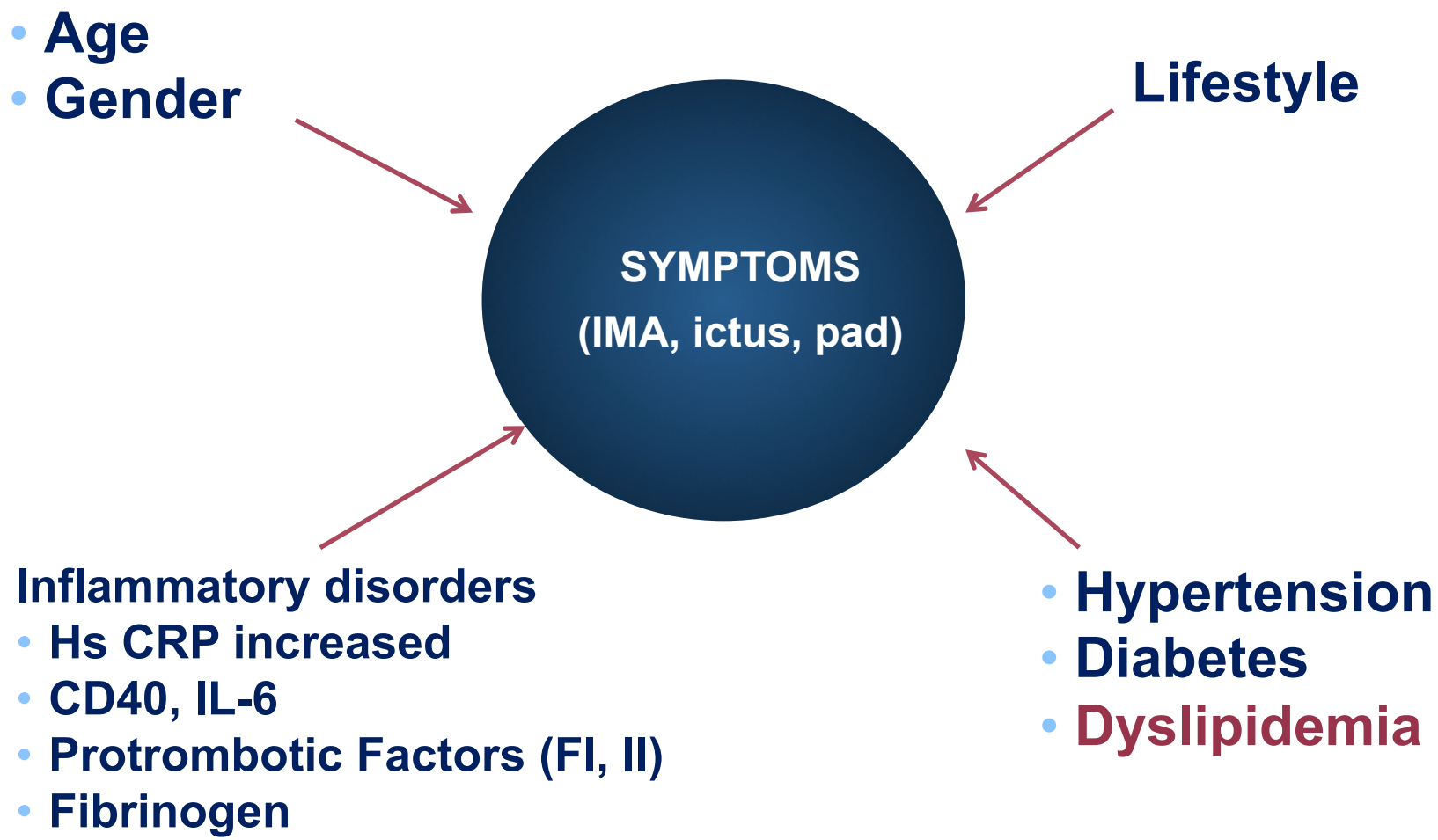
Le Dislipidemie familiari nell'età pediatrica: quale approccio?

O. GUARDAMAGNA

Dipartimento di Scienze della Sanità pubblica e pediatriche

Roma 18 dicembre 2015

Atherotrombosis Risk Factors

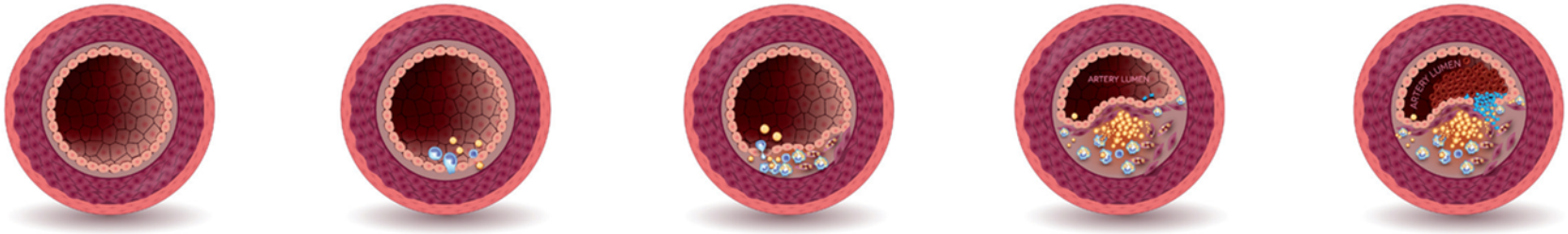


Modified by: Yusuf S, et al. *Circulation.* 2001;104:2746-2753. Drouet L. *Cerebrovasc Dis.* 2002;13(suppl 1):1-6.

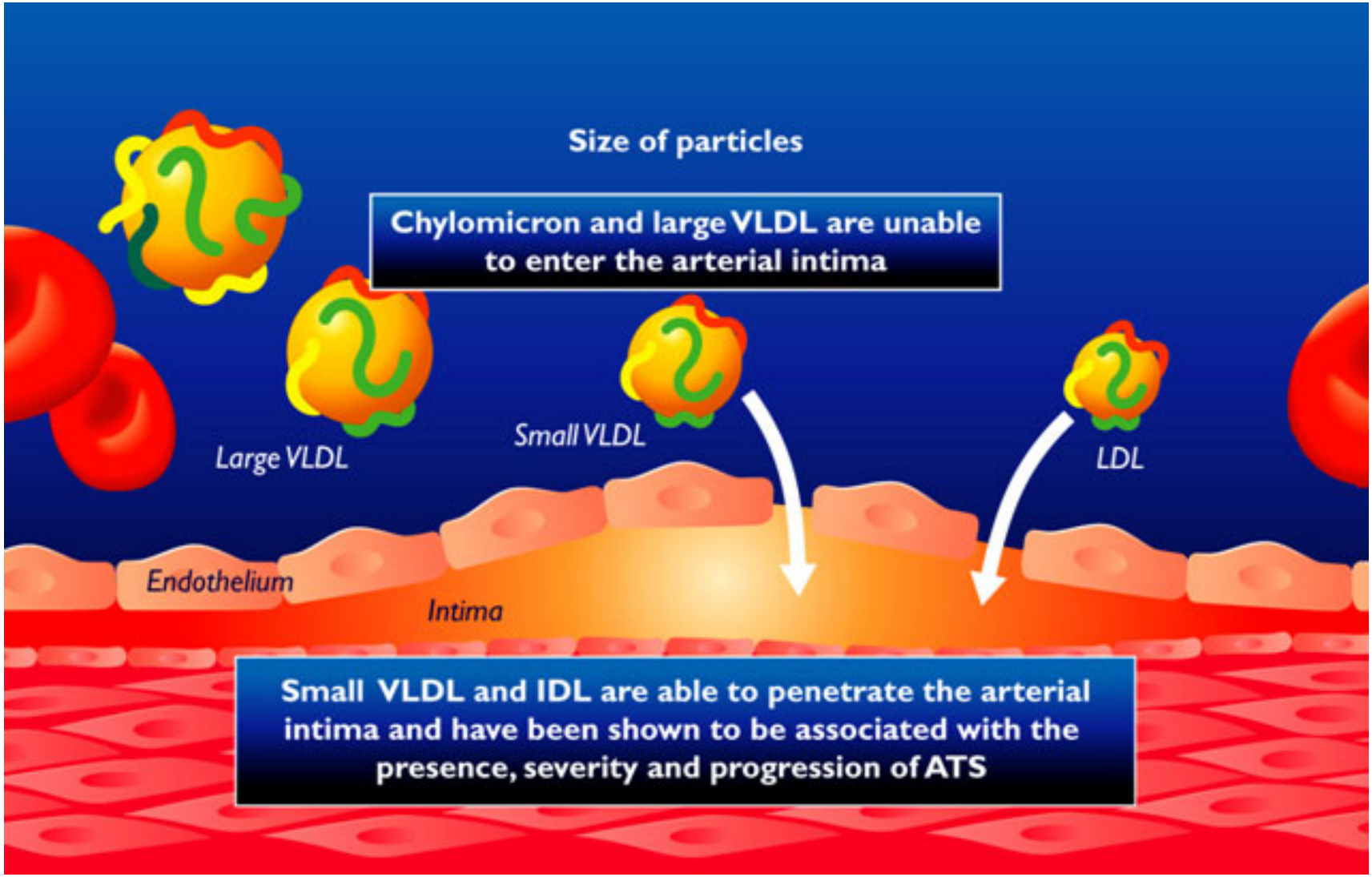
BACKGROUND

- **Why children?**
- Which children?
- Diagnosis
- Treatment

ATHEROSCLEROSIS IN PROGRESS



LDL-C: THE TRIGGER



Muscatine study-adult cIMT and children RFs

Risk Factor	Childhood	Young Adult	Current	Load
Age			0.11*	
BMI	0.09	0.09	0.16†	0.12†
Weight	0.06	0.07	0.14†	0.09
Triceps skin fold	0.04	0.05	0.09	0.08
Waist-hip ratio	—	−0.04	0.14†	0.13*
Total cholesterol	0.17†	0.14*	0.24‡	0.21‡
LDL cholesterol	—	0.21‡	0.31‡	0.29‡
HDL cholesterol	—	−0.14*	−0.13*	−0.16†
Total/HDL cholesterol	—	0.23‡	0.25‡	0.21‡
Apolipoprotein B	—	—	0.28‡	0.29‡
Apolipoprotein A	—	—	−0.08	−0.09
Lipoprotein(a)	—	—	0.01	0.01
Triglycerides	0.10	0.13*	0.14*	0.16†
Systolic BP	0.10	0.17†	0.19‡	0.21‡
Diastolic BP	0.06	0.12*	0.23‡	0.23‡
Homocysteine	—	—	−0.05	—
Fasting insulin	—	—	0.16†	—
Fasting glucose	—	—	0.05	—
Diabetes	—	—	0.03	—
Pack-years of smoking				0.07

BP indicates blood pressure; —, not measured.
*$P<0.05$, †$P<0.01$, ‡$P<0.001$.

Davis, Circ 2001

BACKGROUND

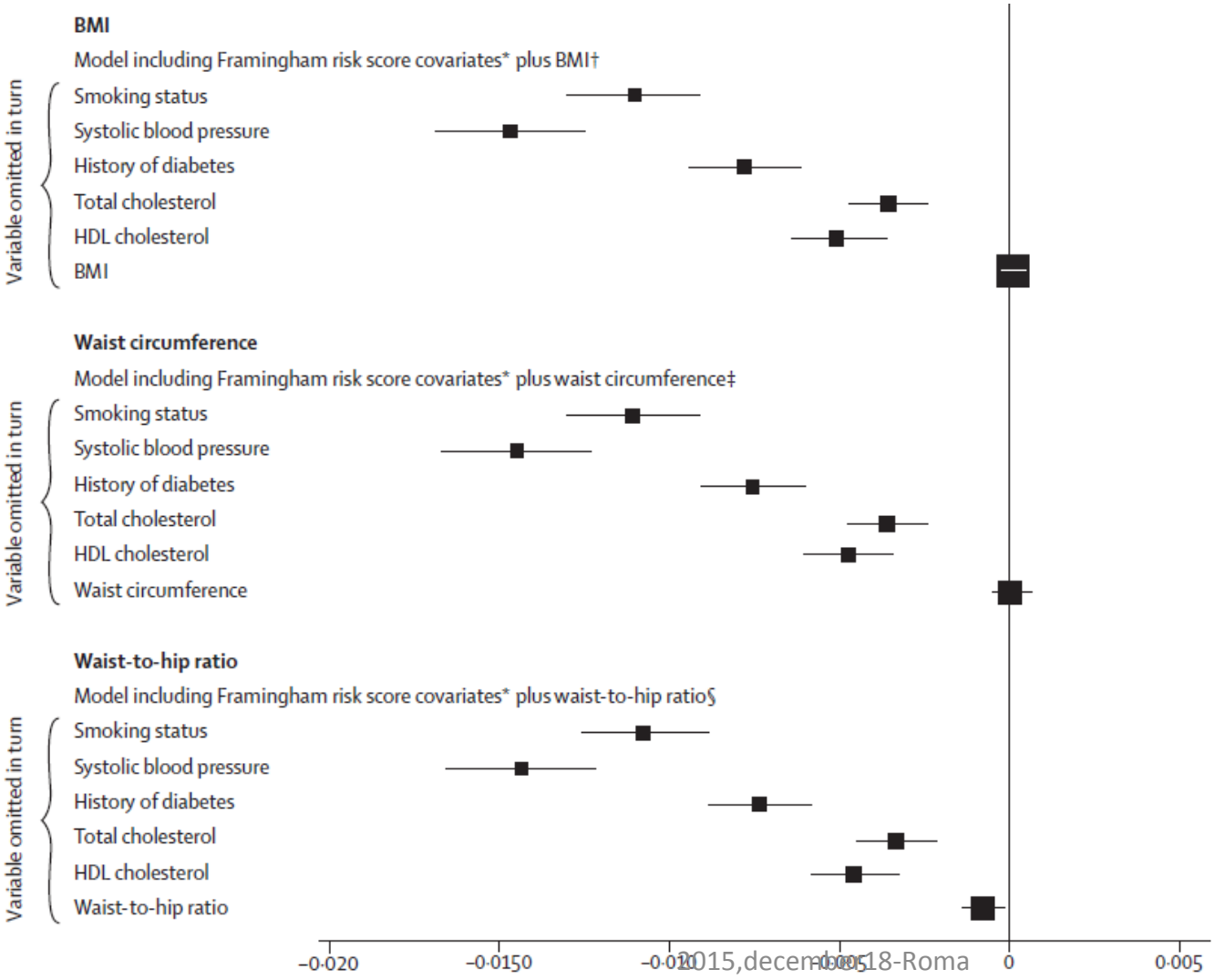
- Why children?
- **Which children?** 
- Diagnosis
- Treatment

RELATED CONDITIONS

ADIPOSITY
is it a player ?

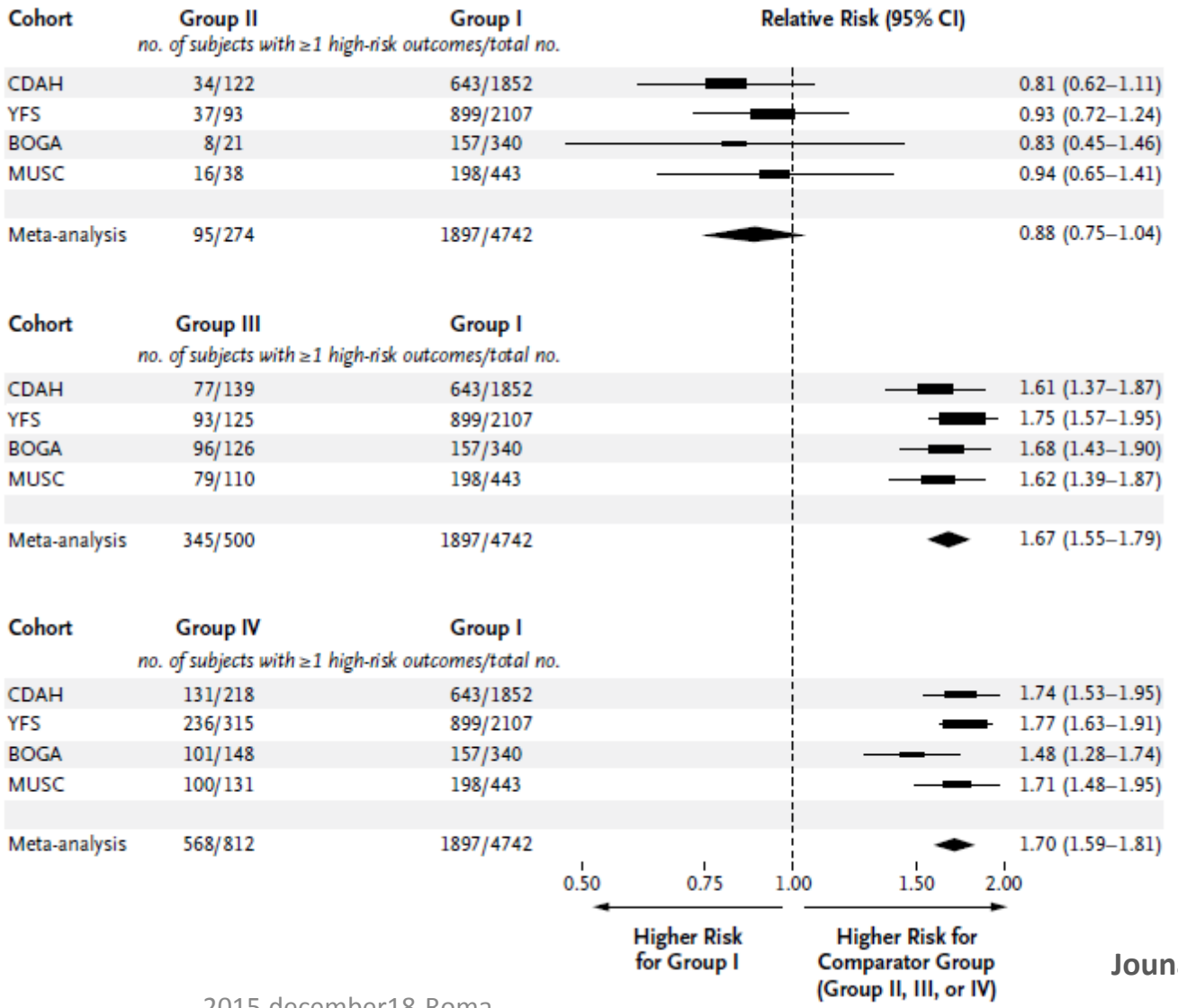
Adiposity and cardiovascular risk factors

Collaborative analysis of 58 prospective studies



The Emerging Risk Factors Collaboration*
Lancet 2011; 377: 1085–95

Children , adult adiposity and CV risk



Jounala M. NEJM 2012;365:1876.

LIPOPROTEIN LEVELS CHILDREN

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

From the National Cholesterol Education Program Expert on Cholesterol Levels in Children (Pediatrics, 1992 and 2011). Values for plasma ApoB, ApoA–I, HDL are from the National Health and Nutrition Examination Survey III (J Clin Endocrinol Metab, 2008).

Monogenic Dyslipidemias

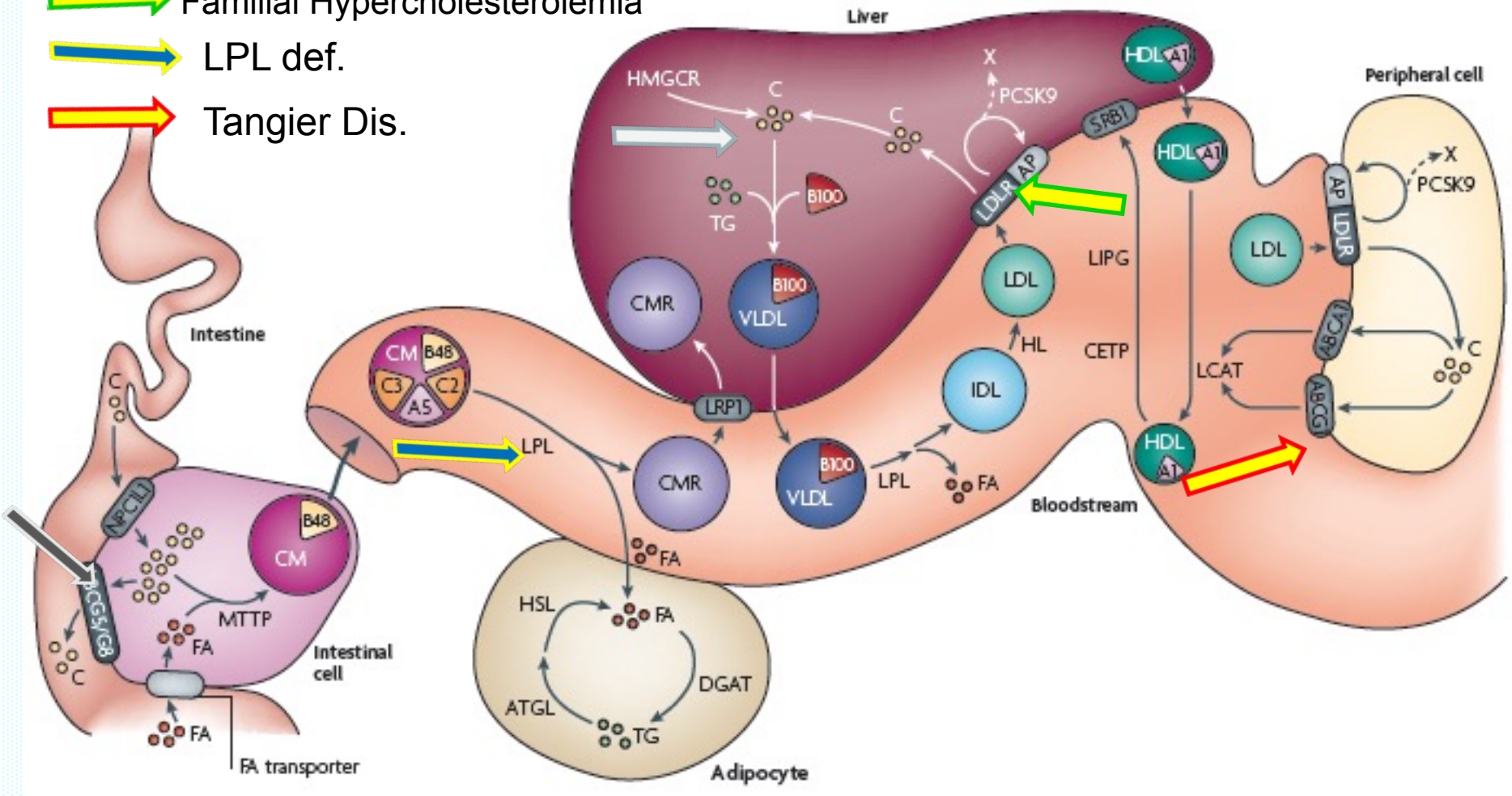
Sitosterolemia

Lysosomal ac. lipase def.

Familial Hypercholesterolemia

LPL def.

Tangier Dis.



Nature reviews 2009;10: 109-121

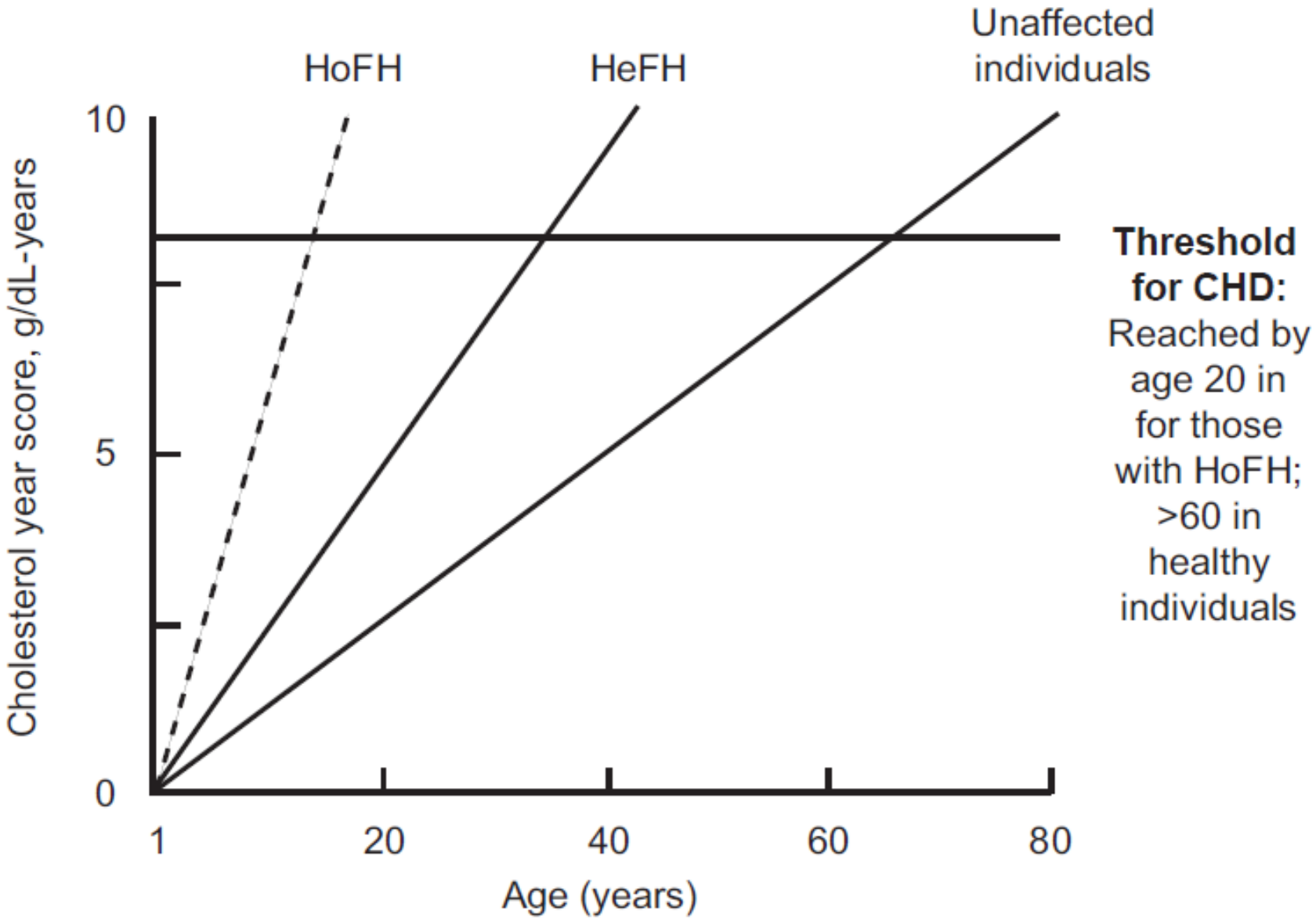
FAMILIAL HYPERCHOLESTEROLEMIA

FH: Autosomal inheritance

ADH	GENE	PREVALENCE	PICTURE
FH1 (classical FH)	LDLR 19p13	1.300–1:500 1:1,000,000	HeFH: TC 250–500 mg/Dl, xanthomas, pCHD (40–60 yrs) HoFH: TC 600–1200 mg/dL Xanthomas, very precocious pCHD (<10yrs)
FH2 (FDB)	ApoB 2p23–24	1:700	HeFH: TC 250-500 mg/dL xanthomas, pCHD (50–60 yrs) HoFH: TC >500 mg/dL Xanthomas, pCHD (<30yrs)
FH3	PCSK9 1p32	VERY RARE	HeFH3: TC 250–400 mg/dL Xanthomas, pCHD
ARH	LDLR AP1	rare	HoFH phenocopy

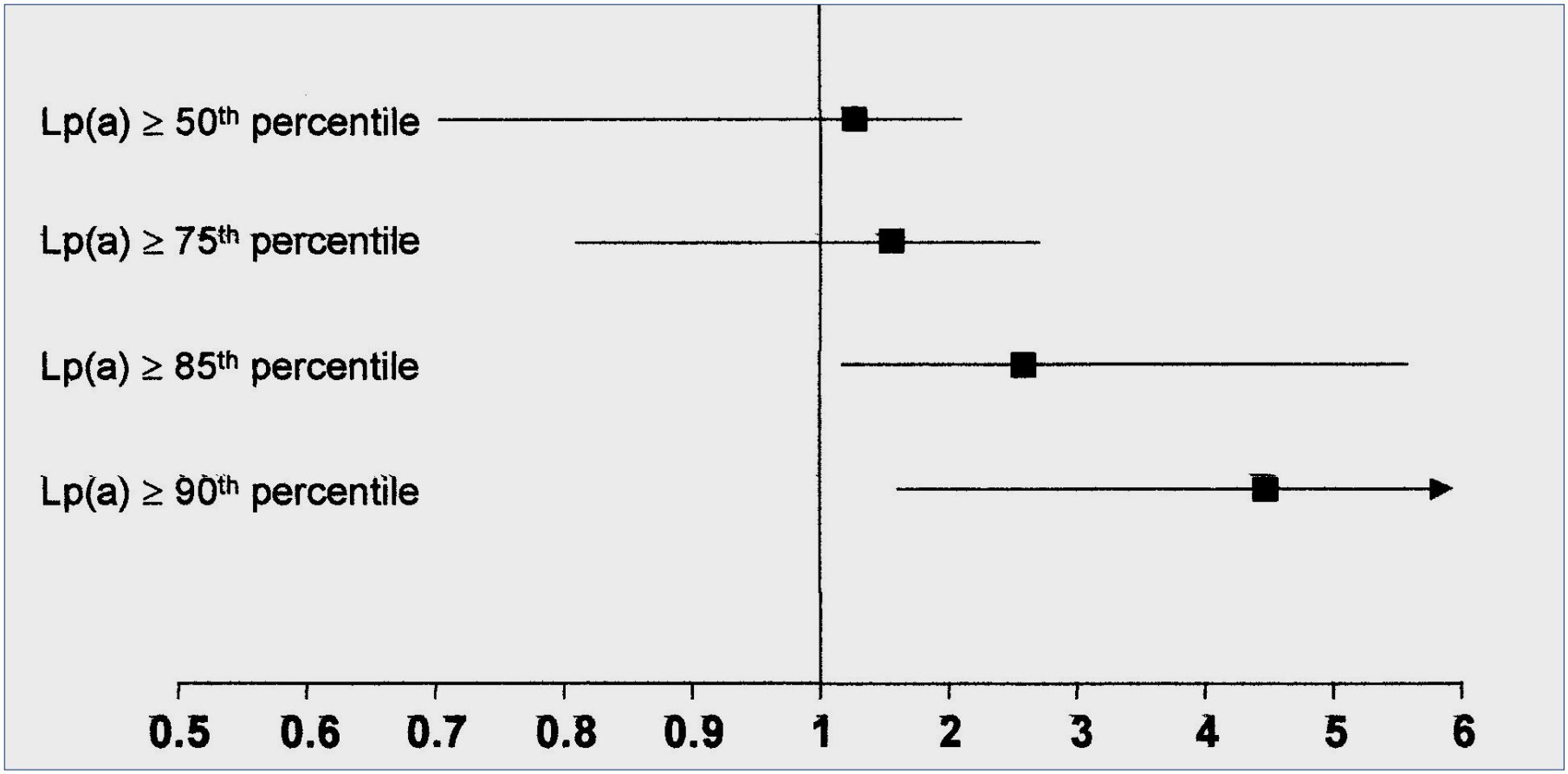
Sniderman Ad, et al . *J Am Coll Cardiol*. 2014. 20;63(19):1935–1947

Cumulative exposure (cholesterol yrs) by age:
FH vs. unaffected (healthy) individuals



Adapted from Horton, et al. *J Lipid Res*. 2009;50:S175.

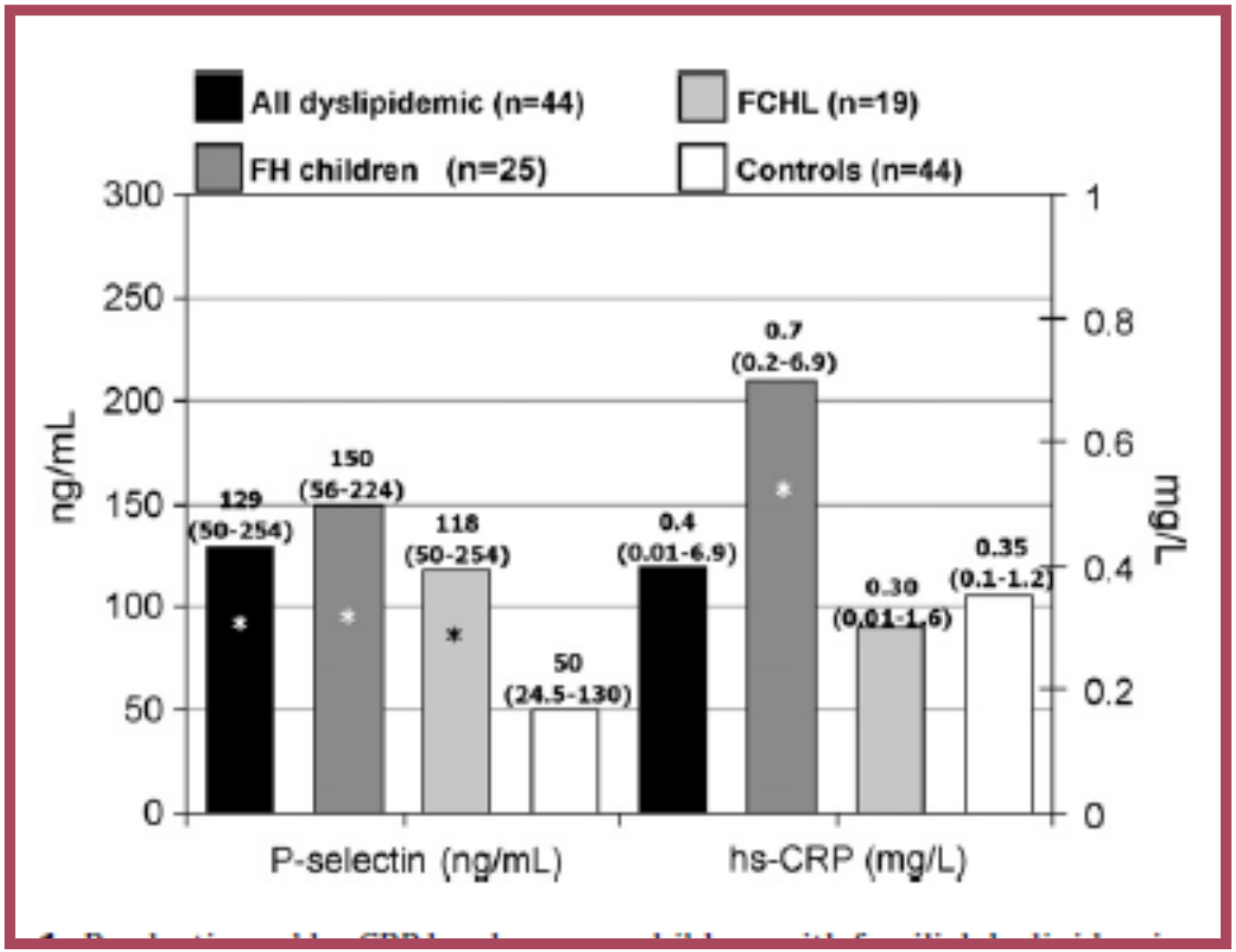
Lp(a) and pCVD



Lp(a) predicts pCVD (OR 2.5, 95% IC: 1.16-5.63, p=0.01)

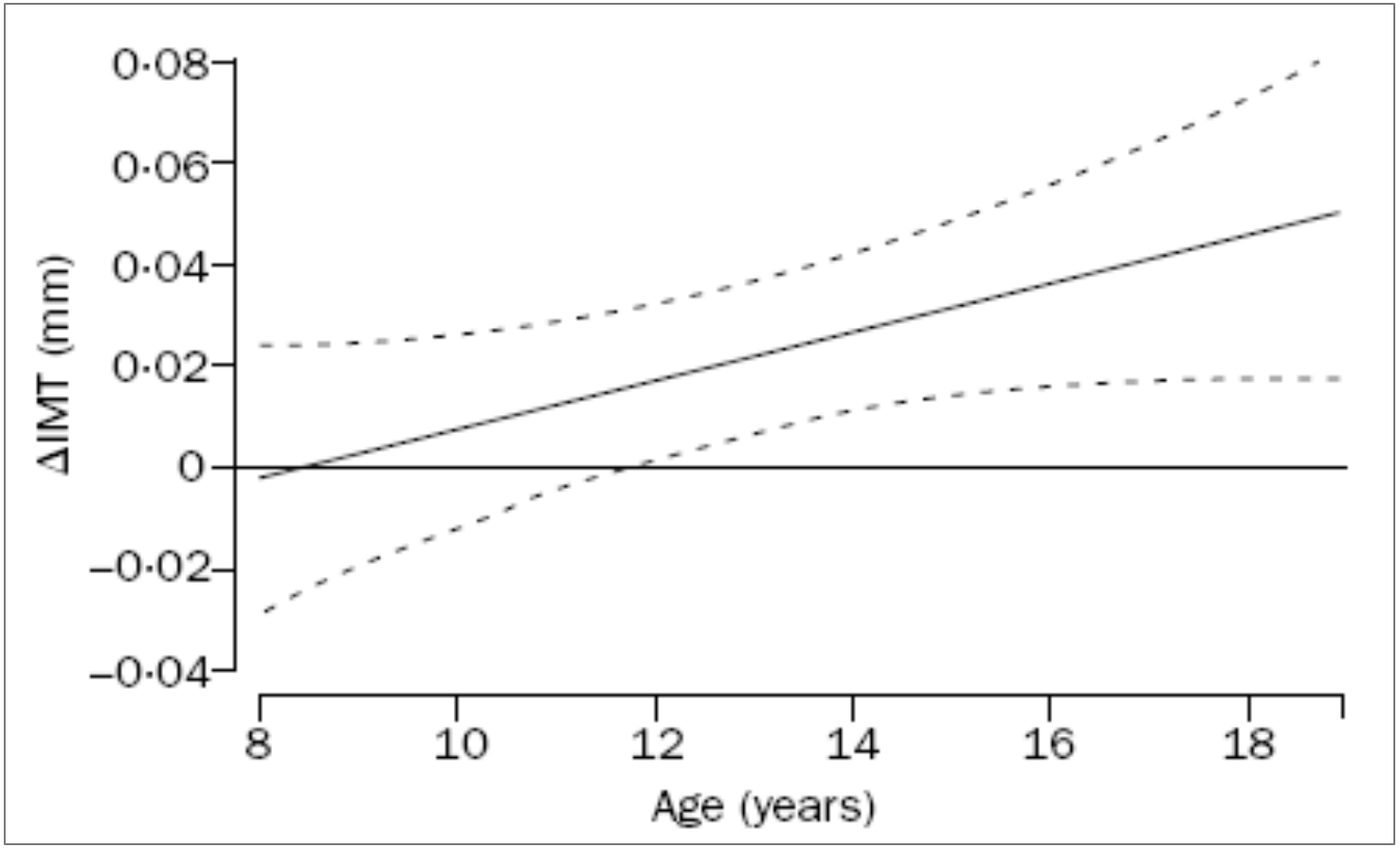
Guardamagna O, J Pediatrics 2011

P-SELECTIN AND HS-CRP IN DYSLIPIDEMIC CHILDREN



Guardamagna O et al. Atherosclerosis 2009

cIMT in HeFH CHILDREN



A Wiegman, Lancet 2004

HeFH in Italy incidence: estimates 1:500 to 1:250

?

HeFH Prevalence and diagnosis in different countries

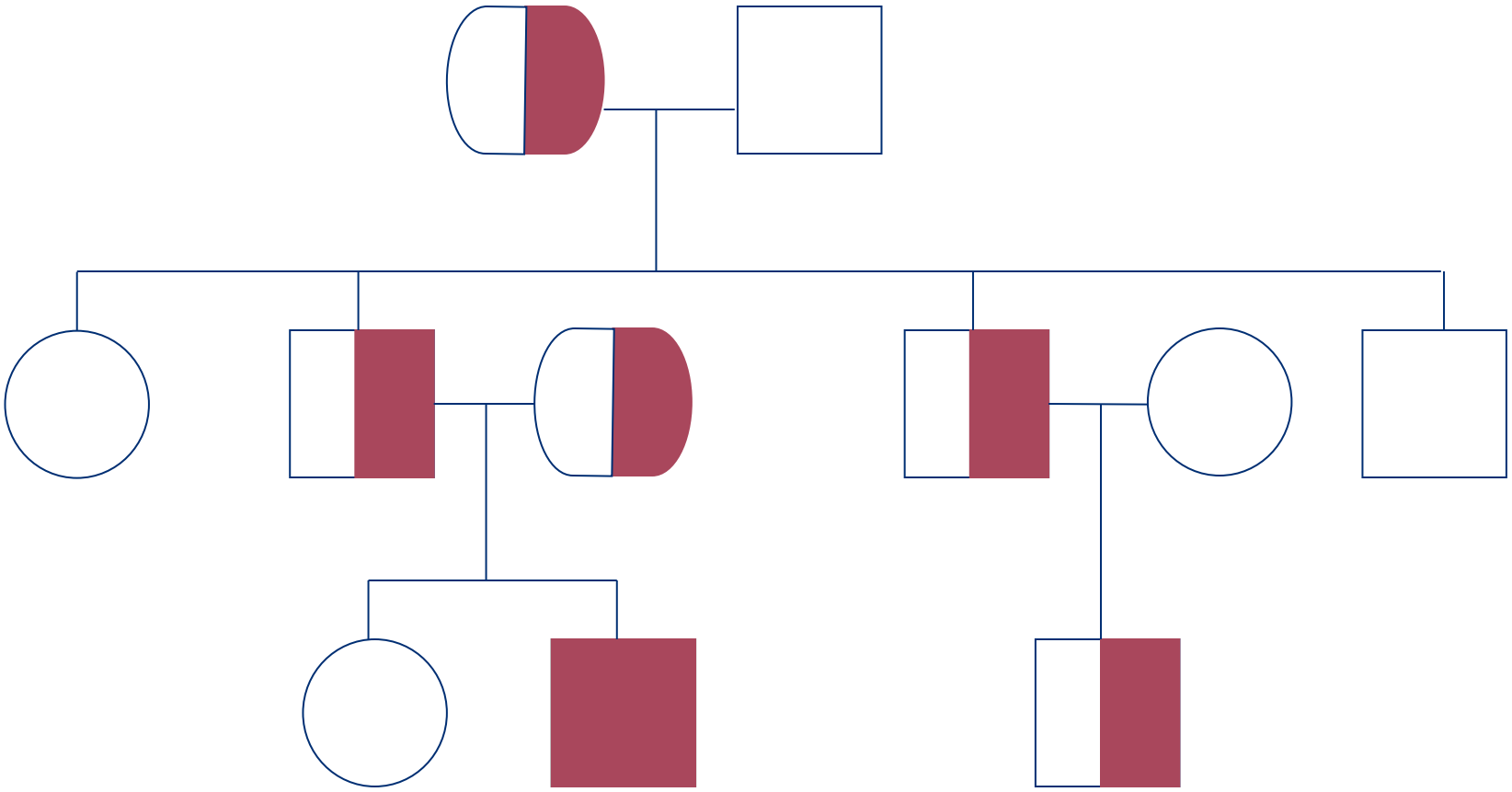
FH is caused by mutations in genes encoding key proteins involved in the LDL receptor endocytic and recycling pathways, leading to decreased cellular uptake of LDL and increased plasma LDL cholesterol concentrations[1] (*Figure 5*). Within hepatocytes, cholesterol is recycled or synthesized de novo, with 3-hydroxy-3-methylglutaryl coenzyme A reductase being rate-limiting; statins block the activity of this enzyme. Cholesterol is packaged into apolipoprotein B-containing very low-density lipoproteins (VLDL), the intravascular precursors of LDL, which in turn transports most cholesterol from the liver to peripheral tissues. Regulated endocytosis of LDL via apolipoprotein B by peripheral cells and hepatocytes occurs through the LDL receptor and an adaptor protein (LDLRAP, alias ARH).[14] Most LDL receptors recycle, although when proprotein convertase subtilisin/kexin type 9 (PCSK9) is complexed to the LDL receptor, it short-circuits its intracellular recycling from the endosome, thereby reducing receptor numbers.

Nortestgaard, Eur heart J 2013

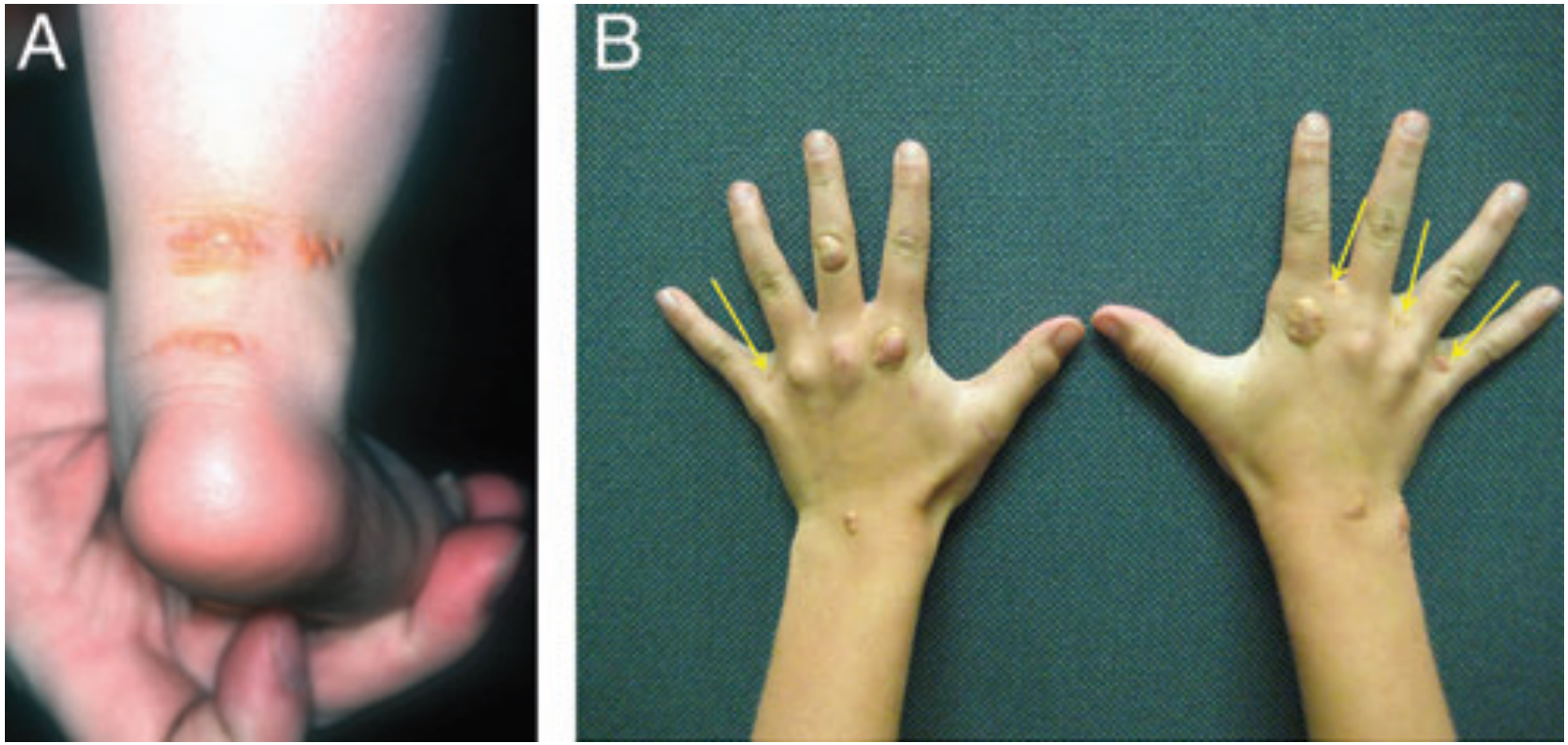
BACKGROUND

- Why children?
- Which children?
- **Diagnosis** 
- Treatment

FH: DOMINANT INHERITANCE

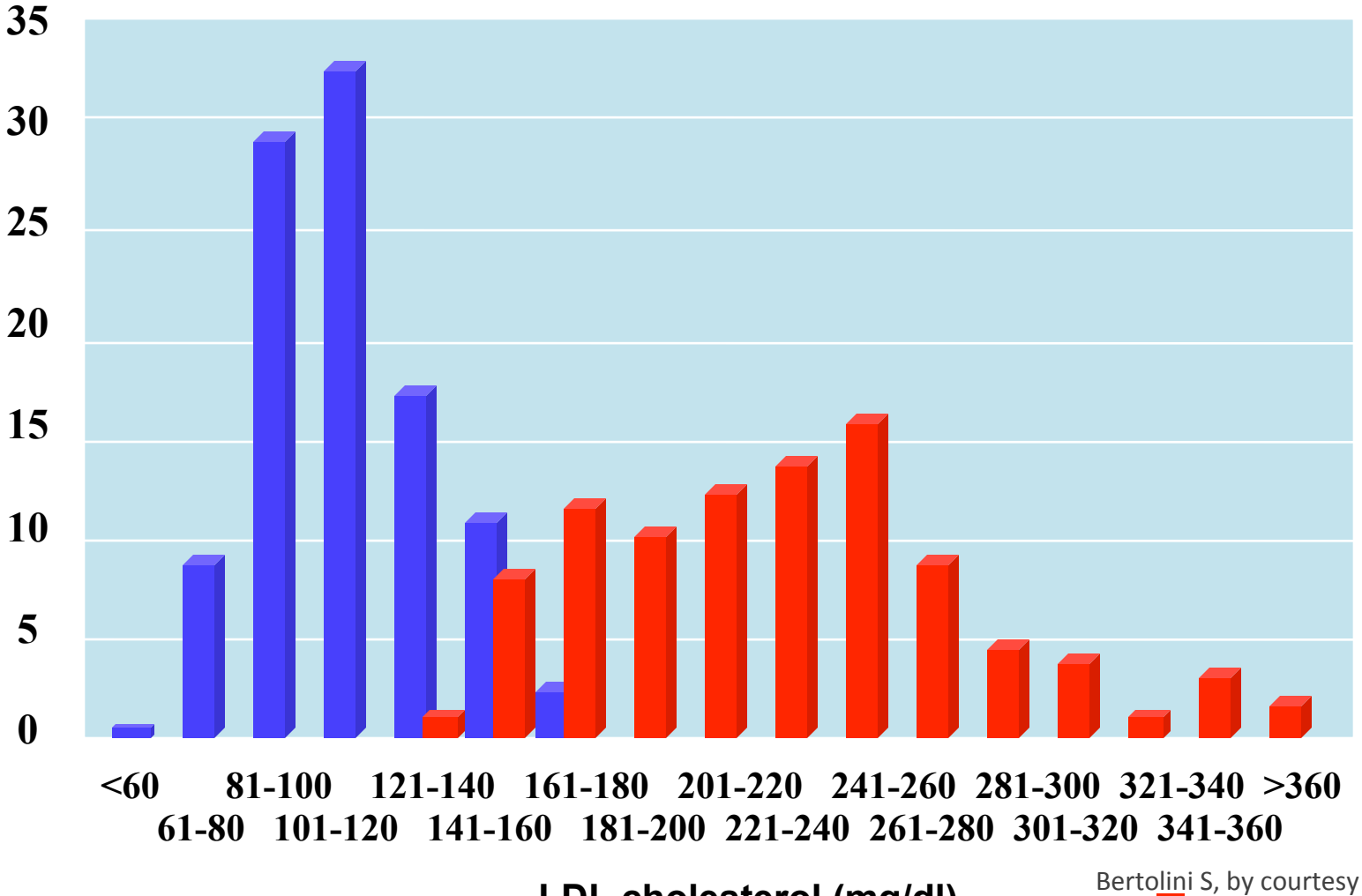


Cutaneous and tuberous xanthomas in homozygous familial hypercholesterolaemia



Photograph (A) kindly provided by Prof. Eric Bruckert. Photograph (B) kindly supplied by Prof. Frederick Raal

LDL cholesterol distribution in subjects <18 years belonging to 230 families genetically characterized



Bertolini S, by courtesy 2012

LDLR MUTATIONS and HeFH LIPOPROTEIN PROFILE

LDLR mutations	Receptor-defective	Receptor-negative	Unclassified
Children with FH			
Number (M/F)	77 (36/41)	123 (62/61)	64 (36/28)
Age, years	10.3 ± 4.5	9.4 ± 4.6	10.5 ± 4.4
BMI, kg/m^2	18.1 ± 3.2	17.9 ± 2.3	18.4 ± 3.5
TC, mmol/L	6.68 (5.10-9.34)	7.89 (5.30-12.28)¶	7.64 (4.4-11.97)¶
LDL-C, mmol/L	4.99 (3.44-7.30)	6.14 (3.53-10.53)¶	5.70 (3.25-10.43)¶
HDL-C, mmol/L	1.37 (0.76-2.29)	1.31 (0.65-2.55)	1.33 (0.69-1.94)
TG, mmol/L	0.81 (0.35-1.76)	0.85 (0.32-2.67)	0.90 (0.42-3.70)
Apo B, g/L	1.29 (0.39-1.71)	1.43 (0.88-1.97)¶	1.39 (0.87-1.97)¶
cIMT, mm	0.44 ± 0.07	0.51 ± 0.09*	0.48 ± 0.06
Families with pCAD	19/60 (31.6%)	55/89 (61.8%)†	27/52 (51.9%)*
Parents with FH			
Number (M/F)	45 (17/28)	70 (39/31)	33 (22/11)
Age, years	40.4 ± 7.4	39.6 ± 6.4	43.1 ± 5.8
BMI, kg/m^2	23.5 ± 3.0	23.9 ± 3.3	24.1 ± 4.2
TC, mmol/L	8.61 (6.83-12.57)	9.35 (6.26-13.73)*	9.38 (6.88-12.77)
LDL-C, mmol/L	6.67 (5.12-10.85)	7.64 (4.69-11.58)†	7.30 (4.67-11.48)
HDL-C, mmol/L	1.29 (0.85-1.84)	1.14 (0.65-2.02)	1.21 (0.83-2.51)
TG, mmol/L	1.18 (0.56-4.88)	1.25 (0.45-3.86)	1.36 (0.68-4.21)
Apo B, g/L	1.42 (1.18-1.85)	1.62 (1.18-2.30)¶	1.62 (1.18-2.30)

O Guardamagna et al, J Ped 2009

Overlap of clinical and mutation diagnosis of heterozygous familial hypercholesterolaemia

termine the threshold for CHD (*Figure 8*), and risk factor counting is critical to assess CHD risk.[26] Importantly, as elevated LDL cholesterol is the major problem in FH, this condition is dominated by CHD, whereas cerebrovascular disease is more common in individuals with hypertension and atherosclerosis in the lower limbs is more common among smokers.

The concept of a cumulative LDL cholesterol burden (*Figure 8*) illustrates the importance of early treatment. The cumulative LDL cholesterol burden of a 55-year-old person without FH is typically 160 mmol, a burden sufficient for CHD to develop (*Figure 8*; data

Palacios L., Atherosclerosis 2012;221:137 – 142

SIMON BROOME SCORE

Definite familial hypercholesterolaemia is defined a

a) Total cholesterol > 6.7 mmol/l or LDL cholesterol above 4.0 mmol/l in a child < 16 years or Total cholesterol >7.5 mmol/l or LDL cholesterol above 4.9 mmol/l in an adult. (Levels either pre-treatment or highest on treatment)

PLUS

b) Tendon xanthomas in patient, or in 1st degree relative (parent, sibling, child), or in 2nd degree relative (grandparent uncle, aunt)

OR

c) DNA-based evidence of an LDL receptor mutation or familial defective apo B-100

Possible familial hypercholesterolaemia is defined as:

a) above **PLUS ONE OF d)** or **e)**

d) Family history of myocardial infarction: below age of 50 in 2nd degree relative or below age 60 in 1st degree relative

e) Family history of raised cholesterols: >7.5 mmol/l in adult 1st or 2nd degree relative or > 6.7 mmol/l in child or sibling under 16

↓

PROBABLE FH

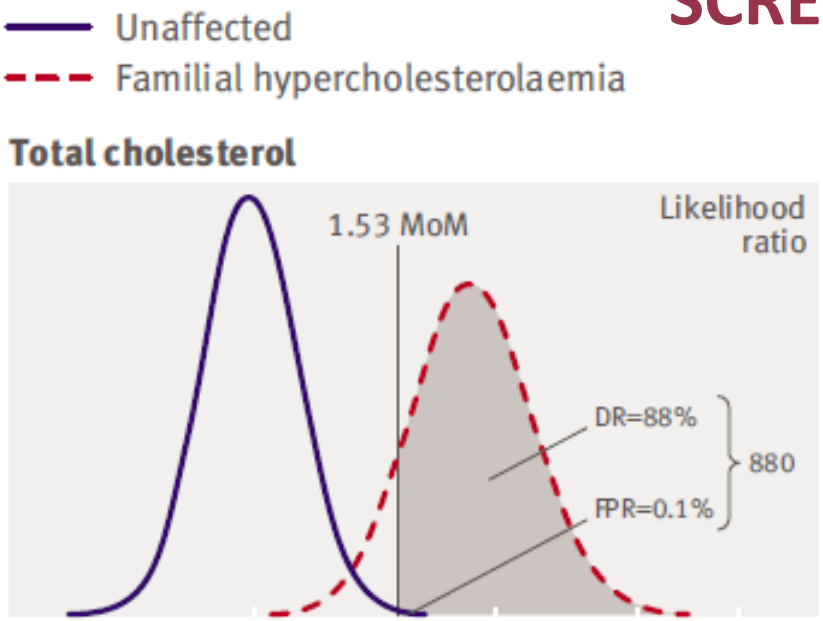
Family History and Cardiovascular Risk in Familial Hypercholesterolemia

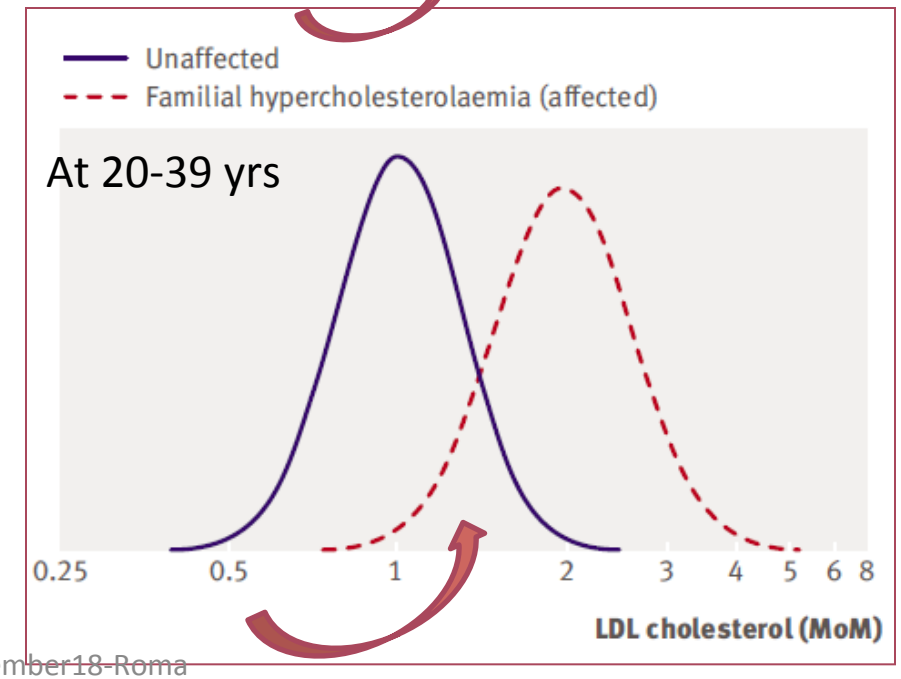
Child with LDL-C ≥ 3.5 mmol/L (135 mg/dL) and one parent with definite FH has 0.98 (95% CI: 0.96-0.99) post-test probability of heterozygosity for LDL receptor mutation

Wiegman A, Circ 2003

SCREENING

At 1-9 yrs





LDL-C overlap at different ages between HeFH and controls

D Wald, BMJ 2007

BACKGROUND

- Why children?
- Which children?
- Diagnosis
- **Treatment** 

ESC/EAS GUIDELINES 2011, Atherosclerosis

Recommendations	Class[a]	Level[b]
Children of parents with FH are recommended: • to be diagnosed as early as possible • to be educated to adopt a proper diet • to receive pharmacological treatment in late childhood or in adolescence.	I	C

Clinical update

European Heart Journal 2014

Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society

Marina Cuchel*, Eric Bruckert, Henry N. Ginsberg, Frederick J. Raal, Raul D. Santos, Robert A. Hegele, Jan Albert Kuivenhoven, Børge G. Nordestgaard, Elisabeth Steinhagen-Thiessen, Anne Tybjærg-Hansen, izio Averna, Catherine Boileau, Jan Borén, Alberico L. Catapano, ees Hovingh, Steve E. Humphries, Petri T. Kovanen, Luis Masana, G. Parhofer, Kausik K. Ray, Anton F. H. Stalenhoef, Erik Stroes, , Albert Wiegman, Olov Wiklund, and M. John Chapman, erosclerosis Society Consensus Panel on Familial ia†

Pediatrics 2011;128;S213

SUPPLEMENT ARTICLES

Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report

Start Statin if after 6-12 months CHILD-2-DIET:

-LDL-C ≥ 190 mg/dl

- LDL-C = 160-189 + (positive family history or ≥ 1 high-level risk factor or ≥ 2 moderate-level risk factors)

- LDL-C ≥ 130-159 mg/dl + (≥ 2 high-level risk factors or 1 high-level risk factors + 2 moderate level risk factors)

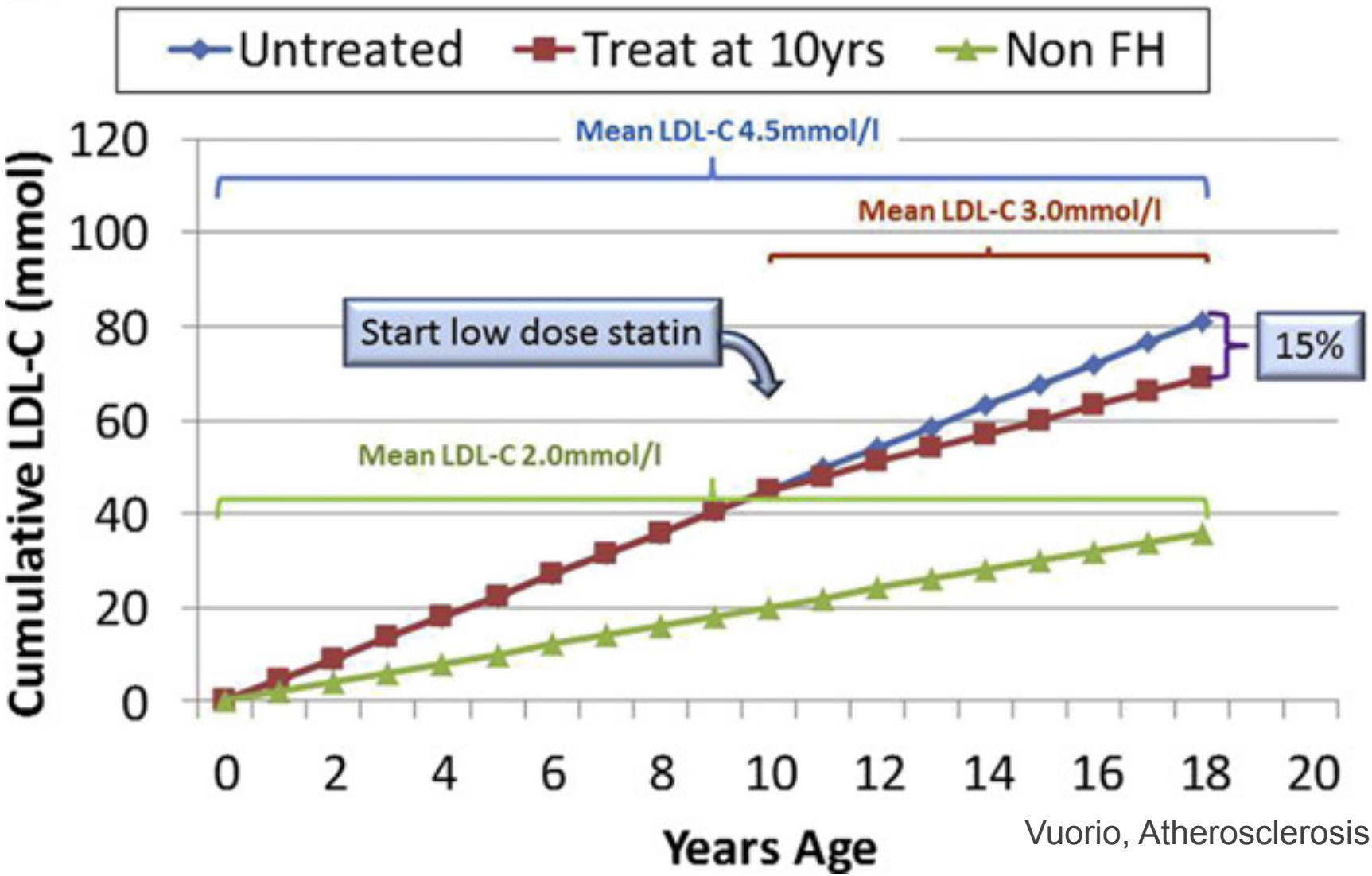
Prevention

European Heart Journal (2015) 36, 2425–2437

Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment

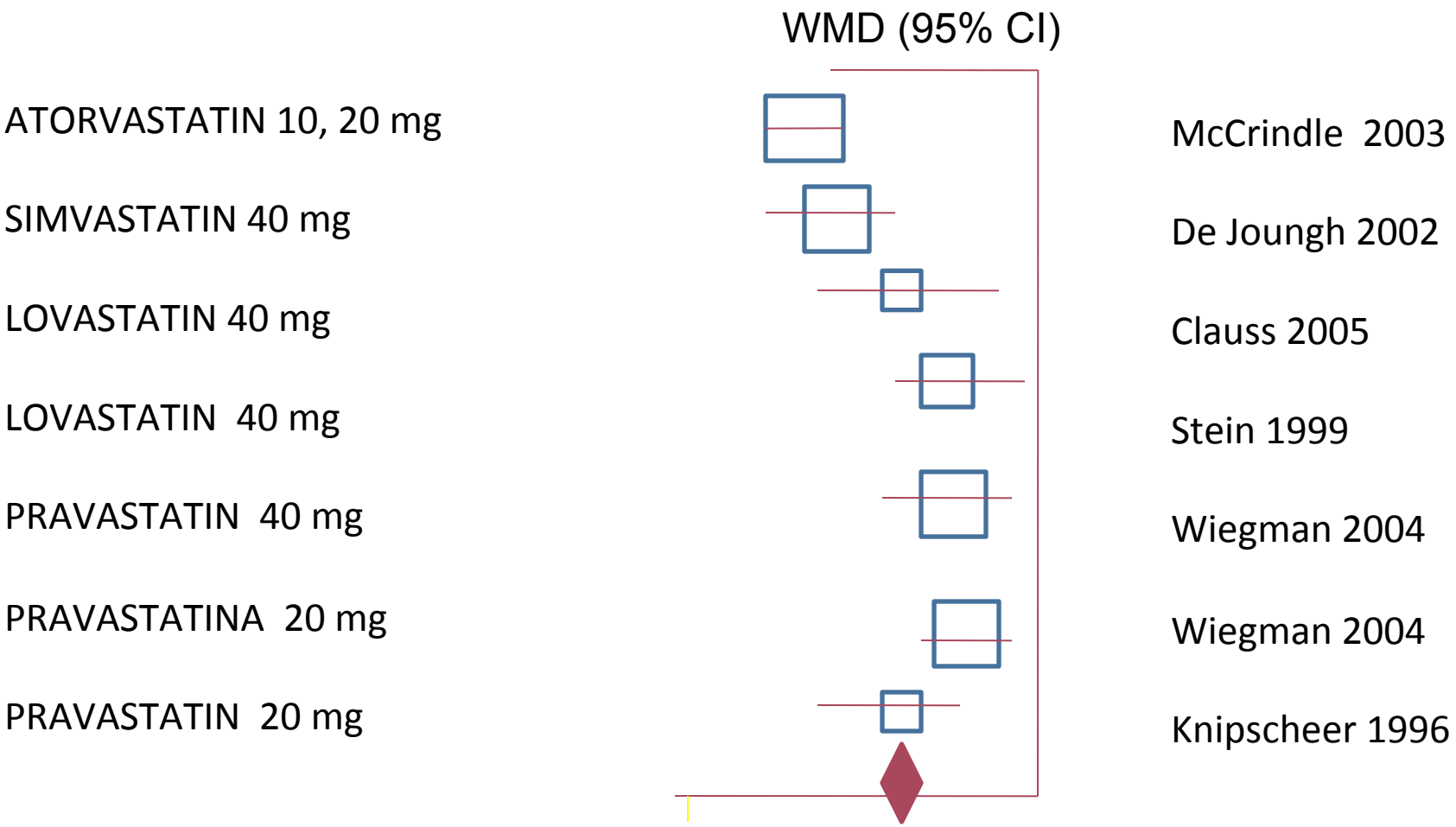
Albert Wiegman[1†*], Samuel S. Gidding[2†], Gerald F. Watts[3], M. John Chapman[4,5], Henry N. Ginsberg[6,7], Marina Cuchel[8], Leiv Ose[9,10], Maurizio Averna[11], Catherine Boileau[12,13,14], Jan Borén[15,16], Eric Bruckert[17], Alberico L. Catapano[18,19], Joep C. Defesche[20], Olivier S. Descamps[21], Robert A. Hegele[22], G. Kees Hovingh[20], Steve E. Humphries[23], Petri T. Kovanen[24], Jan Albert Kuivenhoven[25], Luis Masana[26], Børge G. Nordestgaard[27,28], Päivi Pajukanta[29], Klaus G. Parhofer[30], Frederick J. Raal[31], Kausik K. Ray[32], Raul D. Santos[33,34], Anton F.H. Stalenhoef[35], Elisabeth Steinhagen-Thiessen[36,37], Erik S. Stroes[20], Marja-Riitta Taskinen[38], Anne Tybjærg-Hansen[39,40], and Olov Wiklund[41,42], for the European Atherosclerosis Society Consensus Panel‡

LDL-C burden by the age of 18 years in non-FH and FH patients

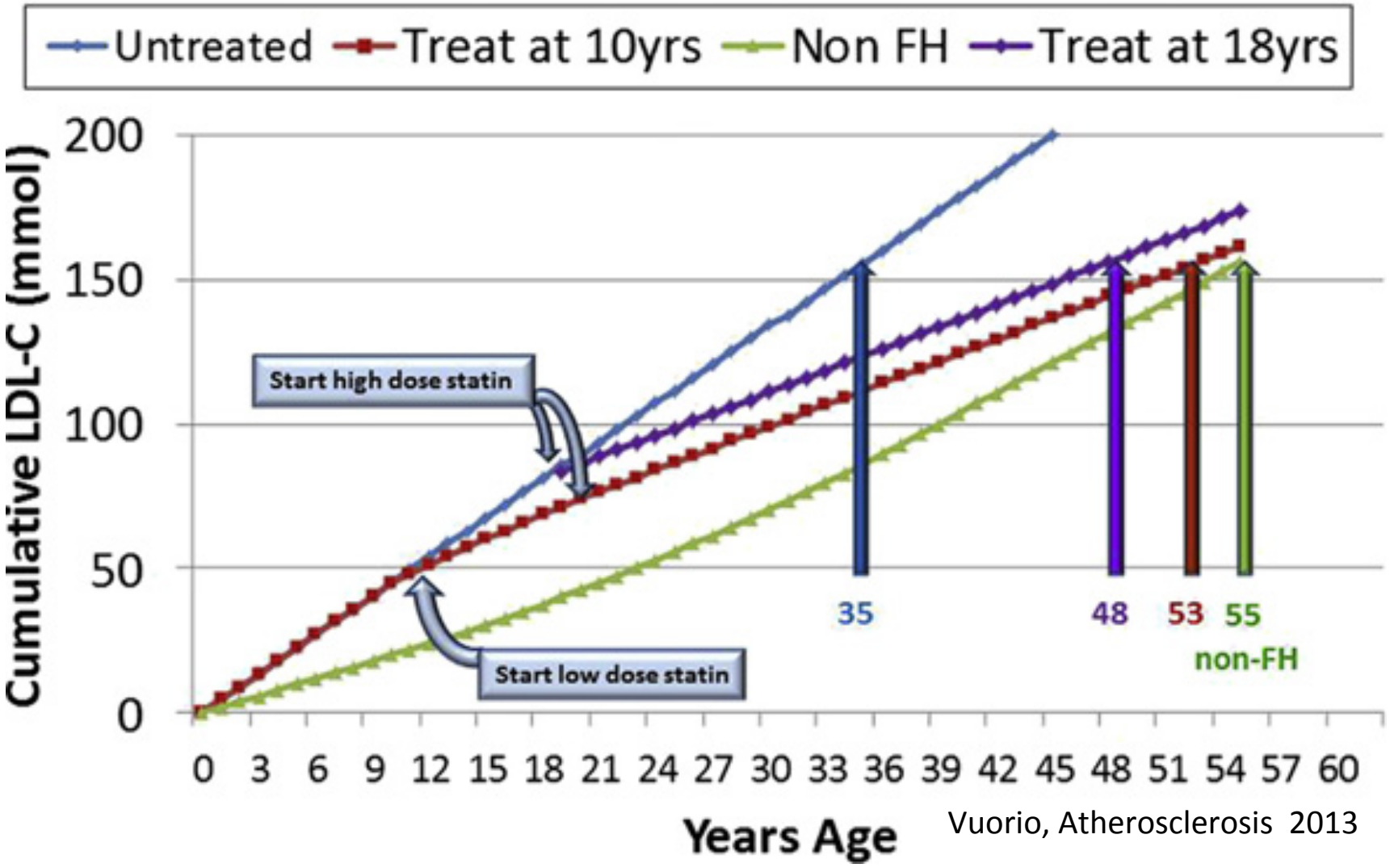


Vuorio, Atherosclerosis 2013

LDL-C (%) CHANGE ON STATIN THERAPY

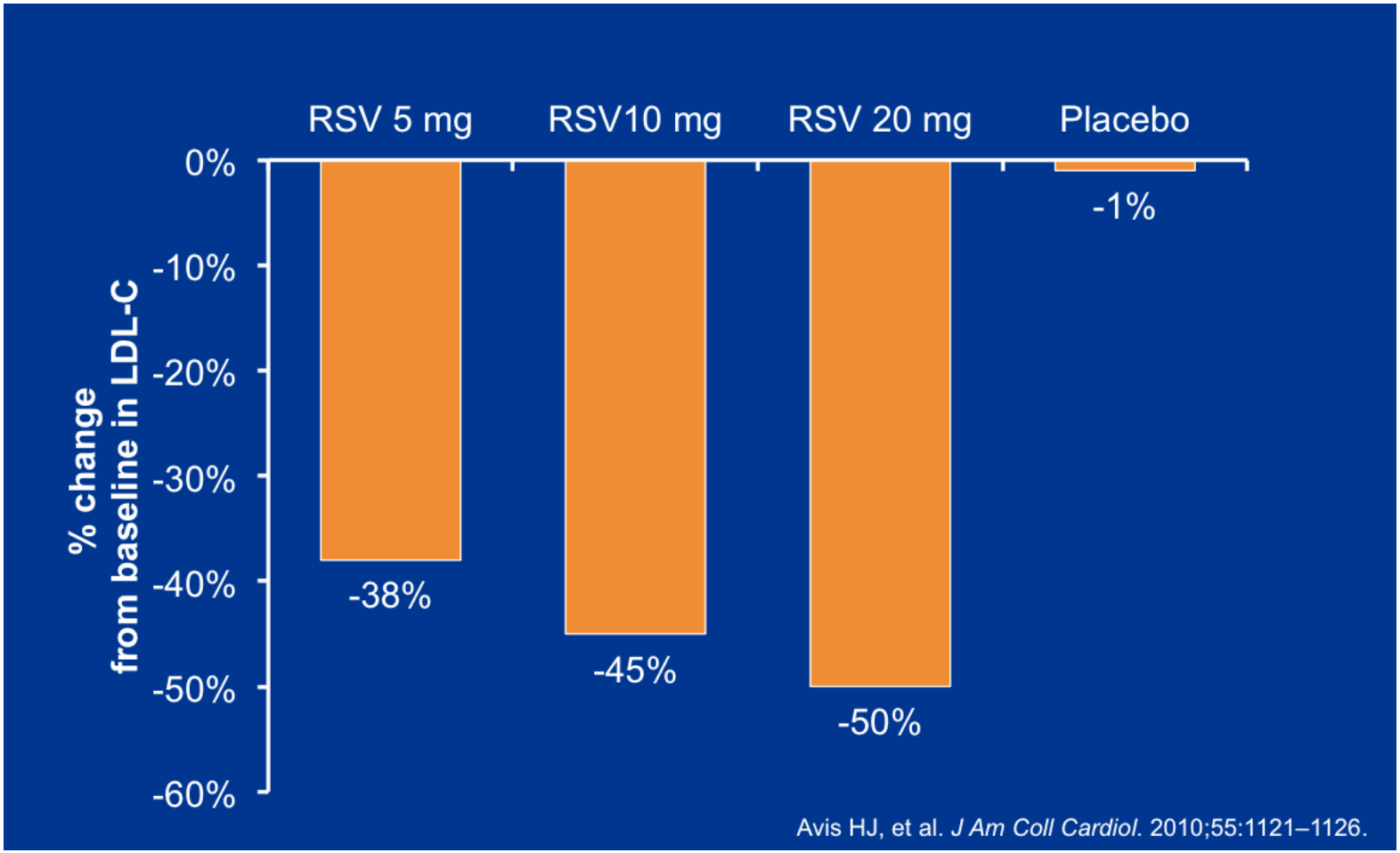


LDL-C burden of FH treated patients



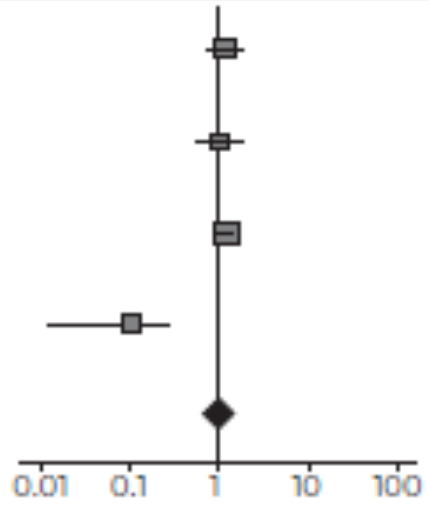
Vuorio, Atherosclerosis 2013

Rosuvastatin:effective in children 10-17 yrs HeFH



ADVERSE EFFECT OF STATIN IN CHILDREN

Statin (dose)	Adverse events		Relative risk (95% CI)	
	Statin n/N	Placebo n/N		
Atorvastatin (10 to 20 mg)	88/140	29/47		1.02 (0.79, 1.32)
Lovastatin (40 mg)	23/35	13/19		0.96 (0.65, 1.42)
Simvastatin (40 mg)	93/106	57/69		1.06 (0.93, 1.21)
Pravastatin (20 mg)	1/18	9/18		0.11 (0.02, 0.79)
Total	205/299	108/153		0.99 (0.79, 1.25)

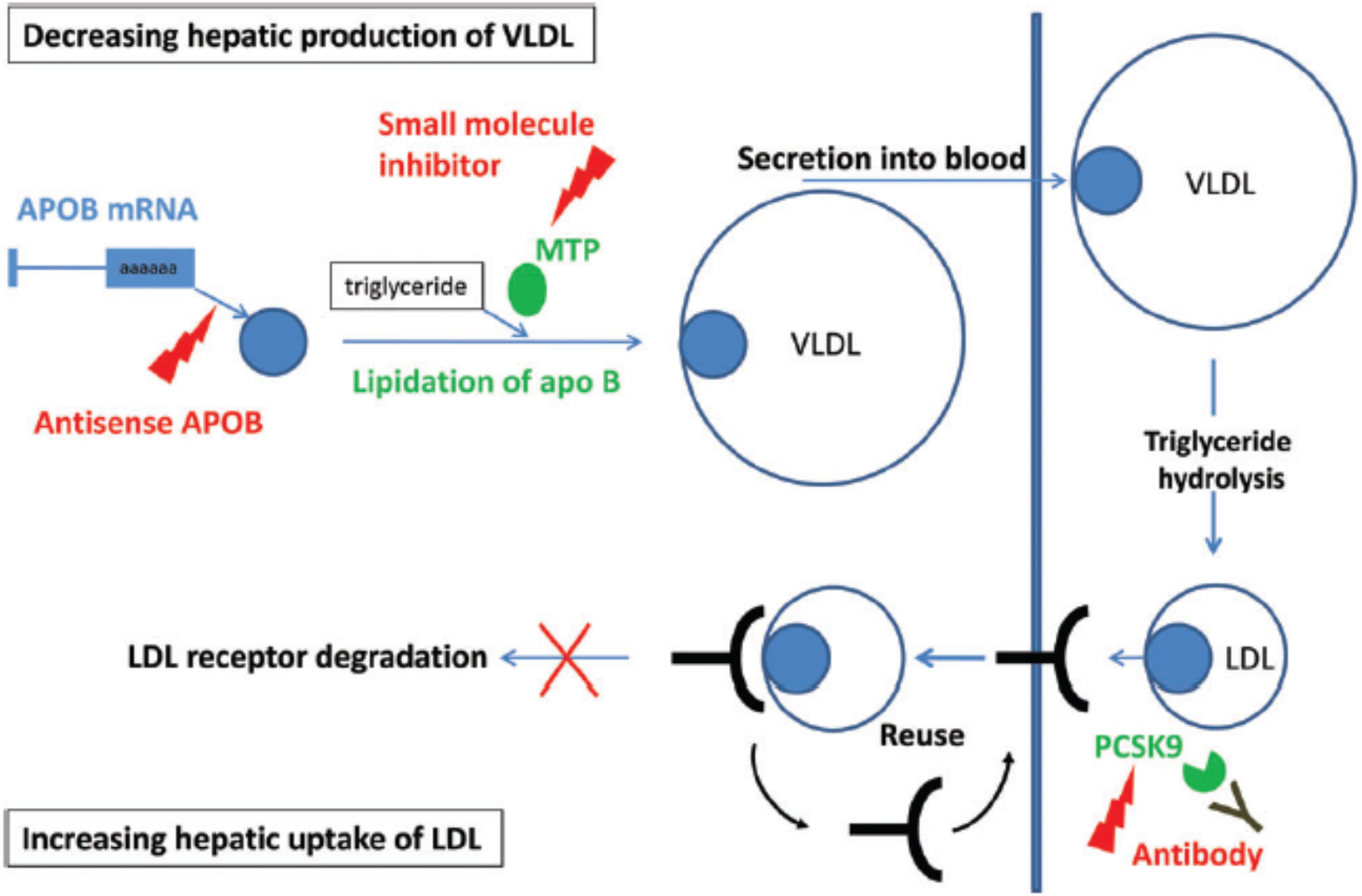


Avis HJ,Curr Opin Invest Drugs 2009

Novel treatment options

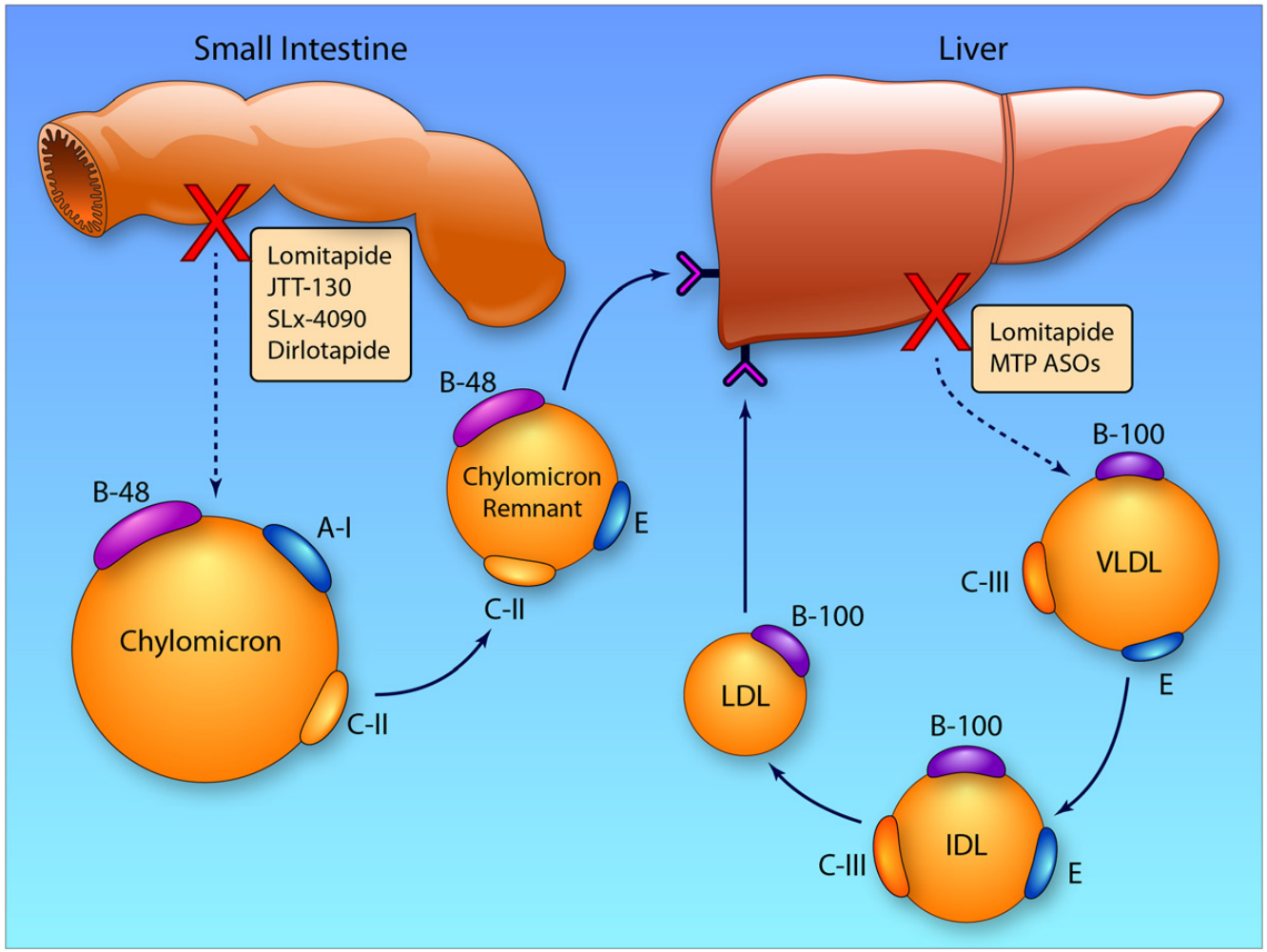
- PCSK9 inhibitors
- MTP inhibitors
- CETP inhibitors
- Apo B mRNA antisense drugs

Novel lipid-regulating drug targets



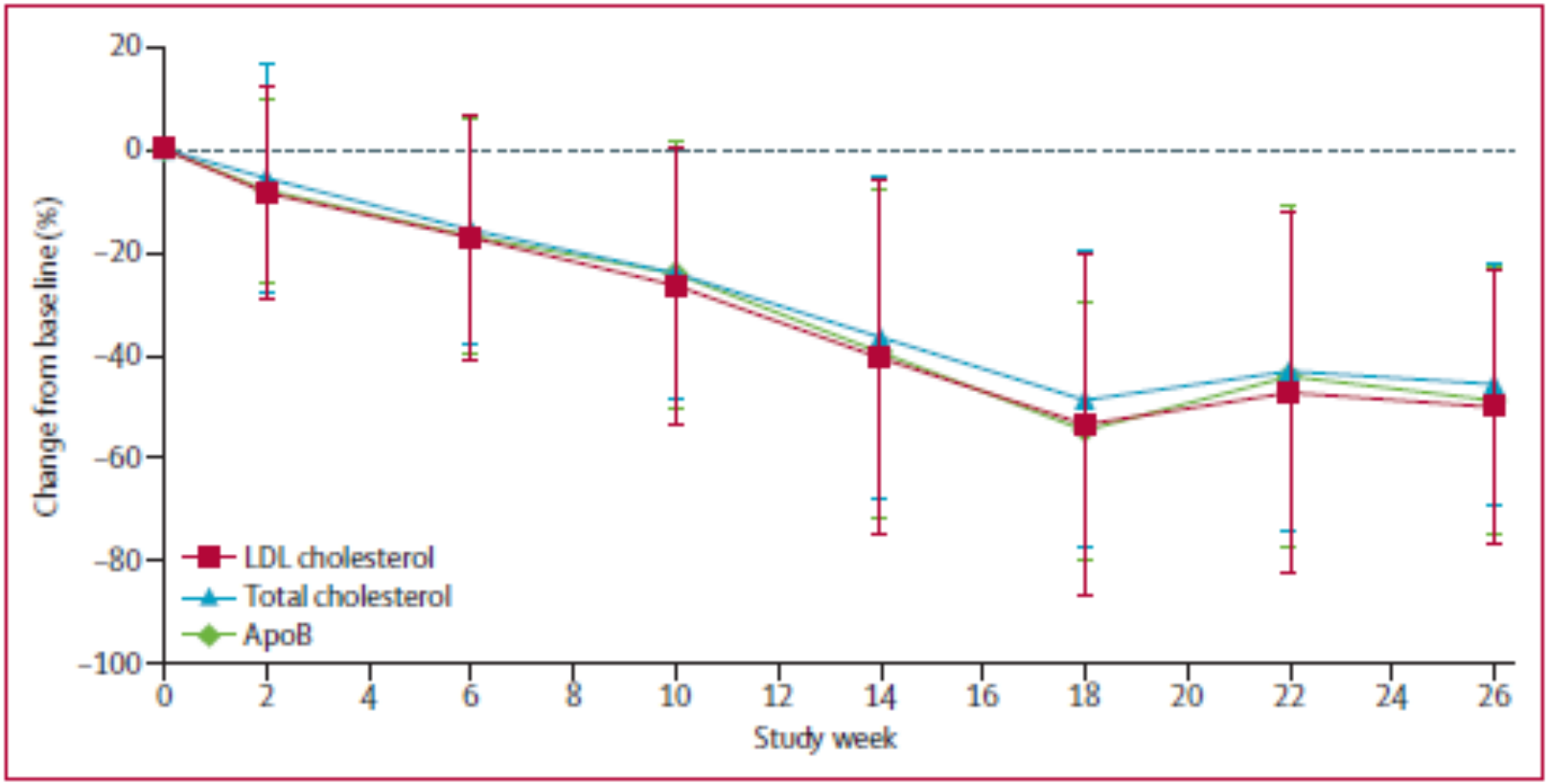
M Cuchel, EHJ 2014

Mechanism of action of microsomal triglyceride transfer protein (MTP) inhibitors.



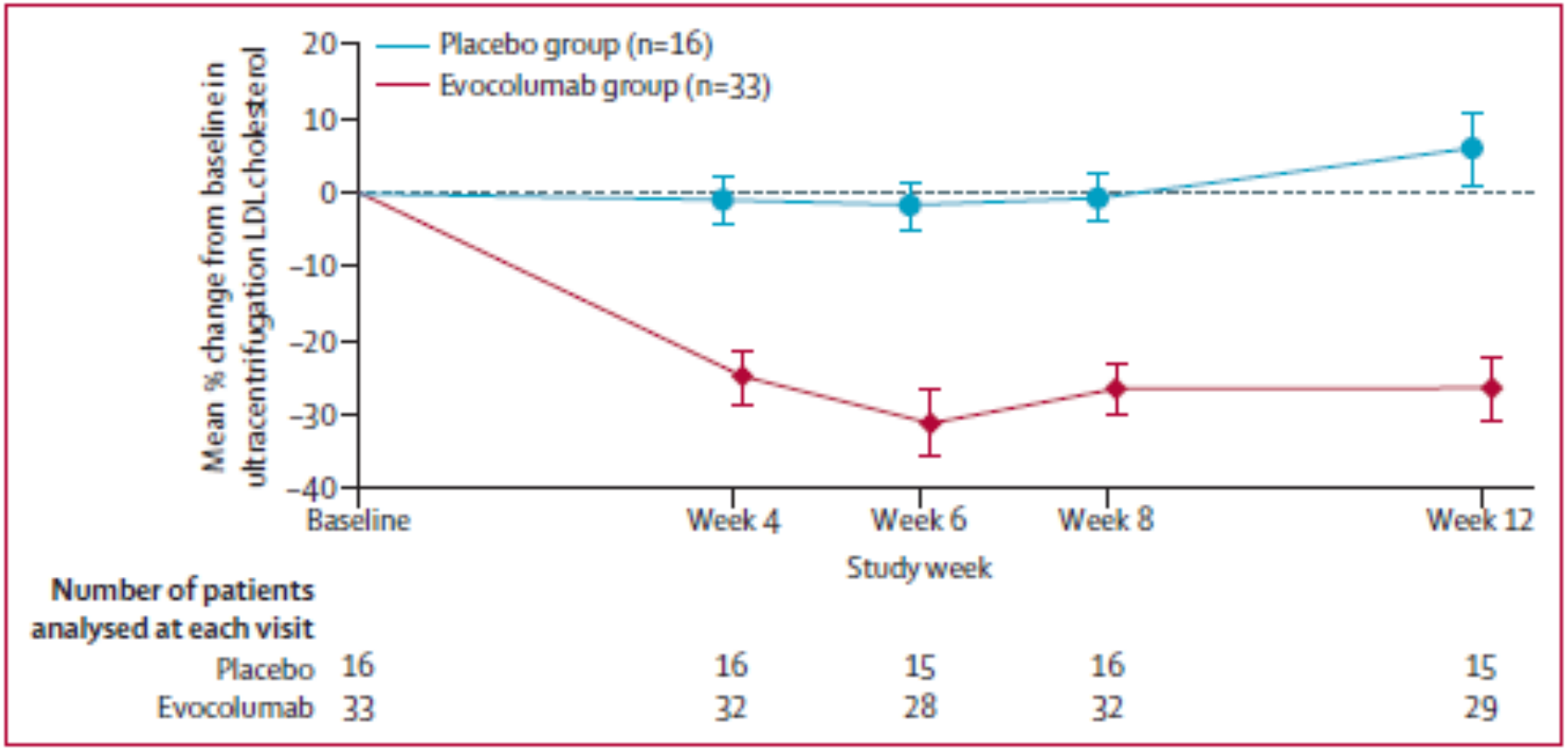
A J Hooper,Circ Res. 2015;116:193-205

Lomitapide in HoFH : Mean percent changes



M Cuchel, Lancet 2013,381

Evocolumab in HoFH: Mean percentage change in LDL-C from baseline to week 12



F J Raal,Lancet 2015; 385: 341–50

sitosterolemia

- Sitosterolemia:
  - ↑serum plant sterol levels
  - Mutation in ABCG5/ABCG8
  - Premature atherosclerosis and xanthomas
- Treatment with ezetimibe:
  - 40-50% reduction of sitosterol and campesterol levels
  - Safe and well tolerated

LYSOSOMAL ACID LIPASE DEFICIENCY

Affect cholesterol esters hydrolisis

Main signs: lipid and transaminases increases

Outcome: liver fibrosis, atherosclerosis

Onset: since childhood

Effects of Sebelipase Alfa on Levels of Alanine Aminotransferase (ALT) and LDL-C

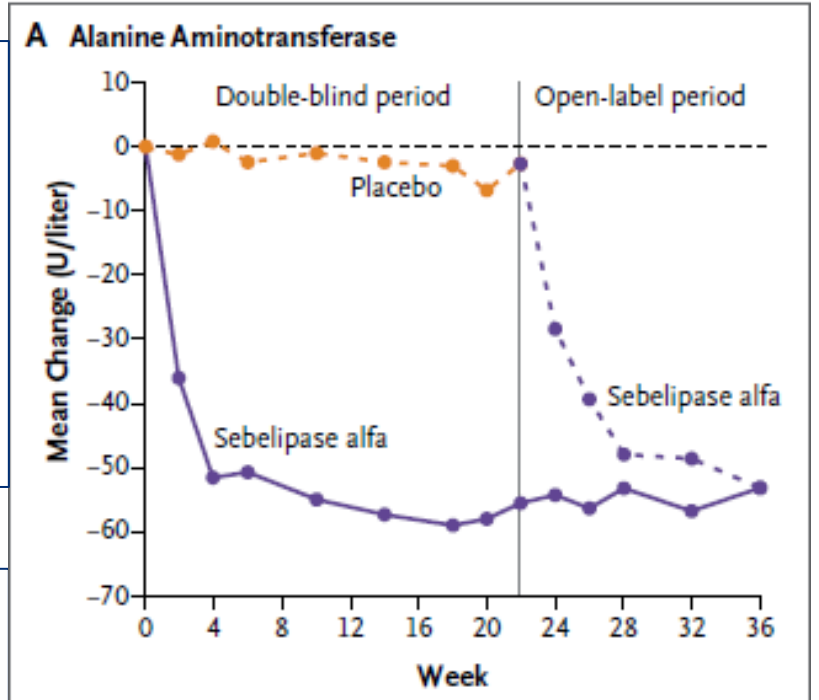
multicenter, randomized, double-blind, placebo-controlled study.

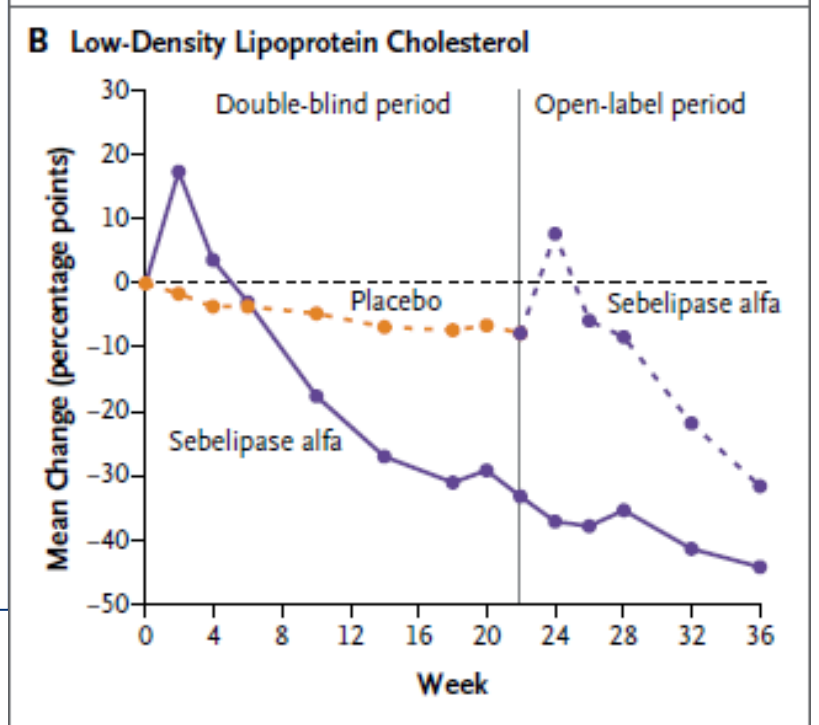
66 patients

therapy with sebelipase alfa (1 mg /kilogram body weight every other week).

Primary end point: normalization of the alanine aminotransferase level (ALT).

Secondary end points included additional disease-related efficacy assessments, safety, and side-effect profile





B.Burton, NEJM 2015

ANSWERS

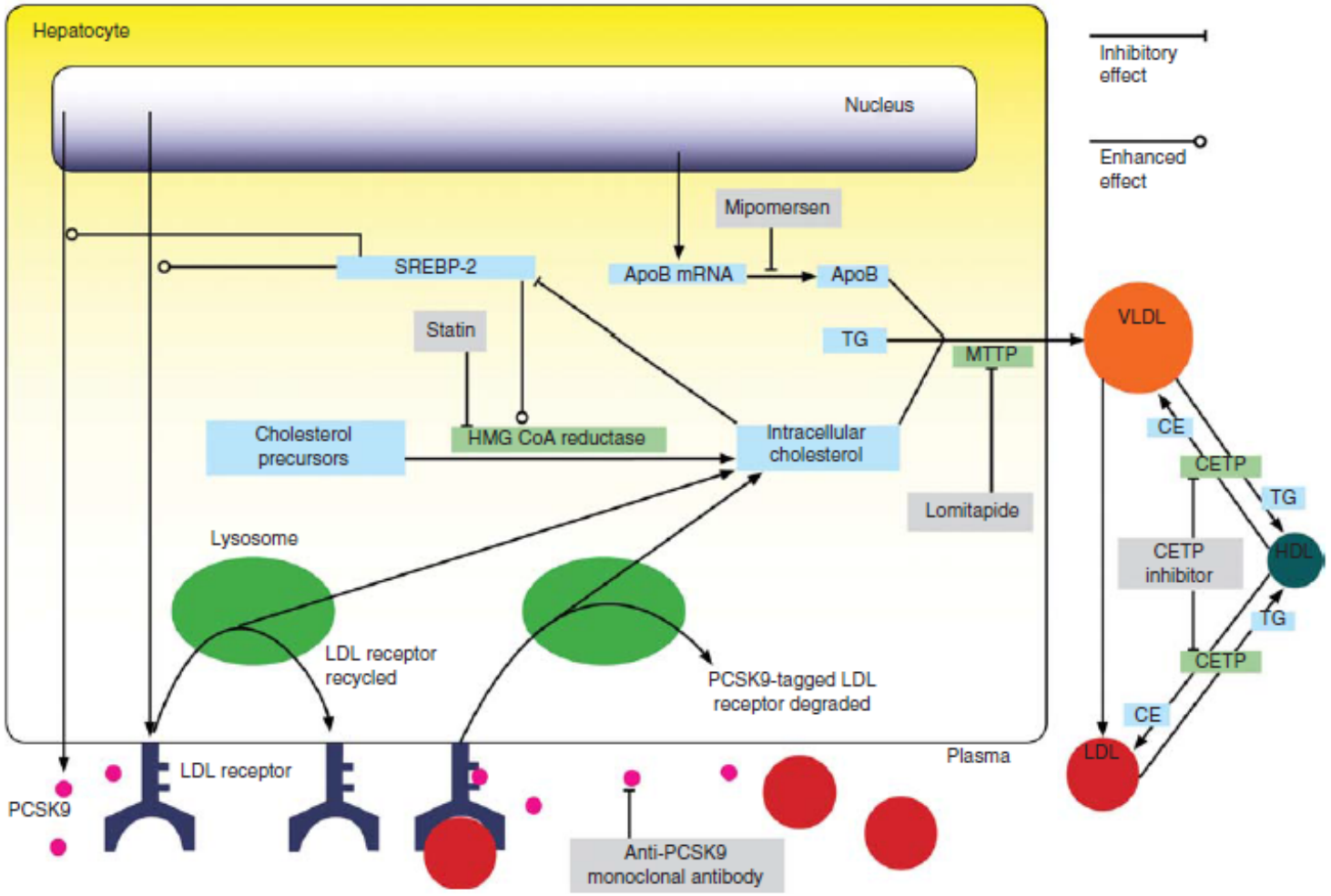
- **Why children?** NEVER TO LATE
- **Which children?** AT HIGH RISK OR SYMPTOMATIC
- **Diagnosis** AS EARLY AS POSSIBLE
- **Treatment** PERSONALIZED

Monogenic Hypercholesterolemia

THE YOUNGER THE BETTER

Jessica Rodenburg, Circulation 2007

sites of action of lipoprotein-lowering drugs



M M page,Expert Opin. Emerging Drugs (2015)

Diagnostic definition of homozygous familial hypercholesterolemia

- Genetic confirmation of 2 mutant alleles at the LDL receptor, APOB, PCSK9, or ARH adaptor protein gene locus

OR

- An untreated LDL cholesterol of 13 mmol/L (>500 mg/dL) or treated LDL cholesterol 7.76 mmol/L (≥300 mg/dL) or treated non-HDL cholesterol 8.5 mmol/L (≥330 mg/dL) together with either:

  - Cutaneous or tendonous xanthoma before age 10 years

  OR

  - Elevated LDL cholesterol levels before lipid-lowering therapy consistent with heterozygous FH in both parents*

Raal FJ, Santos RD. *Atherosclerosis* 2012; in press

MTP inhibitors: lomitapide

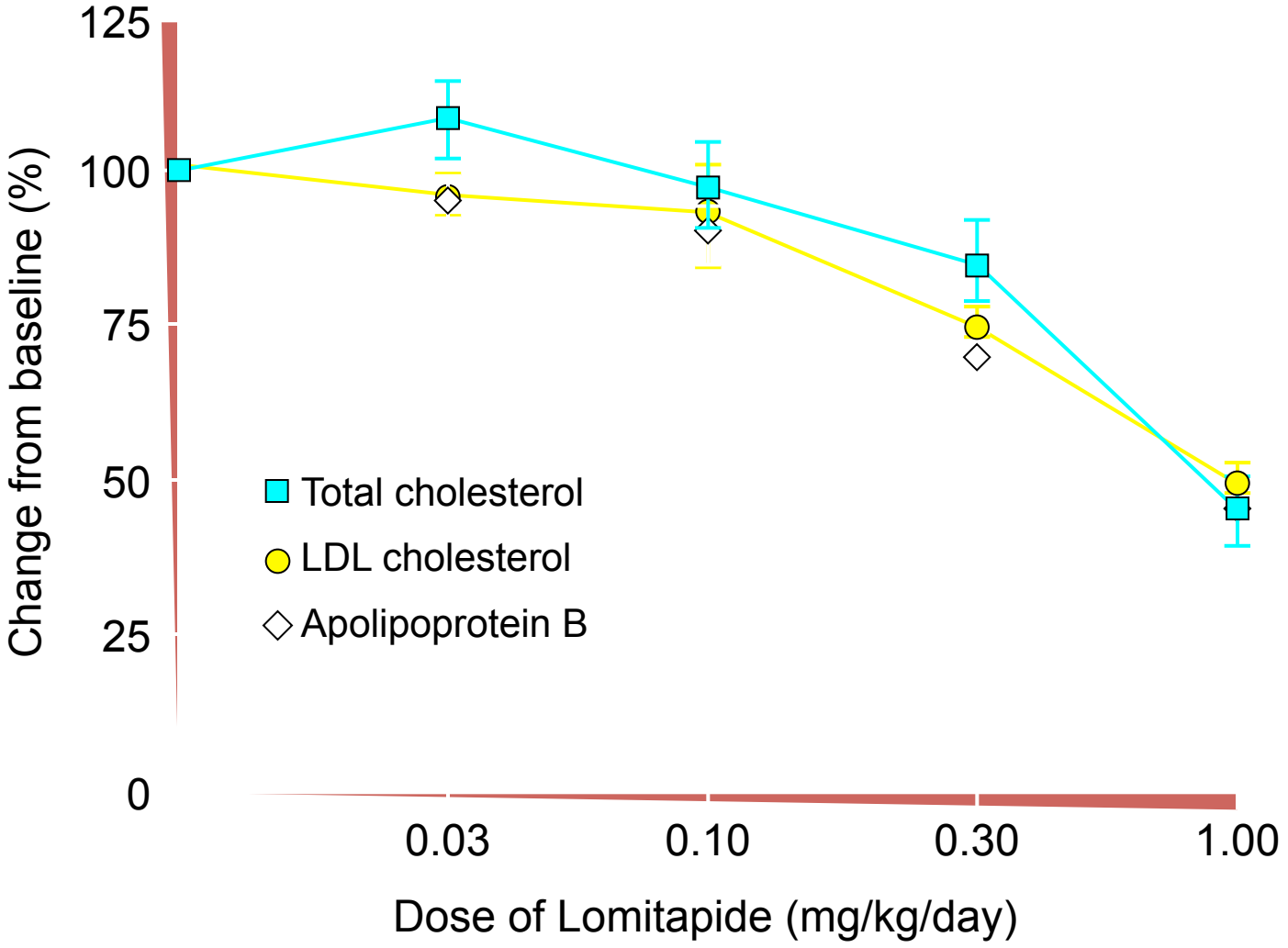
- Inhibition of microsomal triglyceride transfer protein which transfers triglycerides into VLDL and chylomicrons in hepatocytes and enterocytes
- Heterozygous FH:
  - LDL-C ↓ up to 50.9% from baseline
  - ApoB ↓ up to 55.6% from baseline
- Homozygous FH:
  - LDL-C ↓ 50% from baseline
  - ApoB ↓ 49% from baseline
  - Lp(a) -15-19%; no significant change after 78 weeks of treatment
- Approved by US and EMA for homozygous FH patients

MTP Inhibitors e.g. Lomitapide

Problems are:

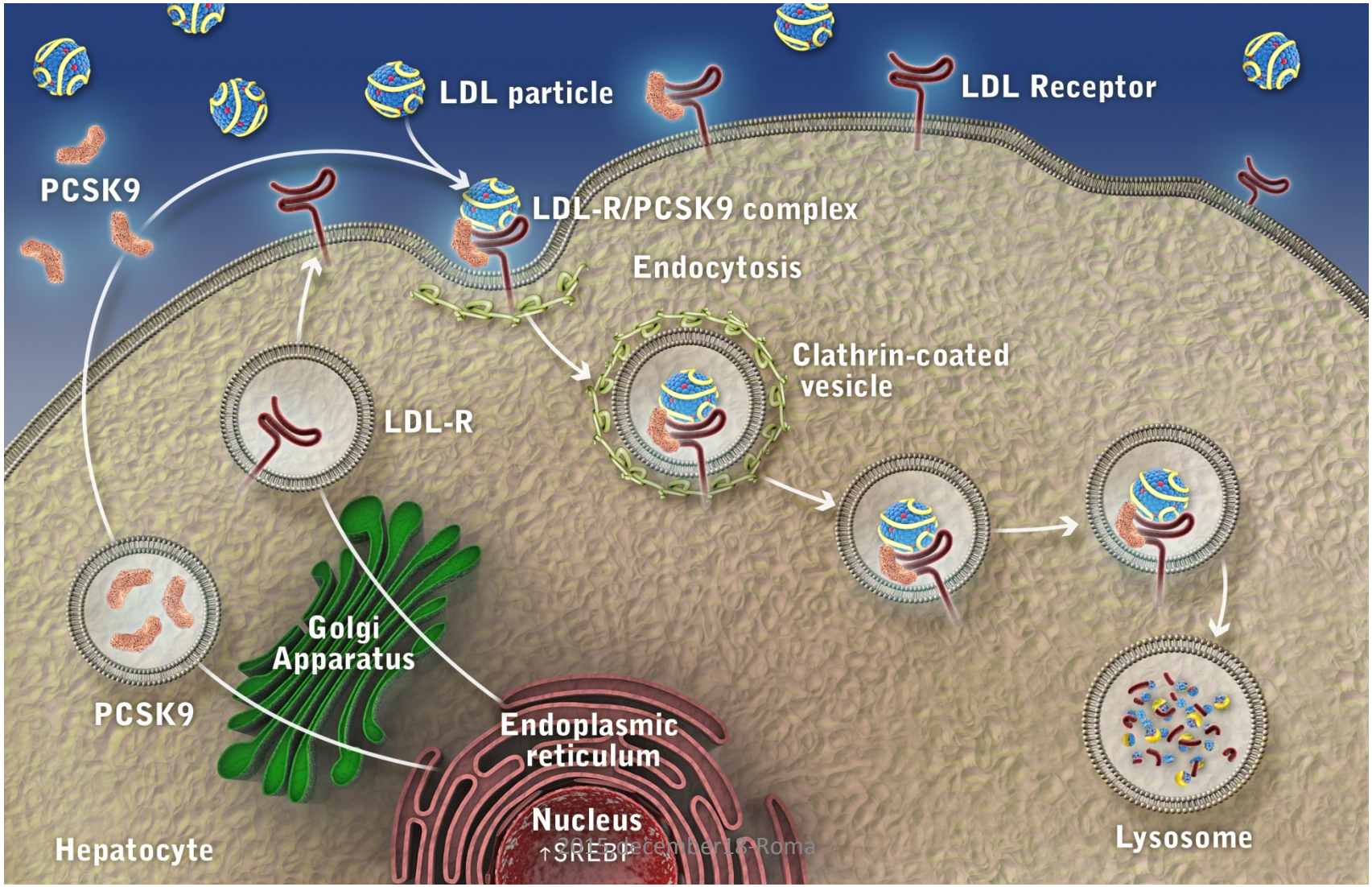
- Narrow therapeutic range, unlike statins
- Hepatic steatosis
- ? Vitamin E malabsorbtion – increased lipid oxidation
- GIT side effects – malabsorbtion, diarrhoea

Mean percent change from baseline levels of total Cholesterol, LDL Cholesterol and Apolipoprotein B after receipt of four doses of Lomitapide, each for 4 weeks



Cuchel M. *N Engl J Med* 2007;356:148-56

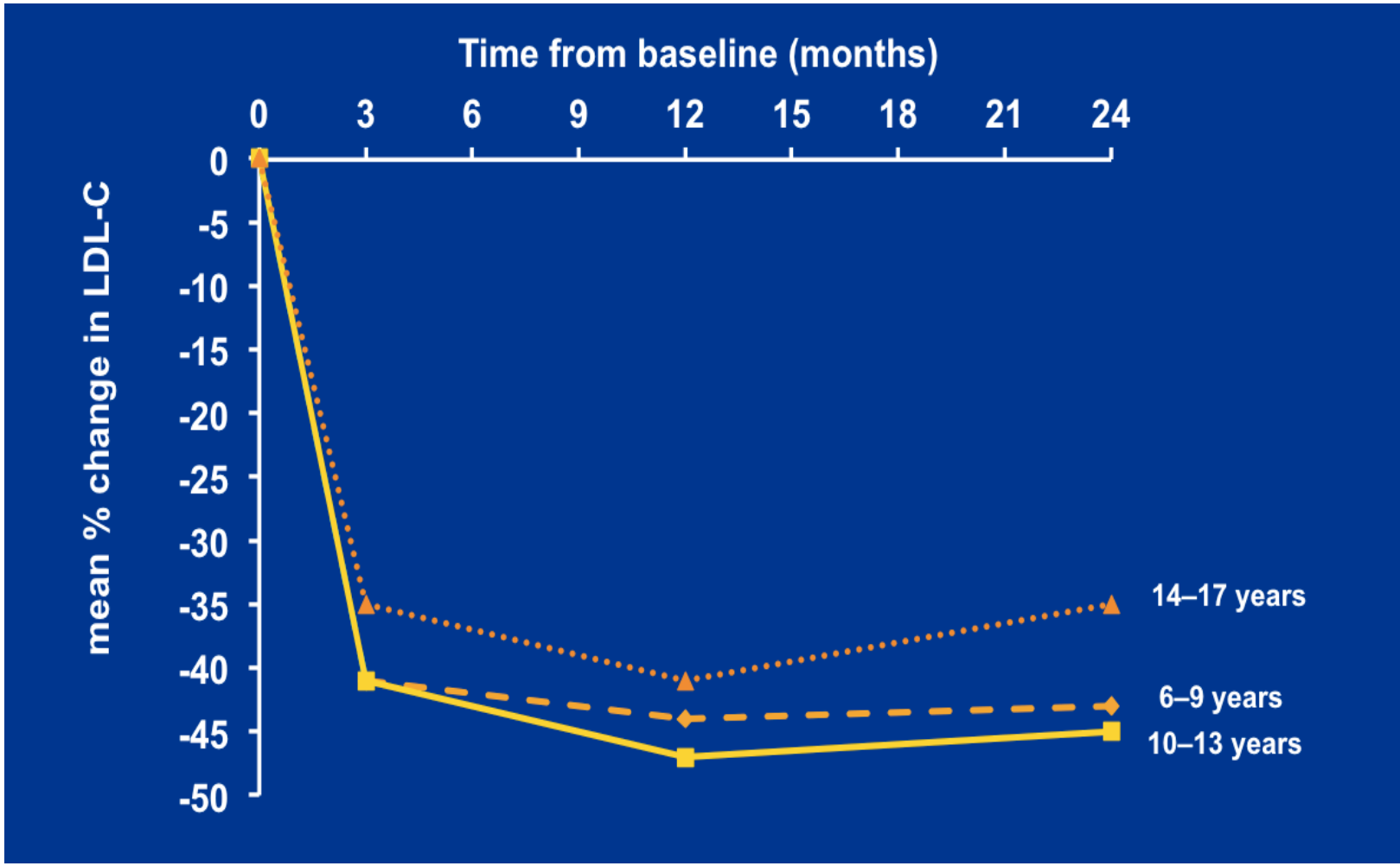
PCSK9 inhibitors



PCSK9 inhibitors

- Inhibition of proprotein convertase subtilisin/kexin type 9, that promotes the lysosomal degradation of the LDLR within hepatocytes
- Heterozygous FH:
  - LDL-C ↓ 61% relative to placebo
  - ApoB ↓ 49% relative to placebo
  - Lp(a) ↓ 32% relative to placebo
- Homozygous FH
  - LDL-C ↓ 32% relative to placebo
  - ApoB ↓ 23% relative to placebo
  - Lp(a) ↓ 12% relative to placebo
- Phase III

Significant change in LDL-C from baseline in all age groups



Ezetimibe in children

- Registered from the age of 10 years
- Kusters DM, J Pediatrics, 2015:
  - Randomized, double blind placebo-controlled trial children 6-10 years of age
  - Mean LDL-C reduction 27%
  - Safe, well tolerated

Ezetimibe in children

- Attractive in children:
  - Low peripheral blood concentrations
  - Limited side effects, palatable tablet

- Significant lipid lowering
- Well tolerated
- Action beyond lipid-lowering?

Heterozygous vs Homozygous FH

Heterozygous FH	Homozygous FH
Prevalence 1: 500	Prevalence 1: 1000 000
One LDL Receptor defective	Both LDL Receptors defective
Plasma Cholesterol 7.0-16 mmol/L (270 – 620 mg/dL)	Plasma Cholesterol 14-28 mmol/L (540 – 1080 mg/dL)
CHD onset usually 30-60 years	CHD onset in childhood
Most patients respond to drug therapy, but individual response quite variable	Poorly responsive to drugs