Pediatric Familial Hypercholesterolemia
State of the art

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The MIGHTY MEDIC
Global Scientific Society

12th Lipid Club
and Therapeutic Apheresis 2017

May 3-4, 2017 Rome
Istituto Salesiano Sacro Cuore

Virchow's Arch. f. path. Anat., **1889**, Volume 116, Issue 1, pp 85-92

Ueber Xanthoma multiplex planum, tuberosum, mollusciforme.

Lehzen G, Knauss K.; Würzburg, Germany

11 yrs. girl: yellow spots and knots and various parts of the body

- **Diagnosis:**
  Xanthoma multiplex planum et tuberosum et en tumeurs, insufficientia valvulae mitralis, possibly caused by Xanthoma endocardii
  similar to "**Xanthoma endocardii**" (described by Prof. Leube on 8th Nov. 1887)

- **Exact description:**
  Yellow tumors on knees, hands and Achilles tendon

- **Therapy:** surgical removal of most of the xanthomas
  10 weeks later: exitus

- **Pathological findings:**
  Aorta: massive fat containing tissue, **Aortenstenosis**
  Pulmonalis: yellow elevations
  Arterial plaques like Xanthomas
  A. carotid sinistra: occluded
  Mitralis: Xanthomaplaques
  Both coronary arteries: multiple yellow elevations

No blood tests!

Sister: 9 years
Similar findings on knew, hands, Achilles Tendon (like chestnuts)
Conclusion: "it is utmost important to examine the heart and the peripheral arteries very carefully by auscultation

Beitrag zur klinischen Chirurgie 90:168, **1914**

Ueber Xanthoma der Haut und der Sehnen.

Hoessli, H.

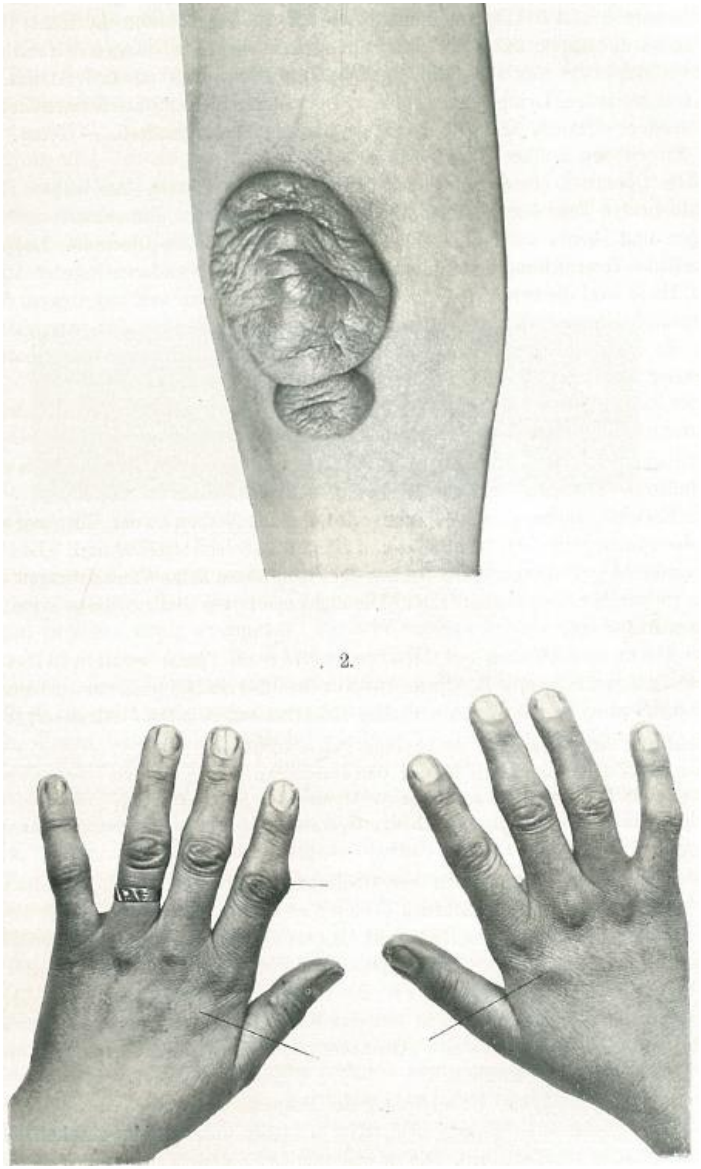
Woman 27 yrs.

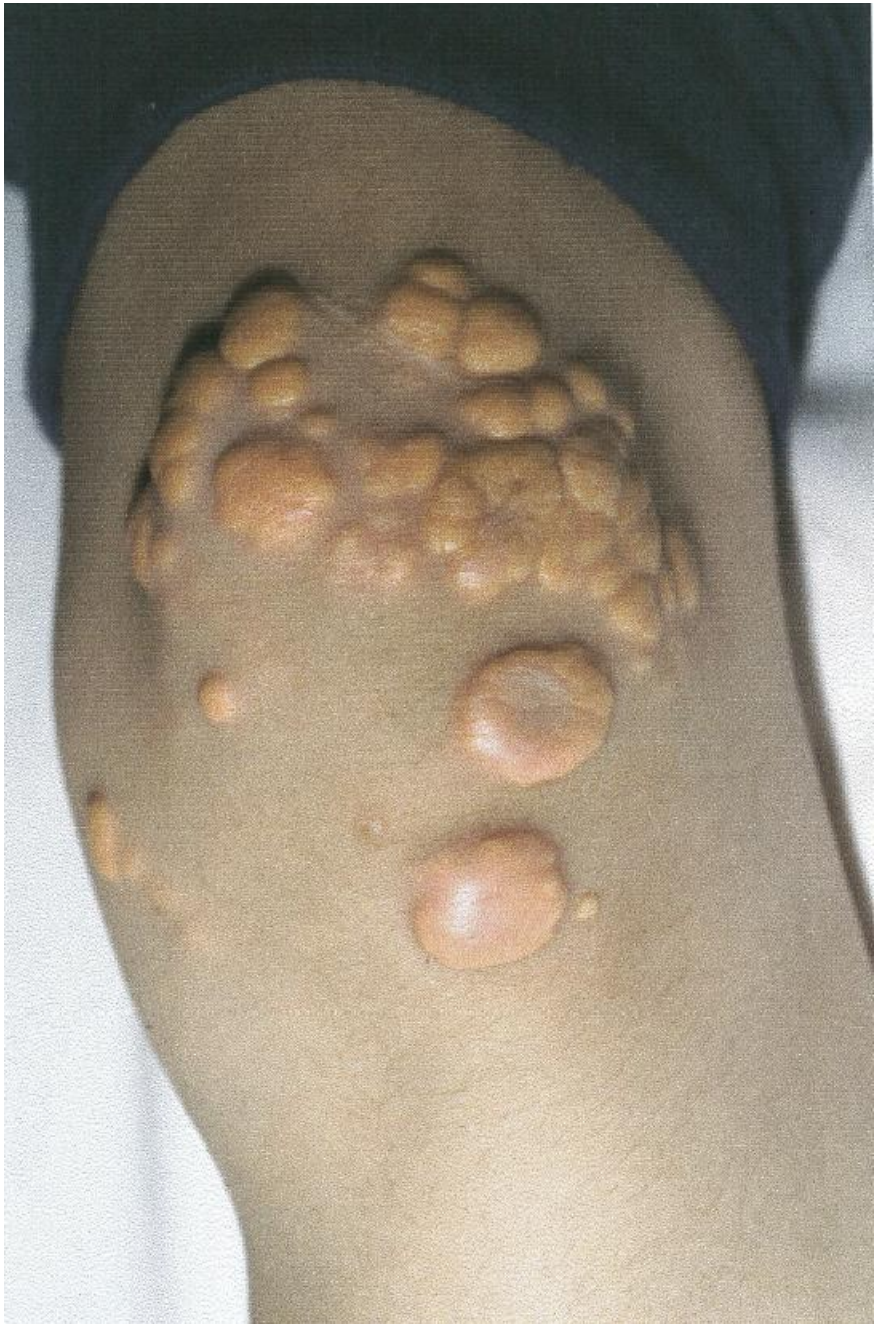
Xanthoma

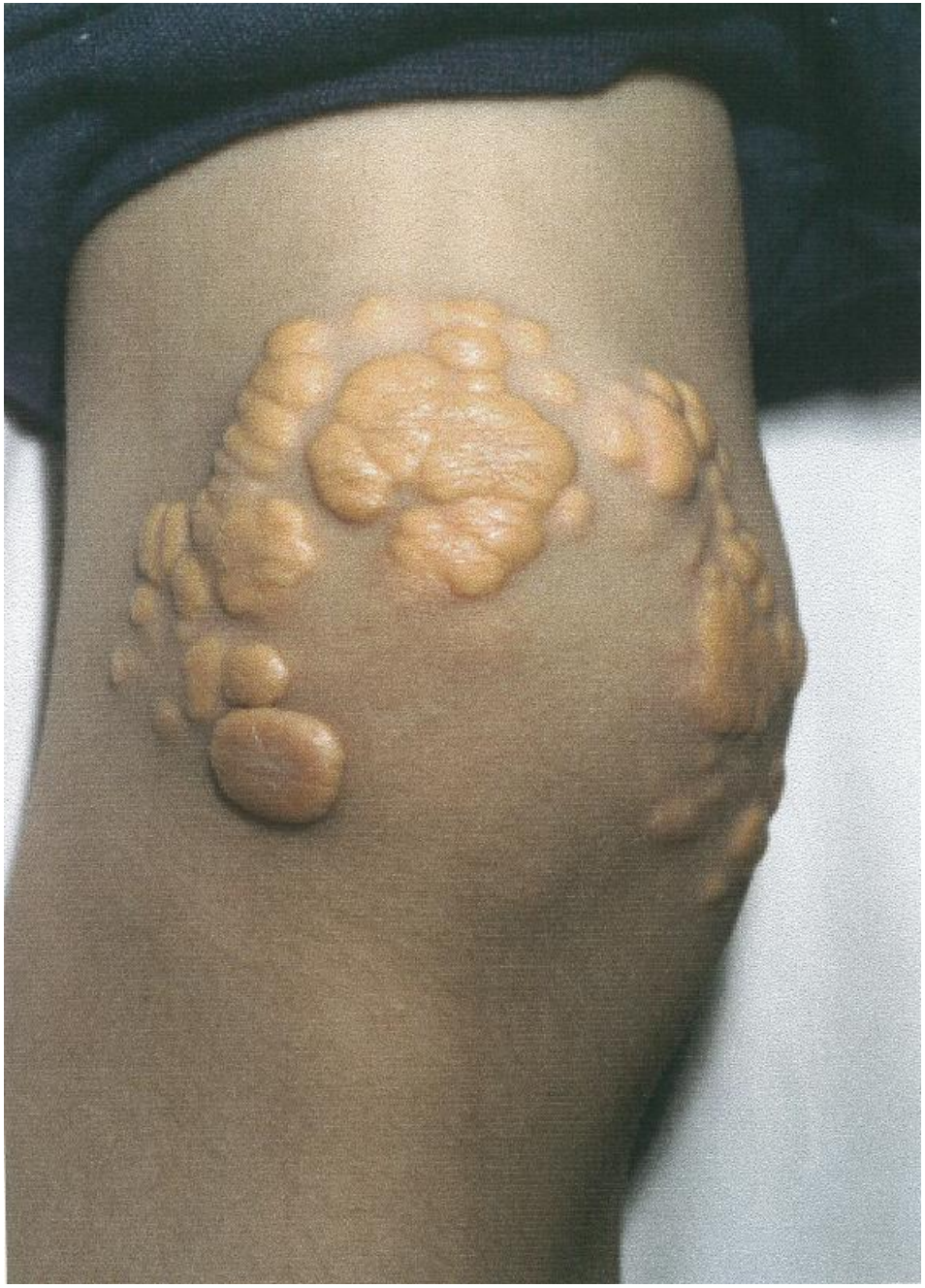
Cholestearin in the blood

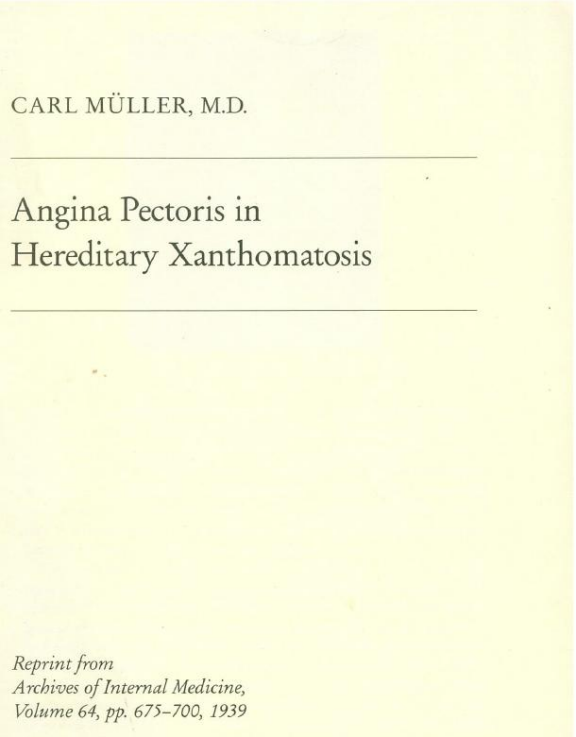
0,58 % = **580 mg/dl**

First description of hypercholesterolemia








CARL MÜLLER, M.D.

Angina Pectoris in
Hereditary Xanthomatosis

Reprint from
Archives of Internal Medicine,
Volume 64, pp. 675–700, 1939

Professor Carl Müller, 1886 – 1983, received his M. D. at the Medical Faculty, University of Oslo, in 1910.

His Doctoral Thesis on blood pressure measurements was published in 1922. From 1927 he was Physician in Chief at the Medical Division VIII, Oslo Community Hospital, and in 1951 Professor in Medicine at the University of Oslo.

He retired in 1956, but he was active in private practice close up to his death in 1983, 97 years of age.

Professor Carl Müller presented his work **on Familial Hypercholesterolemia in 1937** at the Nordic Congress for Internal Medicine in Helsinki.

Families with Xanthoma Tuberosum and Angina Pectoris, Eventually Also Palpebral Xanthelasma.—FAMILY 1 (fig. 9).—A man (case 1) aged 45, an office worker, was admitted on April 13, 1937. When about 30 years old he noticed

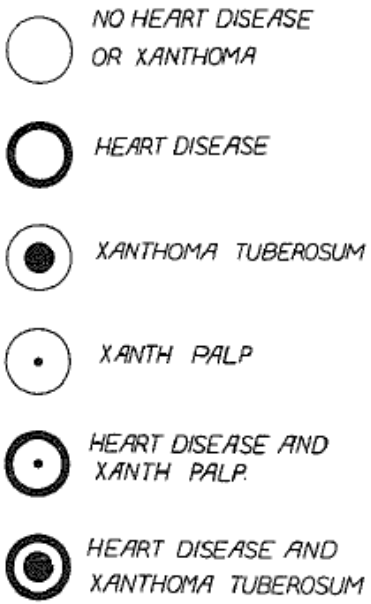


Fig. 8.—Key to the symbols employed in the following charts.

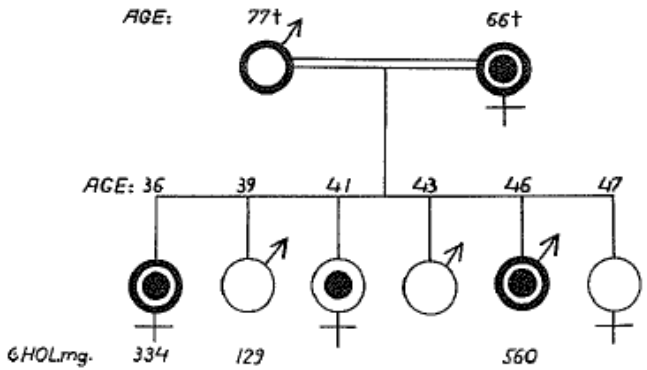


Fig. 9.—Family 1.

tender nodules on the dorsum of several fingers, on the elbows under the patellar ligament and on the achilles tendons (fig. 3). The nodules, almost symmetrically located, increased in size slowly and caused no disturbance except cosmetically. In 1932 a nodule was removed from the back of one finger, and microscopic sections revealed xanthomatous tissue. During the past ten years he had had

HISTORY OF FAMILIAL HYPERCHOLESTEROLEMIA

First description:

Müller C.: Xanthomata, hypercholesterolemia, angina pectoris.
Acta Med Scand 1938; 89 sup: 75-84

Müller C.: Angina pectoris in hereditary xanthomatosis
Arch Intern Med (Chic). 1939;64(4):675-700

LDL-Receptor:

Brown MS, Goldstein JL.: Receptor-mediated control of cholesterol metabolism.
Science. 1976 Jan 16;191(4223):150-4.

Genetics:

Goldstein JL, Dana SE, Brunschede GY, Brown MS. Genetic heterogeneity in familial hypercholesterolemia: evidence for two different mutations affecting functions of low-density lipoprotein receptor.
Proc Natl Acad Sci U S A. 1975 Mar;72(3):1092-6.

Homozygous FH:

Khachadurian AK, Uthman SM. Experiences with the homozygous cases of familial hypercholesterolemia. A report of 52 patients.
Nutr Metab. 1973;15(1):132-40.

Buja LM, Kovanen PT, Bilheimer DW. Cellular pathology of homozygous familial hypercholesterolemia.
Am J Pathol. 1979 Nov; 97(2): 327–357.

The Nobel Chronicles

1985: Joseph Leonard Goldstein (b 1940), Michael Stuart Brown (b 1941)

Two scientists shared the 1985 Nobel Prize for Physiology or Medicine for their work related to cholesterol metabolism.

Born in Sumter, South Carolina, Joseph Goldstein (figure, left) obtained his MD in 1966 from the University of Texas, Southwestern Medical School in Dallas. During an internship at Boston's Massachusetts General Hospital he met and befriended a fellow intern Michael Brown (figure, right)—a New Yorker, who had earned his MD in 1966 from the University of Pennsylvania in Philadelphia. After their respective residency training, both physicians joined the National Institutes of Health in Bethesda, Maryland, and worked as clinical associates—Goldstein in Biochemical Genetics and Brown in Digestive and Hereditary Diseases.

In 1971, Brown joined the division of gastroenterology in Southwestern Medical School in Dallas. The following year, Goldstein also moved to his alma mater and became the head of the new Division of Medical Genetics. These scientists began collaborative research almost immediately, studying patients with familial hypercholesterolaemia (FH). They combined their laboratories in 1974.

The Nobel Foundation

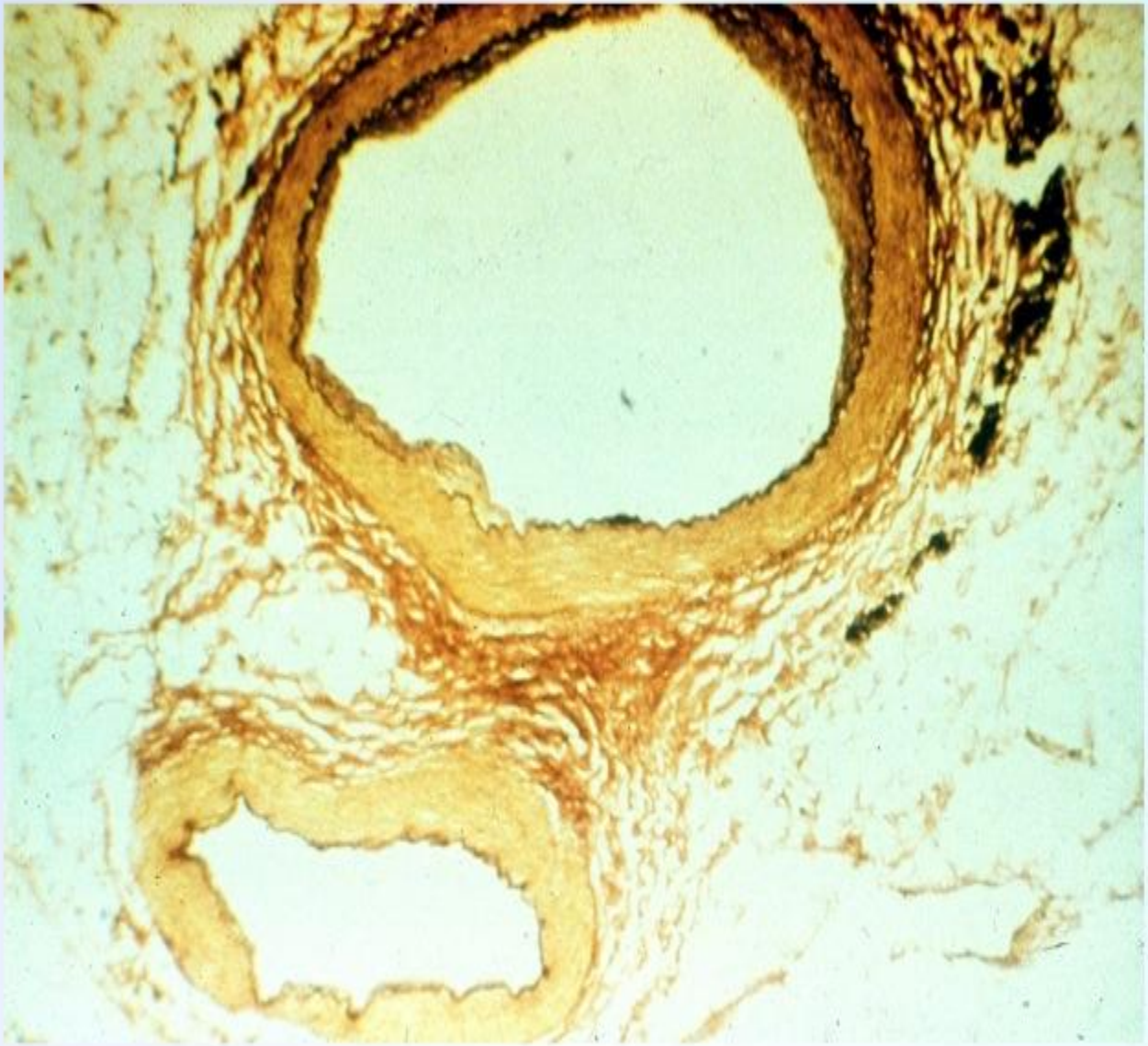
In 1973, Brown, Goldstein, and co-workers discovered that in homozygous FH patients the uptake of low-density lipoproteins (LDL) was markedly deficient, while it was moderately deficient in heterozygous patients. They hypothesised that the defect in LDL uptake was due to the deficiency of receptors on the cell surface, secondary to single-gene mutation. In 1976, the team reported localising the LDL receptors; they were the "coated pits" on cell surfaces, which were deficient or non-existent in FH patients.

Brown and Goldstein proposed that LDL uptake and internalisation occurred through the process of receptor-mediated endocytosis, thereby modulating cholesterol synthesis. In the late 1980s, the human LDL- receptor gene was sequenced and shown to be a mosaic of many exons (domains). Similarly, several mutations were found for the LDL-receptor gene.

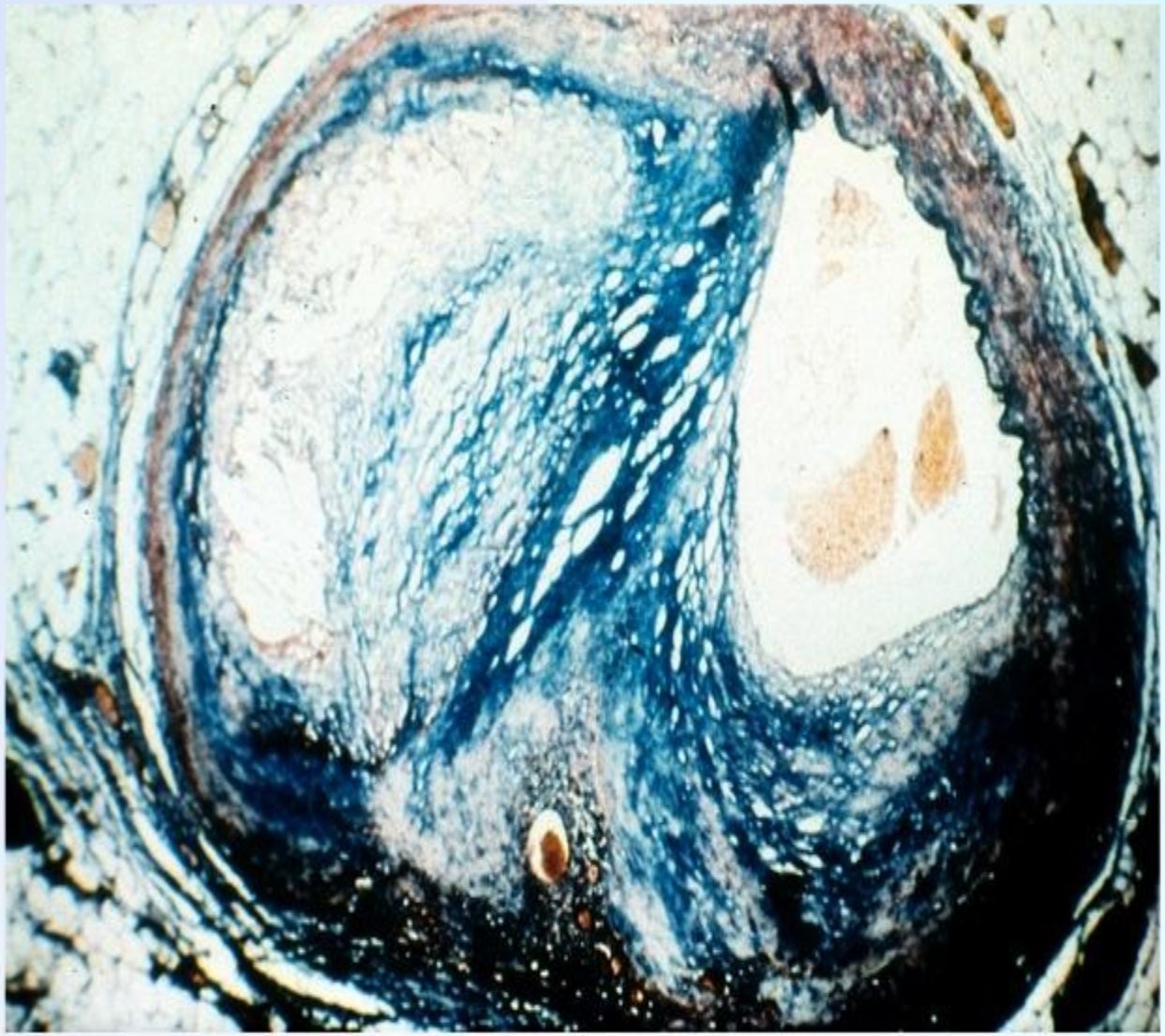
The discovery of the LDL receptors by Brown and Goldstein was a milestone in cholesterol research. Beside helping patients with FH, an understanding of how normal cells handle lipids, cholesterol, and related molecules was pivotal in exploring the intricate link between lipids and atherosclerosis in otherwise normal individuals.

Tonse N K Raju
University of Illinois, Chicago, IL, USA

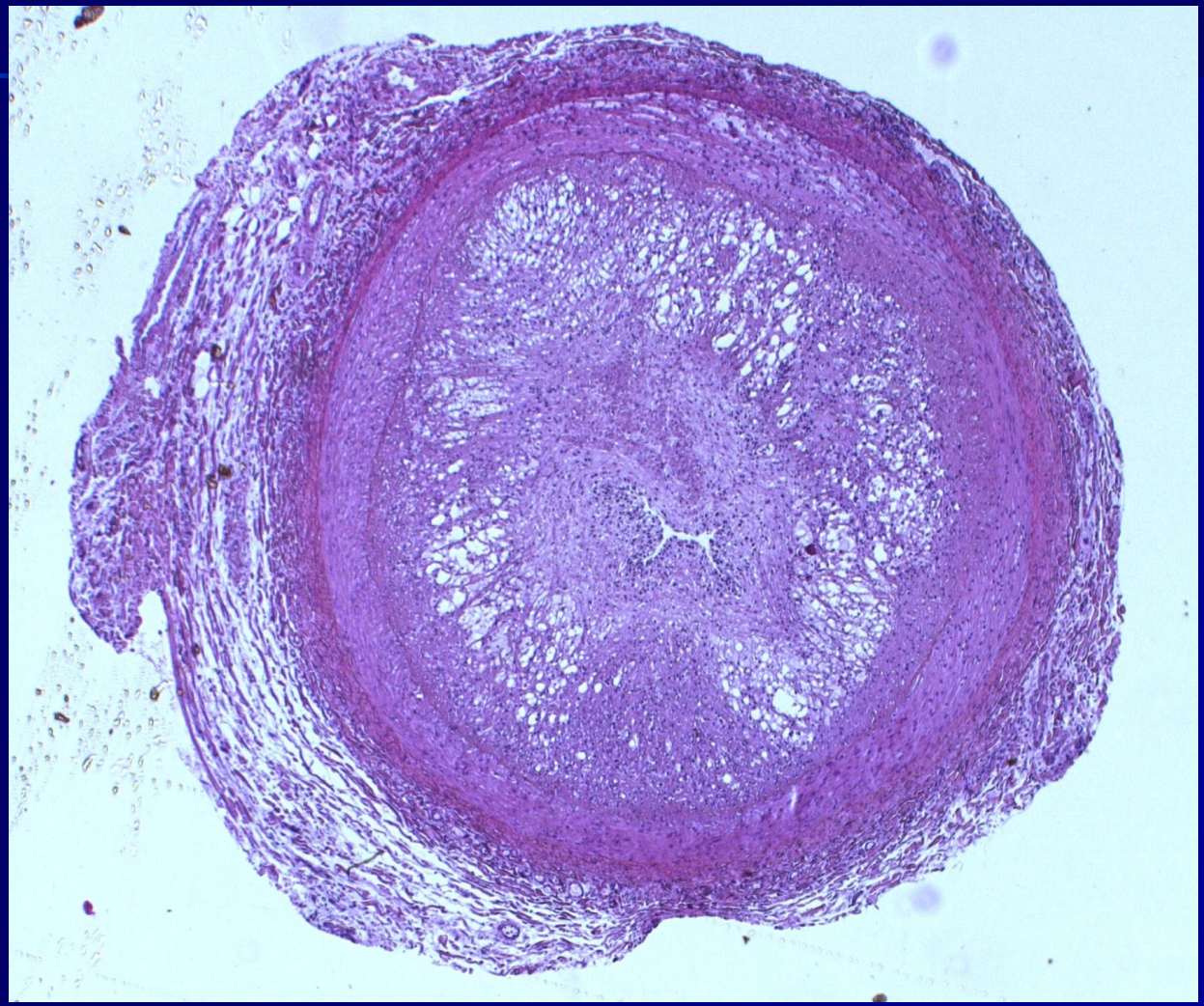
Coronary artery of a newborn



Coronary artery of a 40-year-old man (died due to heart attack, carrier of FH)



Ramus interventricularis anterior of a 4,5 yrs old patient with homoz. FH

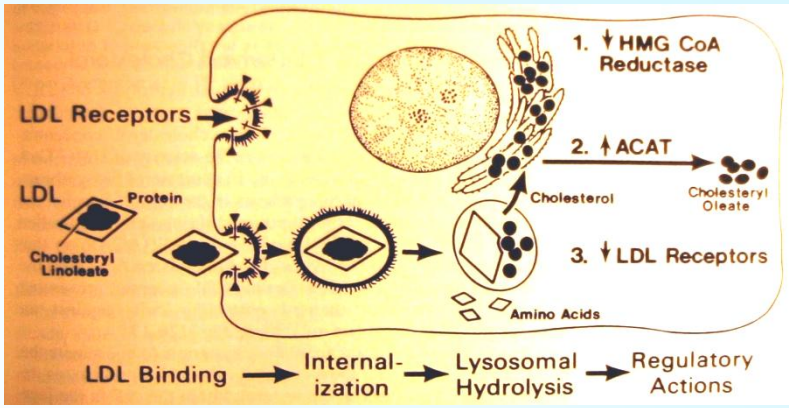


K.Widhalm et al, Journal Pediatrics 2010 July 24

HYPERLIPOPROTEINEMIAS IN CHILDHOOD

DIAGNOSIS and TREATMENT

1. FAM. HYPERCHOLESTEROLEMIA:
   - Diagnostic-Criteria
     LDL - C ↑(> 155mg/dl),
     Ges.-Chol.↑(>220mg/dl), FA
     (MED - PED 1996)

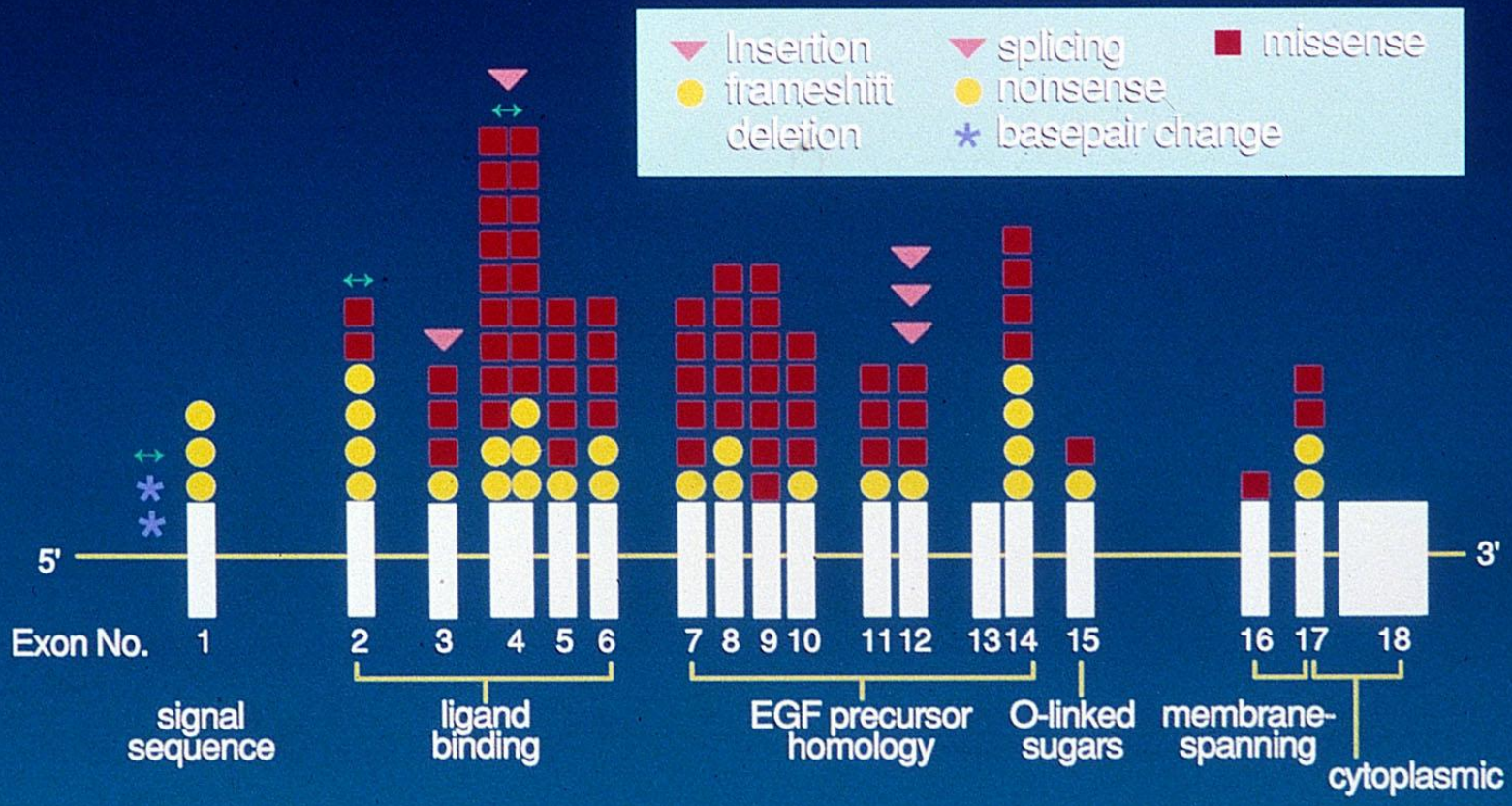


   - Molecular-technique: LDL-Receptor-Gene-Mutations

2. APO-B- 100 - DEFECT :
   - Gene-technology

3. FAM. COMB. HYPERLIPIDEMIA (FCH) :
   - Clinics/Laboratory: Family-testing, VLDL -Apo B ↑

Mutations in the LDL-Receptor Gene Causing FH



Hobbs et al. Human Mutation 1992; 1:446

Table I **Dutch Lipid Clinic Network criteria for diagnosis of heterozygous familial hypercholesterolaemia in adults**

Group 1: family history	Points
(i) First-degree relative with known premature (<55 years, men; <60 years, women) coronary heart disease (CHD) OR	1
(ii) First-degree relative with known LDL cholesterol >95th percentile by age and gender for country	1
(iii) First-degree relative with tendon xanthoma and/or corneal arcus OR	2
(iv) Child(ren) <18 years with LDL cholesterol >95th percentile by age and gender for country	2
Group 2: clinical history	
(i) Subject has premature (<55 years, men; <60 years, women) CHD	2
(ii) Subject has premature (<55 years, men; <60 years, women) cerebral or peripheral vascular disease	1
Group 3: physical examination	
(i) Tendon xanthoma	6
(ii) Corneal arcus in a person <45 years	4
Group 4: biochemical results (LDL cholesterol)	
>8.5 mmol/L (>325 mg/dL)	8
6.5–8.4 mmol/L (251–325 mg/dL)	5
5.0–6.4 mmol/L (191–250 mg/dL)	3
4.0–4.9 mmol/L (155–190 mg/dL)	1
Group 5: molecular genetic testing (DNA analysis)	
(i) Causative mutation shown in the *LDLR*, *APOB*, or *PCSK9* genes	8

A 'definite FH' diagnosis can be made if the subject scores >8 points. A 'probable FH' diagnosis can be made if the subject scores 6 to 8 points. A 'possible FH' diagnosis can be made if the subject scores 3 to 5 points. An 'unlikely FH' diagnosis can be made if the subject scores 0 to 2 points. Use of the diagnostic algorithm: per group only one score, the highest applicable, can be chosen. For example, when coronary heart disease and tendon xanthoma as well as dyslipidaemia are present in a family, the highest score for family history is 2. However, if persons with elevated LDL cholesterol levels as well as premature coronary heart disease are present in a family, but no xanthoma or children with elevated LDL cholesterol levels or a causative mutation are found, then the highest score for family history remains 1.

European Heart Journal (2013)34, 3478–3490 doi:10.1093/eurheartj/eht273

Clinical vs. Mutation diagnosis

Detection of mutations in

LDL-R
Apo B-
PCSK9-
LDL RAP-

} gene is possible and in many countries available

However: 10 – 15 % who meet the clinical criteria will not have a detectable causal mutation

Table IV. Characteristics of molecularly diagnosed children with FH

Characteristics	LDLR+ children n = 39	LDLR− children n = 39	P LDLR+ vs LDLR− children
Age (y)	8.4 ± 4.0	8.5 ± 3.5	Ns
Range	2-18	2-18	
Sex			
Male, n (%)	17 (42.1)	17 (45.0)	Ns
Female, n (%)	22 (57.9)	22 (55.0)	
BMI (kg/m^2)	17.6 ± 3.7	19.0 ± 3.8	Ns
TC (mg/dL)	278.7 ± 55.3	254.1 ± 43.1	.029
HDL-C (mg/dL)	48.7 ± 13.6	55.4 ± 13.3	Ns
TG (mg/dL)	81.5 ± 35.4	85.9 ± 37.4	Ns
LDL-C (mg/dL)	213.6 ± 52.9	181.7 ± 54.0	.002
ApoB (mg/dL)	131.6 ± 38.3	100.3 ± 30.2	.004
ApoAI (mg/dL)	133.0 ± 32.0	149.8 ± 25.7	Ns
Blood glucose (mg/dL)	79.6 ± 9.5	79.5 ± 11.2	Ns
Insulin (U/L)	6.9 ± 3.8	10.0 ± 5.6	.026
Family history of			
Dyslipidemia, n (%)	35 (89.7)	30 (76.9)	Ns
Hypertension, n (%)	20 (52.6)	23 (57.5)	Ns
Diabetes, n (%)	9 (31.0)	20 (69.0)	.018
MI, n (%)	21 (56.8)	16 (43.2)	Ns

ApoAI, Apolipoprotein AI; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; Ns, nonsignificant.

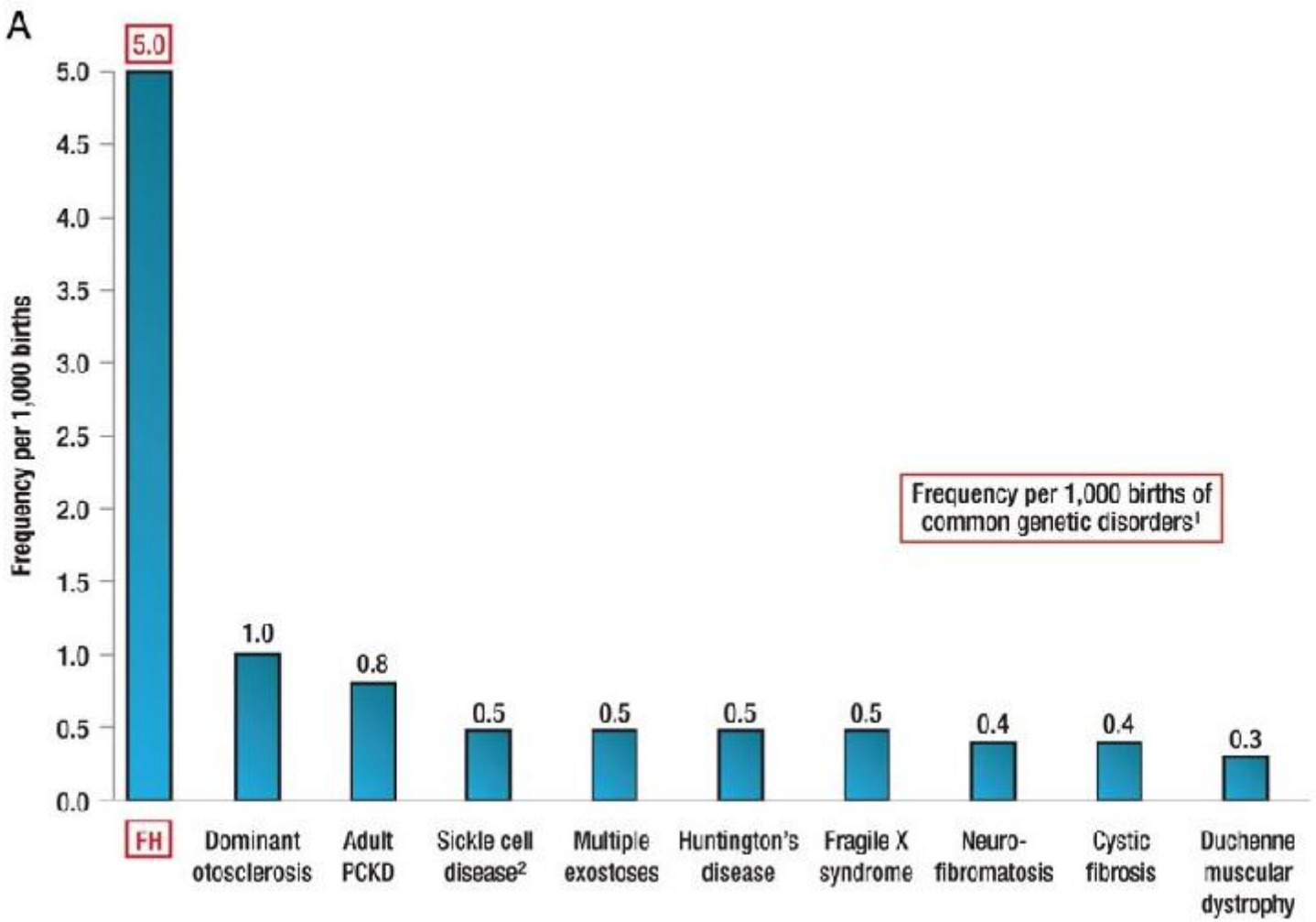
J Pediatr. 2017 Apr;183:100-107.e3. doi: 10.1016/j.jpeds.2016.12.075.

Table V. The ability of Dutch Lipid Clinic Network, EAS, and Simon Broome Register Group criteria to predict the results of the molecular genetic analysis of the LDL receptor gene mutation

	Sensitivity (%)	Mutation detection rate (%)	Specificity (%)	1-specificity (%) = false positive rate
DLCN scores				
Definite or probable or possible FH (DLCN >3)	100.0	58.2	28.2	71.8
Definite or probable FH (DLCN >6)	48.7	82.6	89.7	10.3
Definite FH (DLCN >8)	0.05	100.0	100.0	0
EAS criteria				
LDL-C >160 mg/dL AND family history of CVD ± baseline high cholesterol in 1 parent or LDL-C >190 mg/dL, 2 successive occasion over 3 mo	74.4	63.0	56.4	84.6
LDL-C > 190 mg/dL, 2 successive occasion over 3 mo	64.1	69.4	71.8	28.2
Simon Broome criteria				
Definite FH	0.0	0.0	0.0	1.0
Probable FH or definite FH	2.5	53.5	84.6	15.4
Our criteria				
Children with LDL-C >190 mg/dL and at least 1 parent with LDL-C >95th and TG <75th and/or a parent with premature CHD	64.1	69.4	71.8	28.2

CHD, coronary heart disease; CVD, coronary vascular disease.

J Pediatr. 2017 Apr;183:100-107.e3. doi: 10.1016/j.jpeds.2016.12.075.



European Heart Journal (2015) 36, 2425–2437 doi:10.1093/eurheartj/ehv157

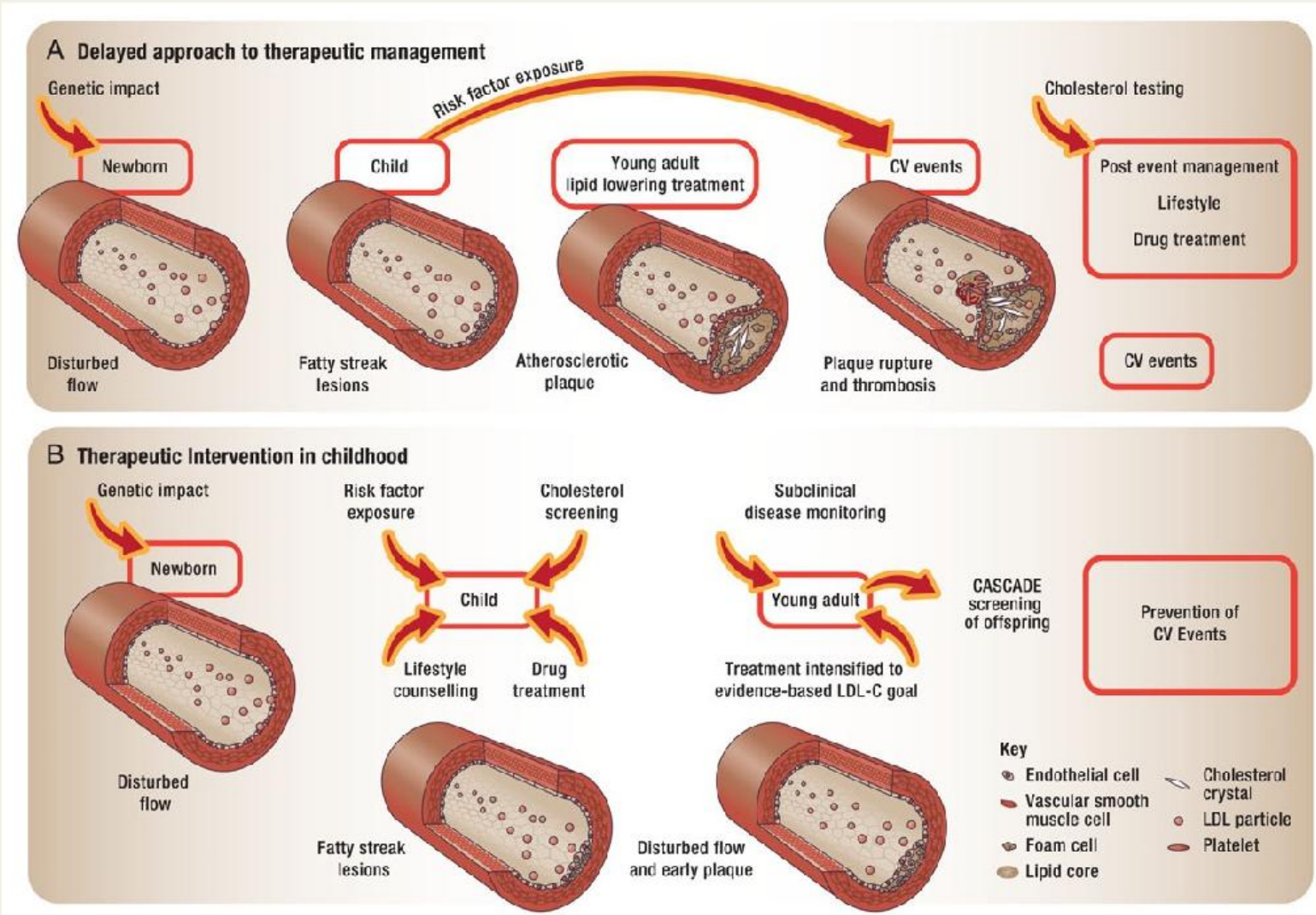
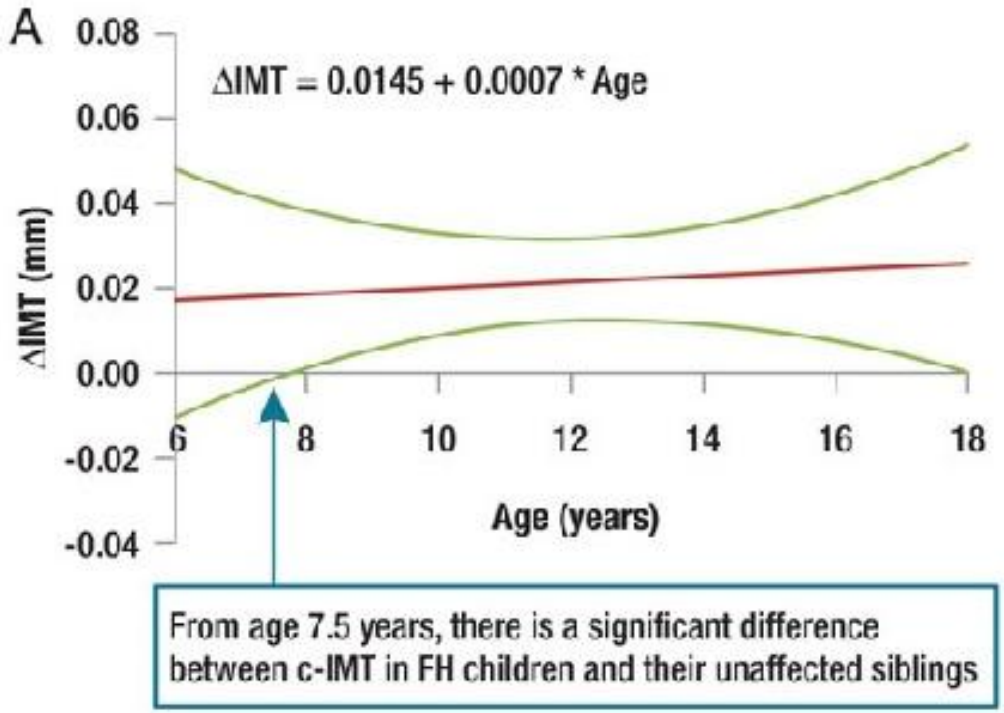


Figure 2 Development of early atherosclerotic vascular disease in familial hypercholesterolaemia showing the potential impact of early recognition and treatment on evolution of the condition. CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol.

European Heart Journal (2015) 36, 2425–2437 doi:10.1093/eurheartj/ehv157



European Heart Journal (2015) 36, 2425–2437 doi:10.1093/eurheartj/ehv157

Table 2 Diagnosis of familial hypercholesterolaemia in children and adolescents

- Family history of premature CHD plus high LDL-C) levels are the two key selective screening criteria: (F + H = FH).[a]
- Cholesterol testing should be used to make a phenotypic diagnosis.
- An LDL-C level ≥5 mmol/L (190 mg/dL) on two successive occasions after 3 months diet indicates a high probability of FH. A family history of premature CHD in close relative(s) and/or baseline high cholesterol in one parent, together with an LDL-C ≥4 mmol/L (160 mg/dL) indicates a high probability of FH. If the parent has a genetic diagnosis, an LDL-C ≥3.5 mmol/L (130 mg/dL) suggests FH in the child.
- Secondary causes of hypercholesterolaemia should be ruled out.
- DNA testing establishes the diagnosis. If a pathogenic *LDLR* mutation is identified in a first-degree relative, children may also be genetically tested.
- If a parent died from CHD, a child even with moderate hypercholesterolaemia should be tested genetically for FH and inherited elevation in Lp(a).

[a]Acknowledgement to the FH Foundation (http://thefhfoundation.org/).

European Heart Journal (2015)36, 2425–2437

Table 3 Screening for familial hypercholesterolaemia in children and adolescents

- If DNA testing is available, cascade screening of families is recommended using both a phenotypic and genotypic strategy. If DNA testing is not available, a phenotypic strategy based on country, age- and gender-specific LDL-C levels should be used.
- Children with suspected HeFH should be screened from the age of 5 years; screening for HoFH should be undertaken when clinically suspected (both parents affected or xanthoma present) and as early as possible.
- Age at screening should be similar for boys and girls.
- Universal screening in childhood may also be considered.

European Heart Journal (2015)36, 2425–2437

Cardiovascular risk in relation to functionality of sequence variants in the gene coding for the low-density lipoprotein receptor: a study among 29 365 individuals tested for 64 specific low-density lipoprotein-receptor sequence variants

Roeland Huijgen[1]*, Iris Kindt[2], Joep C. Defesche[1], and John J.P. Kastelein[1]

[1]Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Room F4-159.2, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands; and [2]Foundation for the Identification of Persons with Inherited Hypercholesterolemia, Amsterdam, The Netherlands

Received 3 July 2011; revised 24 December 2011; accepted 2 February 2012

Methods and results

We assessed 29 365 individuals tested the 64 most prevalent *LDLR* variants. First, we determined pathogenicity for each of these sequence variants. Subsequently, a Cox-proportional hazard model was used to compare event-free survival, defined as the period from birth until the first CAD event, between carriers and non-carriers of *LDLR* mutations. Fifty-four sequence variants in the *LDLR* gene were labelled as pathogenic and 10 as non-pathogenic. The 9 912 carriers of a pathogenic *LDLR* mutation had a shorter event-free survival than the 18 393 relatives who did not carry that mutation; hazard ratio 3.64 [95% confidence interval (CI): 3.24–4.08; $P < 0.001$]. In contrast, the 355 carriers of a non-pathogenic *LDLR* variant had similar event-free survival as the 705 non-carrying relatives; hazard ratio 1.00 (95% CI: 0.52–1.94; $P = 0.999$).

Conclusion

These findings with respect to clinical outcomes substantiate our criteria for functionality of *LDLR* sequence variants. They also confirm the CAD risk associated with FH and underline that these criteria can be used to decide whether a specific sequence variant should be used in cascade screening.

LETTER TO JMG

Genetic causes of familial hypercholesterolaemia in patients in the UK: relation to plasma lipid levels and coronary heart disease risk

S E Humphries, R A Whittall, C S Hubbart, S Maplebeck, J A Cooper, A K Soutar, R Naoumova, G R Thompson, M Seed, P N Durrington, J P Miller, D J B Betteridge, H A W Neil, for the Simon Broome Familial Hyperlipidaemia Register Group and Scientific Steering Committee

J Med Genet 2006;**43**:943–949. doi: 10.1136/jmg.2006.038356

Key points

- Patients with familial hypercholesterolaemia with a detectable *LDLR* mutation have a higher risk of early CHD than those in whom no mutation was detected.

84%↑

PEDIATRICS®

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

EXPERT PANEL ON INTEGRATED GUIDELINES FOR CARDIOVASCULAR HEALTH AND RISK REDUCTION IN CHILDREN AND ADOLESCENTS

Pediatrics 2011;128;S213; originally published online November 14, 2011;
DOI: 10.1542/peds.2009-2107C

TABLE 9-1 Acceptable, Borderline-High, and High Plasma Lipid, Lipoprotein, and Apolipoprotein Concentrations for Children and Adolescents

Category	Low, mg/dL[a]	Acceptable, mg/dL	Borderline-High, mg/dL	High, mg/dL[a]
TC	—	<170	170–199	≥200
LDL cholesterol	—	<110	110–129	≥130
Non-HDL cholesterol	—	<120	120–144	≥145
Apolipoprotein B	—	<90	90–109	≥110
Triglycerides				
0–9 y	—	<75	75–99	≥100
10–19 y	—	<90	90–129	≥130
HDL cholesterol	<40	>45	40–45	—
Apolipoprotein A-1	<115	>120	115–120	—

Values for plasma lipid and lipoprotein levels are from the NCEP Expert Panel on Cholesterol Levels in Children. Non-HDL cholesterol values from the Bogalusa Heart Study are equivalent to the NCEP Pediatric Panel cut points for LDL cholesterol. Values for plasma apolipoprotein B and apolipoprotein A-1 are from the National Health and Nutrition Examination Survey III. Note that values shown are in mg/dL; to convert to SI units, divide the results for TC, LDL cholesterol, HDL cholesterol, and non-HDL cholesterol by 38.6; for triglycerides, divide by 88.6.

[a] Low cut points for HDL cholesterol and apolipoprotein A-1 represent approximately the 10th percentile. The cut points for high and borderline-high represent approximately the 95th and 75th percentiles, respectively.

Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report
Pediatrics 2011; 128; S213

TABLE 9-5 Evidence-Based Recommendations for Lipid Assessment

Birth to 2 y	No lipid screening
2 to 8 y	No routine lipid screening
	Measure fasting lipid profile twice,[a] average results if: Parent, grandparent, aunt/uncle, or sibling with MI, angina, stroke, CABG/stent/angioplasty at <55 y in males, <65 y in females Parent with TC ≥ 240 mg/dL or known dyslipidemia Parent with TC ≥ 240 mg/dL or known dyslipidemia Child has diabetes, hypertension, BMI ≥ 95th percentile or smokes cigarettes Child has a moderate- or high-risk medical condition (Table 5-2)
	Use Table 9-1 for interpretation of results, algorithms in Figs 9-1 and 9-2 for management.

Pediatrics 2011;128;S213

INTERNATIONAL ATHEROSCLEROSIS SOCIETY

Lifestyle Therapies: Other Dietary Factors

- Maintain relatively high intakes of fruits, vegetables, and fiber
- Replace excess saturated fatty acids with either complex, fiber-rich carbohydrates (with emphasis on whole grains) or monounsaturated/polyunsaturated fatty acids
- Consume some fish rich in n-3 fatty acids
- Other cardioprotective foods include nuts, seeds, and vegetable oils
- Consider using plant sterols/stanols (2 g/day) and soluble/viscous fiber (10 to 25 g/day) as a dietary adjunct to further lower LDL-C levels

Elevated triglycerides or non-HDL cholesterol: CHILD-2–TG	
Refer to a registered dietitian for family medical nutrition therapy[b]	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 fats as much as possible	Grade A Recommend
Decrease sugar intake	Grade B Recommend
Replace simple with complex carbohydrates	
No sugar-sweetened beverages	
Increase dietary fish to increase ω-3 fatty acids[c]	Grade D Recommend

Pediatrics 2011;128;S213 doi:10.1542/peds.2009-2107

Therapeutic targets for LDL cholesterol for children and adolescents

1) Should not be similar, nor as intense as for adults
2) Should be similar for boys and girls
3) Aim for LDL cholesterol < 4mmol/L if age <10 yr.
4) Aim for LDL cholesterol < 3 mmol/L if age >10 yr plus other risk factors

Nordestgaard BG et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J. 2013 Dec;34(45):3478-90a. Epub 2013 Aug 15.

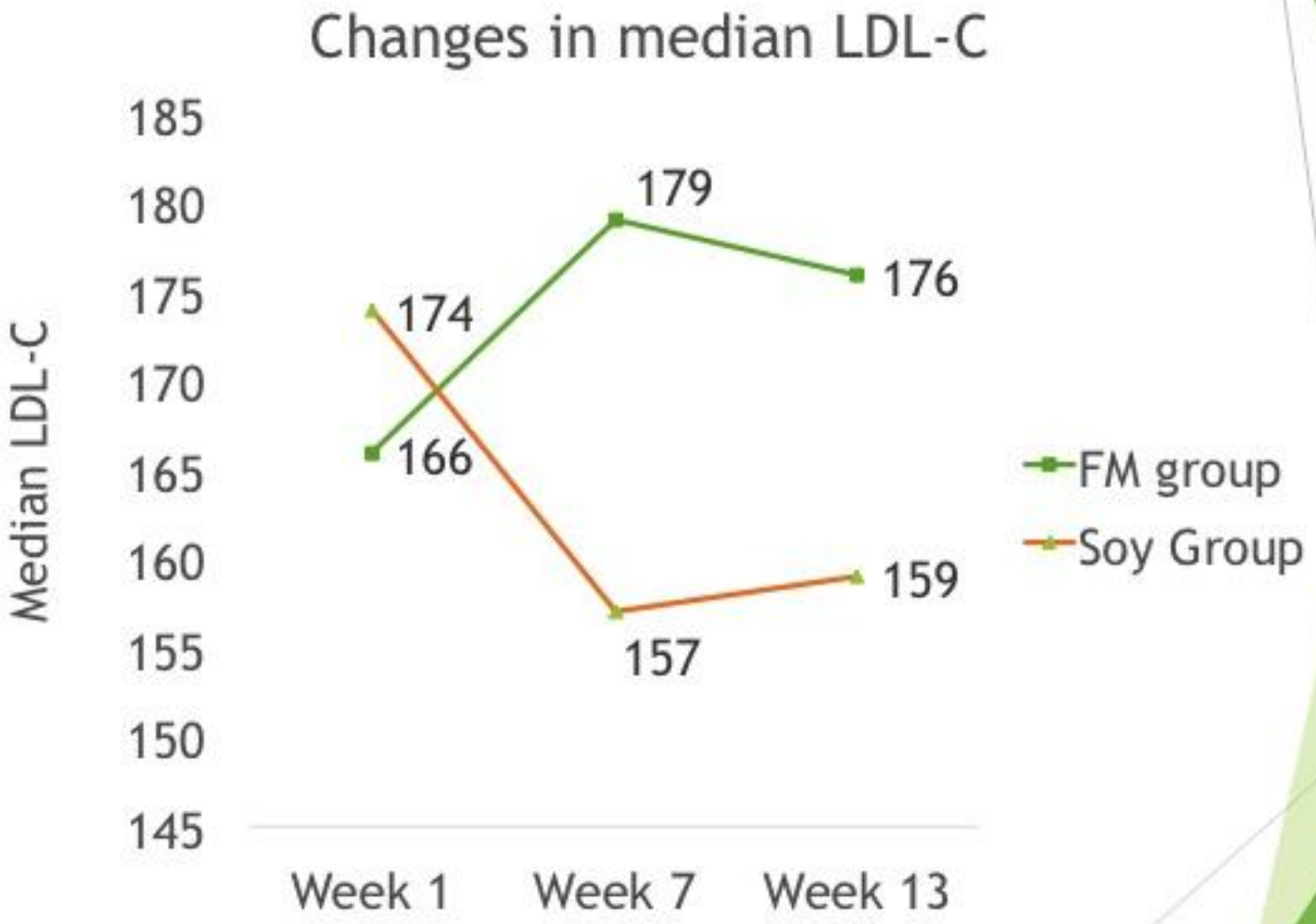
Table 3. Difference in RO vs SO diet after 13 weeks shown as mean ± s.d. with the percentage change

Lipid (mg/dl)	*RO (n = 12)*			*SO (n = 9)*			*Difference between groups[a] (P-value)*
	Begin	*End*	*Change (%)*	*Begin*	*End*	*Change (%)*	
Total cholesterol	237.0 ± 26.1	214.7 ± 29.4	−9.4**	268.3 ± 51.2	243.2 ± 51.2	−9.4*	0.788
LDL cholesterol	153.4 ± 26.8	134.0 ± 21.3	−12.7***	187.3 ± 55.9	166.2 ± 60.0	−11.3*	0.860
HDL cholesterol	64.1 ± 12.0	60.9 ± 9.3	−4.9	63.6 ± 20.2	57.0 ± 15.0	−10.3	0.485
Triglycerides	97.2 ± 31.6	98.6 ± 55.5	+ 1.5	86.8 ± 36.4	100.9 ± 47.8	+ 16.3	0.417
Apolipoprotein A1	148.3 ± 18.4	139.8 ± 22.9	−5.7	154.8 ± 37.0	141.0 ± 31.2	−8.9	0.685
Apolipoprotein B100	113.0 ± 16.6	108.0 ± 31.6	−4.4	129.7 ± 30.5	116.6 ± 29.7	−10.1*	0.454
hs-CRP	0.15 ± 0.15	0.13 ± 0.20	−16.8	0.07 ± 0.06	0.07 ± 0.04	−1.7	0.249
LDL/HDL cholesterol	2.5 ± 0.7	2.3 ± 0.6	−9.0	3.3 ± 1.5	3.1 ± 1.4	−3.5	0.724

Abbreviations: HDL, high-density lipoprotein; hs-CRP, high-sensitive C-reactive protein; LDL, low-density lipoprotein; RO, rapeseed oil; SO, sunflower oil. *$P < 0.05$, **$P < 0.005$, ***$P < 0.0005$, change between Begin and End. [a]Statistical analysis: analysis of variance.

Negele et al.: Effect of a low-fat diet enriched either with rapeseed oil or sunflower oil on plasma lipoproteins in children and adolescents with familial hypercholesterolaemia. Results of a pilot study. Eur J Clin Nutr. 2015 Mar;69(3):337-43

Effects of soy consumption on blood lipids



Helk O., Kulling S., Widhalm K.; British Journal of Nutrition, in review

Drug therapy in children with heterozygous FH

1) Should be instituted at age 8 to 10 yrs.
2) Boys and girls should be treated at similar ages.
3) Treatment should not be delayed until age 18 yr.

Nordestgaard BG et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J. 2013 Dec;34(45):3478-90a. Epub 2013 Aug 15.

Table 1. Patient Characteristics at Baseline and After 10 Years of Follow-up[a]

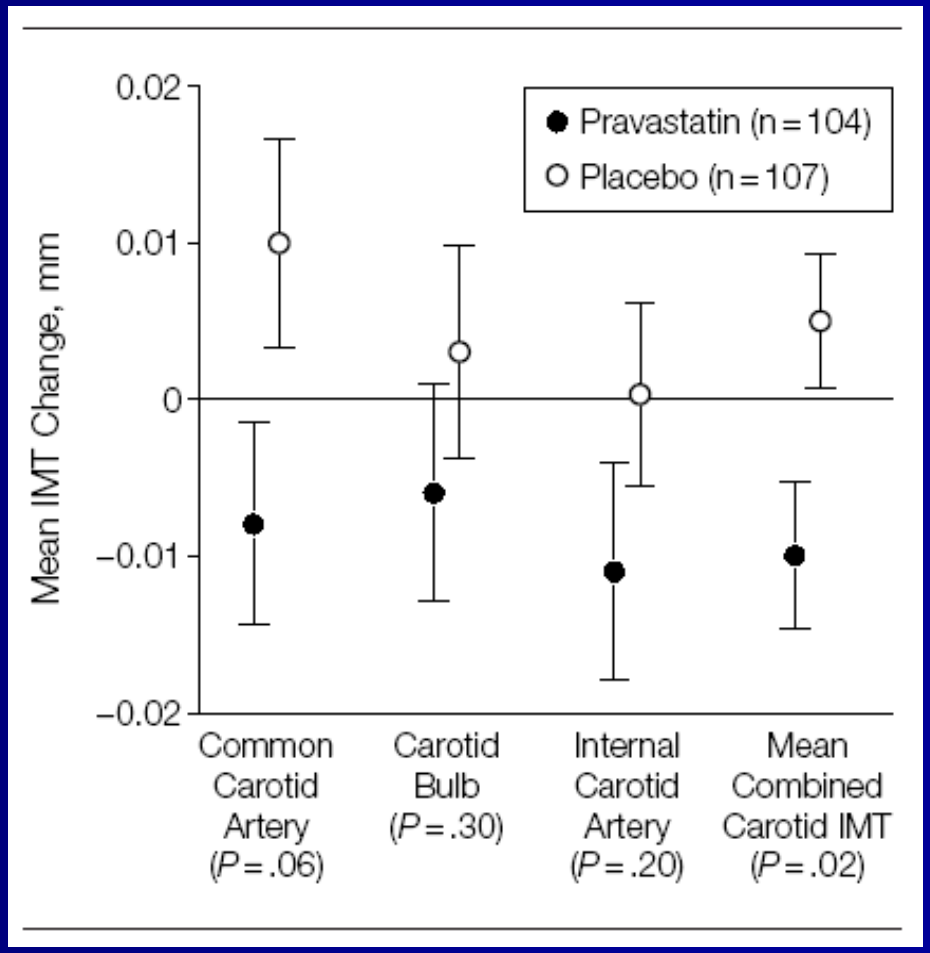
	At Baseline			After 10 y of Follow-up		
	FH (n = 194)	Siblings (n = 83)	*P* Value[b]	FH (n = 194)	Siblings (n = 83)	*P* Value[b]
Age, y	12.9 (12.5-13.4)	13.0 (12.3-13.6)	.99	24.0 (23.6-24.5)	23.8 (23.2-24.5)	.63
Male sex, No. (%)	90 (46.4)	46 (55.4)	.17	90 (46.4)	46 (55.4)	.17
Height, m	1.56 (1.54-1.58)	1.57 (1.54-1.61)	.67	1.74 (1.73-1.76)	1.76 (1.74-1.77)	.25
Weight, kg	48.8 (46.6-50.9)	48.0 (44.4-51.5)	.71	74.2 (72.2-76.3)	73.8 (71.0-76.6)	.81
BMI[c]	19.4 (18.9-19.9)	18.9 (18.1-19.6)	.26	24.4 (23.8-25.2)	23.9 (23.1-24.8)	.32
Cholesterol, mg/dL[e]						
Total	301 (293-308)	169 (164-174)	<.001	241 (231-251)	196 (189-204)	<.001
LDL	237 (230-244)	100 (95-105)	<.001	173 (164-183)	124 (117-131)	<.001
HDL	48 (47-50)	56 (52-59)	<.001	50 (48-52)	53 (50-56)	.13
Triglycerides, median (IQR), mg/dL[e]	65 (49-95)	56 (42-93)	.12	80 (60-105)	89 (61-125)	.21
Apolipoprotein, mg/dL[e]						
Carotid IMT, mm	0.442 (0.436-0.449)	0.433 (0.424-0.441)	.03[f]	0.480 (0.472-0.489)	0.469 (0.459-0.480)	.02[f]

Kusters DM et al. Ten-Year Follow-up After Initiation of Statin Therapy in Children With Familial Hypercholesterolemia. JAMA. 2014 Sep 10;312(10):1055-7.

Efficacy and safety of statin therapy in children with familial hypercholesterolemia

(Wiegman et al, JAMA 2004; 293:331-337)

- n=214 children with FH,
- age 8-18 yrs
- Double-blind randomized
- clinical trial 20-40 mg pravastatin
- for 2 years; assessed CIMT
- at baseline and 2 years
- LDL at 2 years – 4.72 mmol/L (180 mg/dL)



CONCLUSION
FH – children

- Familial hypercholesterolemia (FH) is a well described and very common genetic lipoprotein disorder with a high probability of premature CVB even in young adults (1:200)
- Diagnosis of FH (based on clinical and genetic criteria) is feasible, even in young children
- There is enough evidence that precursors of atherosclerosis can be detected in affected subjects, particularly in early childhood
- There is a body of evidence that early treatment can prevent or postpone manifestation of atherosclerosis
- WHY ARE SO MANY AFFECTED CHILDREN UNDIAGNOSED AND UNTREATED?

CONCLUSION
Familial hypercholesterolemia in children Reasons for Underdiagnosis and Undertreatment

- There is no clinical visible sign of the disease in the pediatric patient
- There is no general awareness that CVD and/or hypercholesterolemia could be caused by a treatable genetic disease
- These is not enough awareness among cardiologists, internists etc. that FH can be diagnosed/treated in children
- There is a general uncertainty of parents/physicians to cope with a genetic disease, which is not characterized by clinical symptoms
- There is a general fear to treat children with diet or drugs if they don't show symptoms

CONCLUSION

Strategies to give FH in children public notice

- Excellent education and presentation of impressive material of physicians (cardiologists, pediatricians, general practioners etc.) health professionals, health care workers etc.
- Establishment of active parents patient-groups
- Public relations:

Contact to media: patient stories
Continuous information of entire journalists

- Via Media → pressure on public health officers
- Creation of specialised (centers of excellence) subunits in children hospitals
- Support of research programs
- Support of parents/patient-groups
- International networking and publishing