Familial Hypercholesterolaemia

How do we recognize FH in clinical practice?

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PCSK9FORUM

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Disclosure slide, Eric Bruckert

- **Research contracts: AMGEN, Danone**
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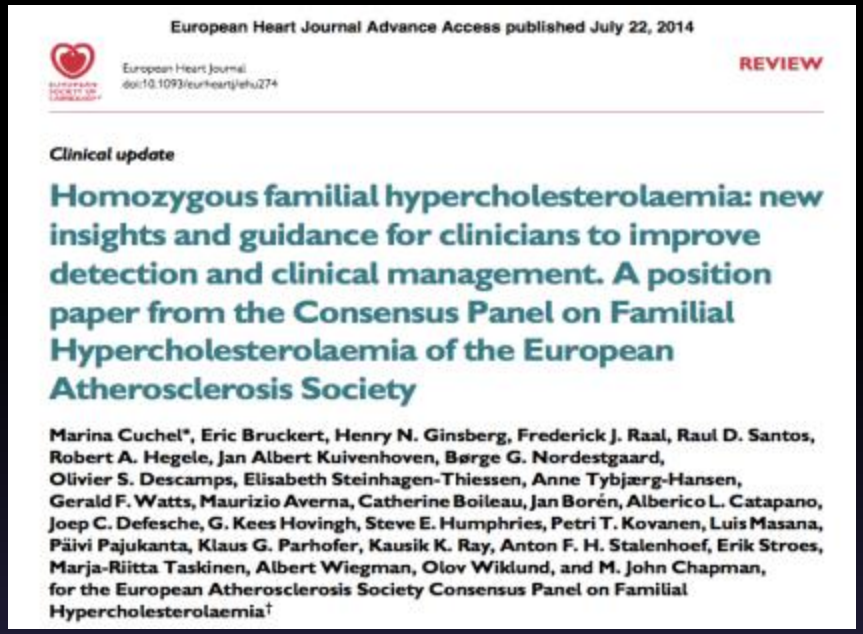

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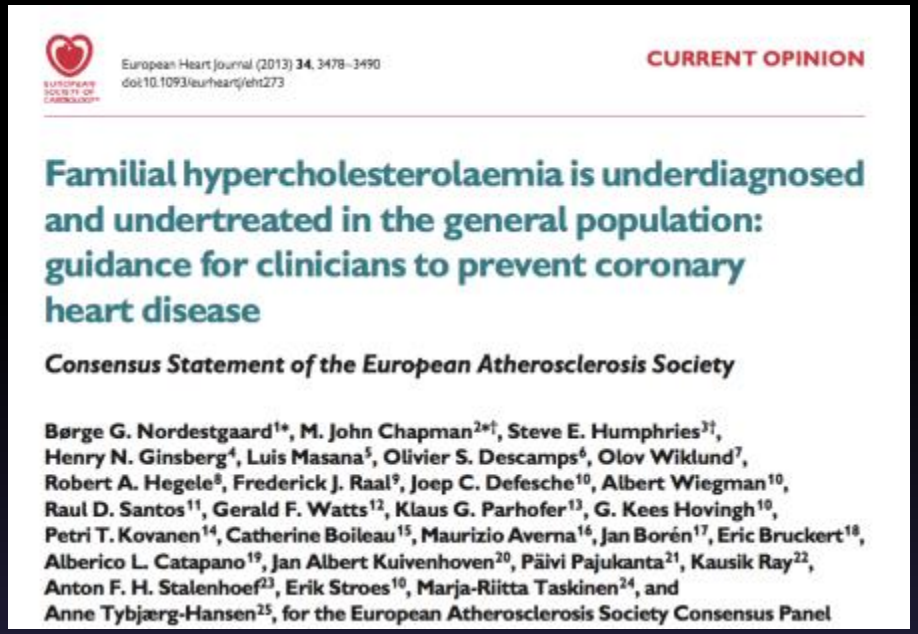
REVIEW

Clinical update

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, Olivier S. Descamps, Elisabeth Steinhagen-Thiessen, Anne Tybjærg-Hansen, Gerald F. Watts, Maurizio Averna, Catherine Boileau, Jan Borén, Alberico L. Catapano, Joep C. Defesche, G. Kees Hovingh, Steve E. Humphries, Petri T. Kovanen, Luis Masana, Päivi Pajukanta, Klaus G. Parhofer, Kausik K. Ray, Anton F. H. Stalenhoef, Erik Stroes, Marja-Riitta Taskinen, Albert Wiegman, Olov Wiklund, and M. John Chapman, for the European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolaemia†



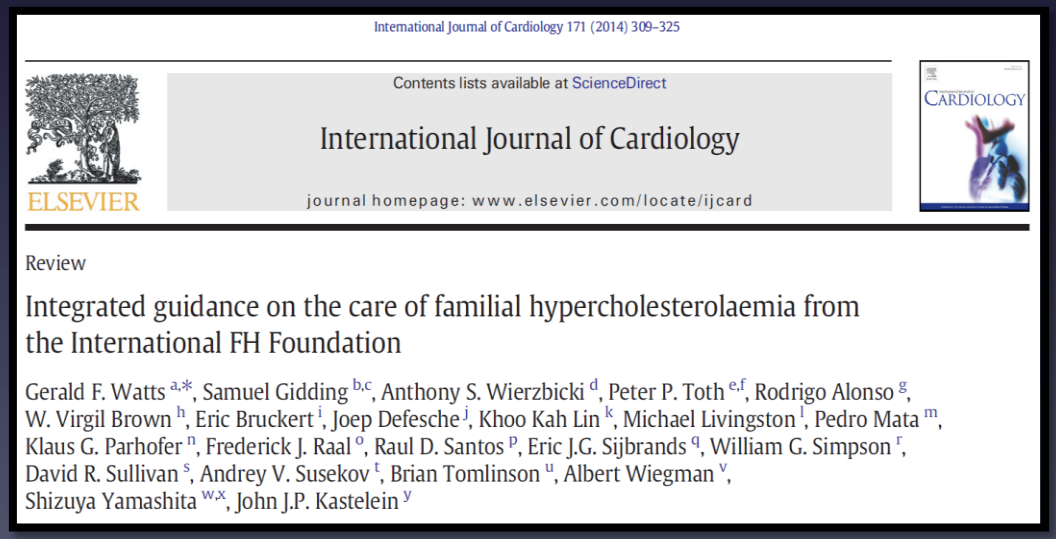
European Heart Journal (2013) 34, 3478–3490
doi:10.1093/eurheartj/eht273

CURRENT OPINION

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

Børge G. Nordestgaard[1*], M. John Chapman[2*†], Steve E. Humphries[3†], Henry N. Ginsberg[4], Luis Masana[5], Olivier S. Descamps[6], Olov Wiklund[7], Robert A. Hegele[8], Frederick J. Raal[9], Joep C. Defesche[10], Albert Wiegman[10], Raul D. Santos[11], Gerald F. Watts[12], Klaus G. Parhofer[13], G. Kees Hovingh[10], Petri T. Kovanen[14], Catherine Boileau[15], Maurizio Averna[16], Jan Borén[17], Eric Bruckert[18], Alberico L. Catapano[19], Jan Albert Kuivenhoven[20], Päivi Pajukanta[21], Kausik Ray[22], Anton F. H. Stalenhoef[23], Erik Stroes[10], Marja-Riitta Taskinen[24], and Anne Tybjærg-Hansen[25], for the European Atherosclerosis Society Consensus Panel



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Review

Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation

Gerald F. Watts [a,*], Samuel Gidding [b,c], Anthony S. Wierzbicki [d], Peter P. Toth [e,f], Rodrigo Alonso [g], W. Virgil Brown [h], Eric Bruckert [i], Joep Defesche [j], Khoo Kah Lin [k], Michael Livingston [l], Pedro Mata [m], Klaus G. Parhofer [n], Frederick J. Raal [o], Raul D. Santos [p], Eric J.G. Sijbrands [q], William G. Simpson [r], David R. Sullivan [s], Andrey V. Susekov [t], Brian Tomlinson [u], Albert Wiegman [v], Shizuya Yamashita [w,x], John J.P. Kastelein [y]

Homozygous Familial Hypercholesterolaemia

HoFH: Definition according to the EAS Consensus Panel Statement

Box 1 Criteria for the diagnosis of homozygous familial hypercholesterolaemia

- Genetic confirmation of two mutant alleles at the *LDLR*, *APOB*, *PCSK9*, or *LDLRAP1* gene locus

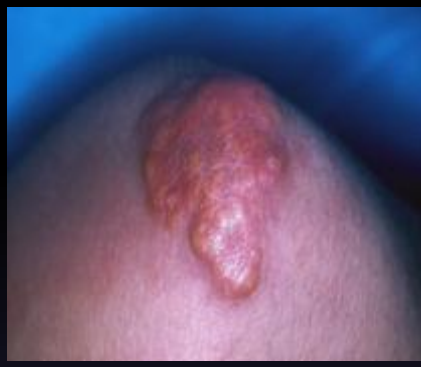
OR

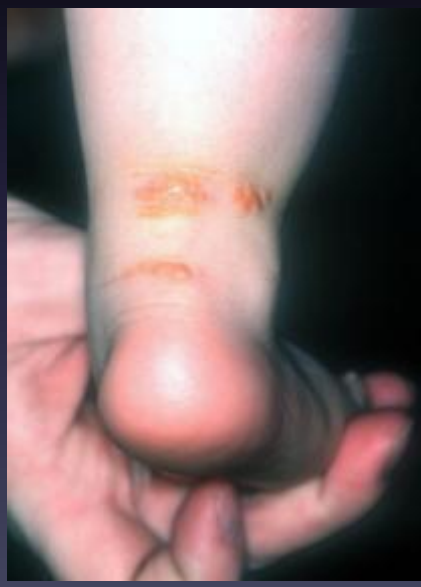
- An untreated LDL-C > 13 mmol/L (500 mg/dL) or treated LDL-C ≥ 8 mmol/L (300 mg/dL)* together with either:
  - Cutaneous or tendon xanthoma before age 10 years

or

  - Untreated elevated LDL-C levels consistent with heterozygous FH in both parents

* These LDL-C levels are only indicative, and lower levels, especially in children or in treated patients, do not exclude HoFH





Cuchel M, Bruckert E, Ginsberg H et al. Eur Heart Journal 2014

Late referral of HoFH patients to specialised centers due to underestimation of CVD complications

Box 2 Cardiovascular complications of homozygous familial hypercholesterolaemia

- HoFH is characterized by accelerated atherosclerosis, typically affecting the aortic root, although other vascular territories may also be affected.
- The first major cardiovascular events often occur during adolescence, possibly younger when patients are *LDLR*-negative and/or untreated.
- In young children, early symptoms and signs are often linked to aortic stenosis and regurgitation, due to massive accumulation of cholesterol at the valvular levels.
- As aortic and supra-valvular aortic valve diseases may progress even when cholesterol levels are reduced, regular screening for subclinical aortic, carotid, and coronary heart disease is indicated.

Cuchel M, Bruckert E, Ginsberg H et al. Eur Heart Journal 2014

Differentiation from sitosterolaemia

Extremely rare disease with transient major elevation of cholesterol and clinical features resembling HoFH

But

No family history (recessive disorder)
Decrease of serum cholesterol upon diet, BAS* or ezetimibe
Dramatic increase of serum plant sterol
Good CVD prognosis when diagnosis made at a young age**
Mutations in two ATP binding cassette transporter genes, ABCG5 and/or ABCG8

*Bile Acid Sequestrant

**Hansel B et al. Atherosclerosis 2014

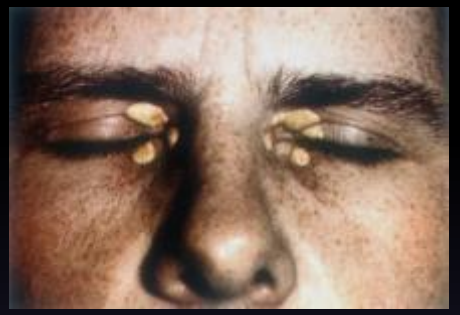
Heterozygous Familial Hypercholesterolaemia

Patients with HeFH should be identified for at least 4 reasons

- **Population at higher risk and thus with lower LDL-C target. Treatment needs to be started at a young age**
- **Diagnosis of FH is the basis for cascade screening**
- **Diagnosis of FH Improves medical care and compliance**
- **Diagnosis of FH might be useful for reimbursment in some countries and might be an indication for future therapeutic options**

Why should we identify patients with FH?

Clinical case



Man, 41 years of age, non smoker, blood pressure 128/88 mmHg, no diabetes mellitus

No cardiovascular disease

With optimal diet

LDL-C 188 mg/dl, TG 128 mg/dl, HDL-C 43 mg/dl

According to European EAS/ESC recommendations*

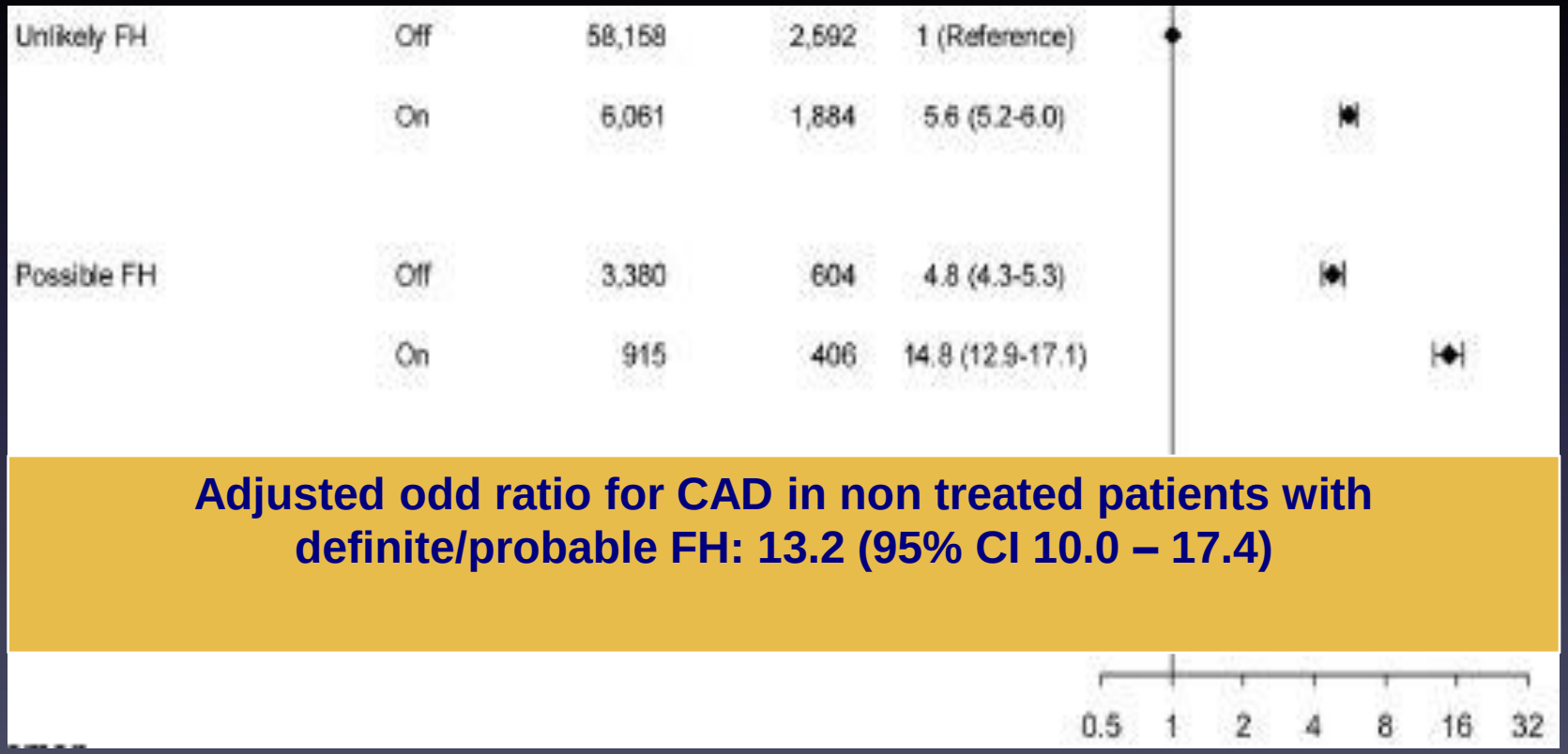
If the patient does has not FH: Lifestyle intervention. Consider drug if uncontrolled

If the patient has FH: Statin treatment with LDL-C target below 100 mg/dl

*Eur Heart J 2011

Risk of CHD in HeFH

Copenhagen General Population Study (n=69,209)
Dutch criteria (no use of xanthoma or corneal arcus)
After exclusion of hypothyroidism, there were 0.20% of definite FH, 0.53% of probable, 6.3% of possible FH and 93% of unlikely FH

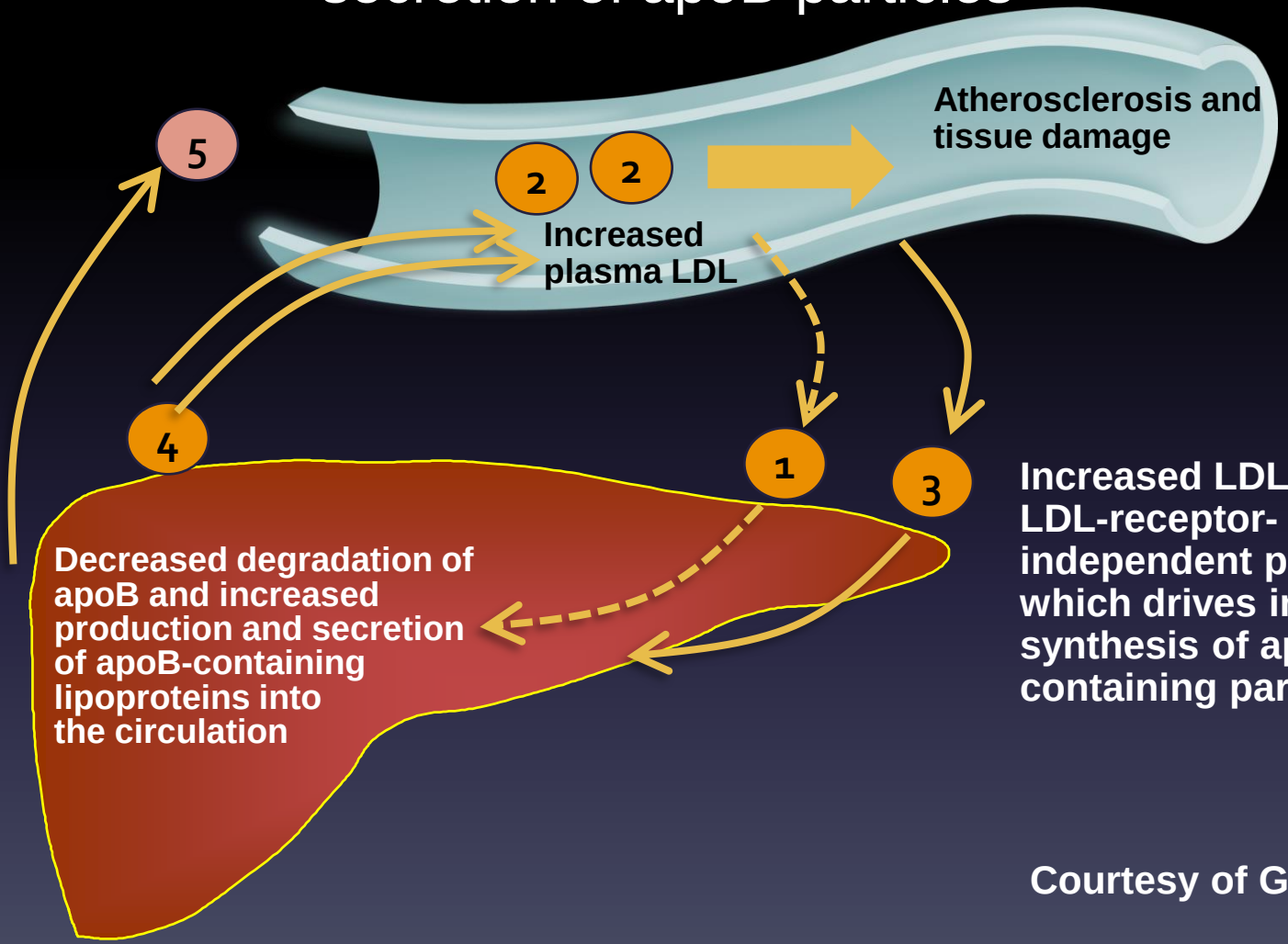


Adjusted odd ratio for CAD in non treated patients with definite/probable FH: 13.2 (95% CI 10.0 – 17.4)

Benn M et al. JCEM 2012

Why such a high risk (1)?

FH: Primary impairment in LDL clearance with increased secretion of apoB particles



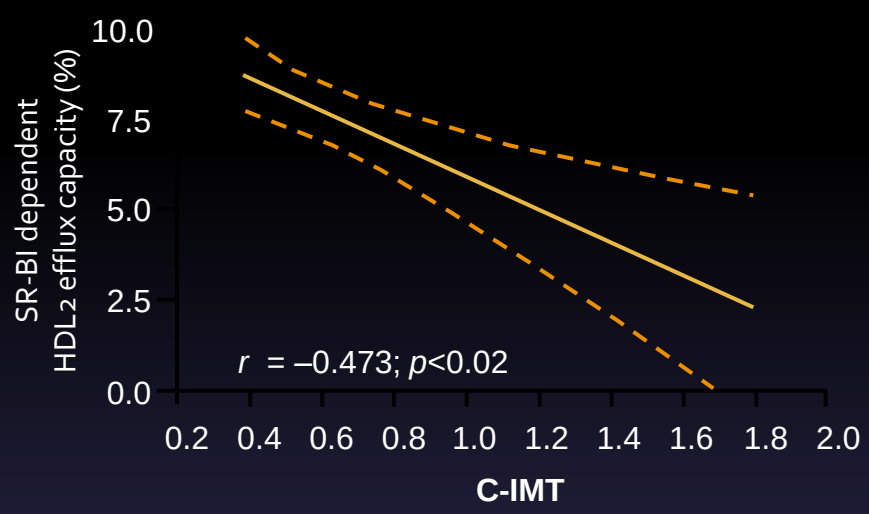
Increased LDL uptake by LDL-receptor-independent pathway which drives increased synthesis of apoB containing particles

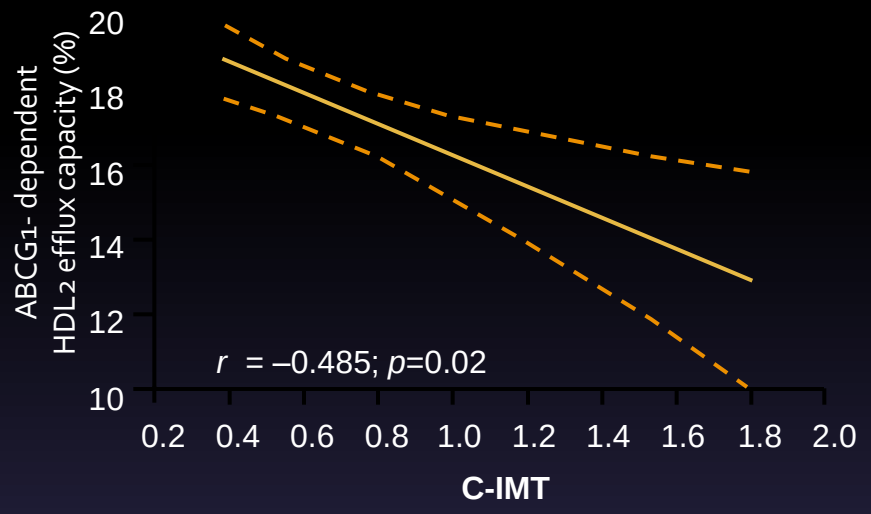
Courtesy of G Watts

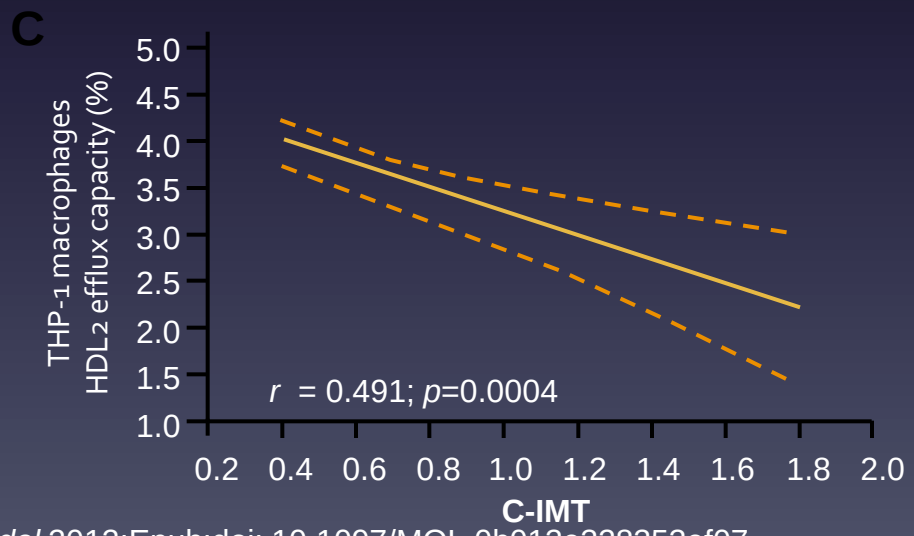
1. Barrett PH, Watts GF. *Atheroscler Suppl* 2002;2:1
2. Sniderman AD *et al. Clin Sci (Lond)* 2009;118:333
3. Fisher WR *et al. Arterioscler Thromb* 1994;14:501
4. Cummings MH *et al*. *Atherosclerosis* 1995;113:79
5. Tremblay AJ *et al*. *J Lipid Res* 2004;45:866
6. Twisk J *et al*. *J Clin Invest* 2000;105:521

Why such a high risk (2)?

Efflux capacity of large HDL2 particles is linked to premature atherosclerosis in FH







1. Guérin M. *Curr Opin Lipidol* 2012;Epub;doi: 10.1097/MOL.0b013e328353ef07

FH has a life-time exposure to cholesterol

This may even include fetal exposure

- **Lesions in aortic arch and abdominal aorta progress strikingly faster in children (age 1–13 years) of hypercholesterolaemic mothers than in those of normocholesterolaemic ones ($p<0.0001$)[1]**
- **FH inherited through the mother is associated with higher excess mortality than when transmitted by the father (RR 2.2; $p=0.048$)[2]**
- **Aortic and myocardial function in young adulthood is associated with intralipid exposure during neonatal life for preterm infants[3]**
  - **This occurs in a graded manner, relative to cholesterol increase**

1. Napoli C *et al. Lancet* 1999;354:1234
2. Versmissen J *et al. Atherosclerosis* 2011;219:690
3. Lewandowski AJ *et al. Arterioscler Thromb Vasc Biol* 2011;31:2125

“Clinical diagnosis” with the use of score

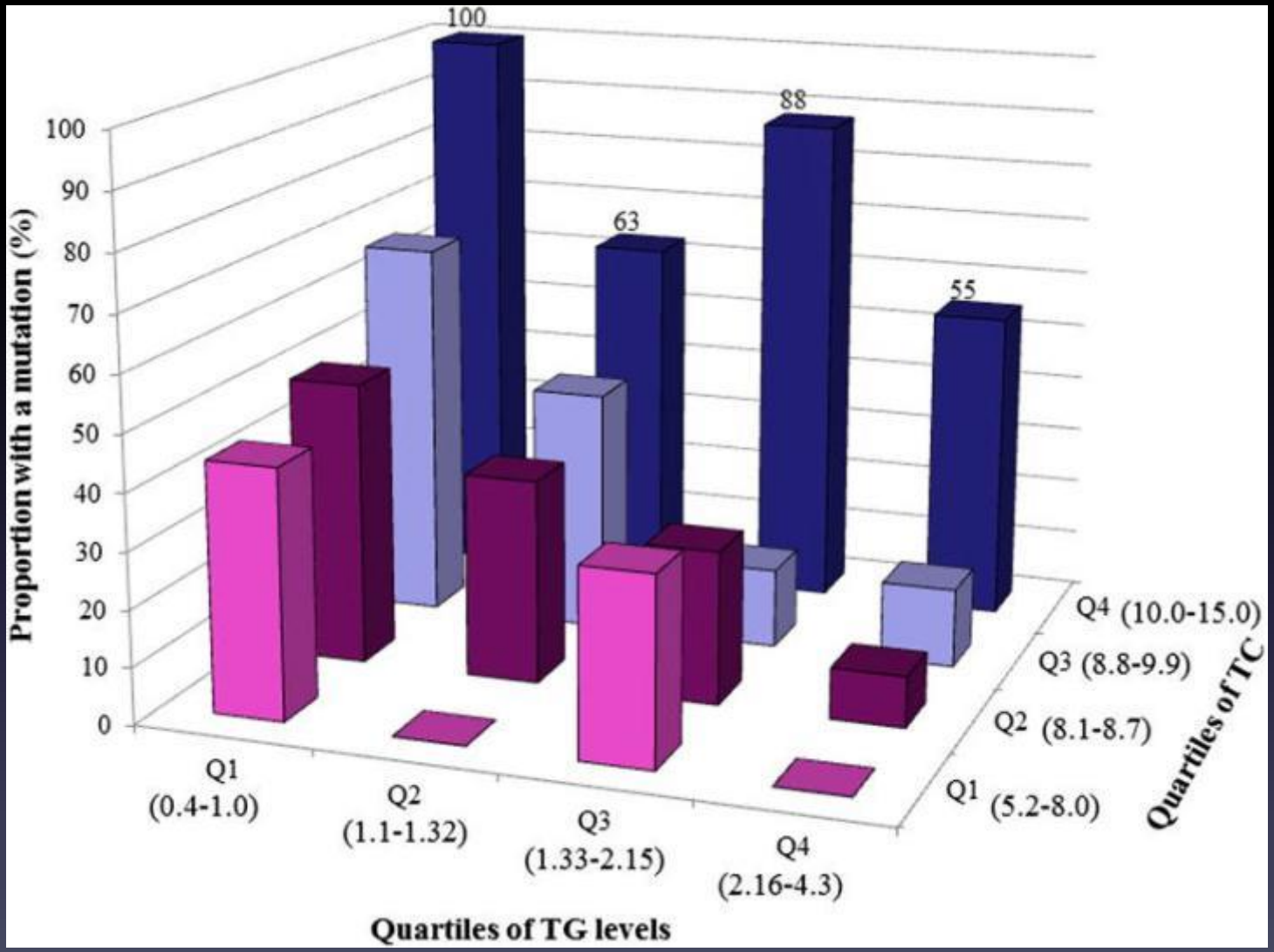
MEDPED
Dutch criteria
Simon Broome criteria
Japanese criteria

High level of TC or LDL-C

Family history

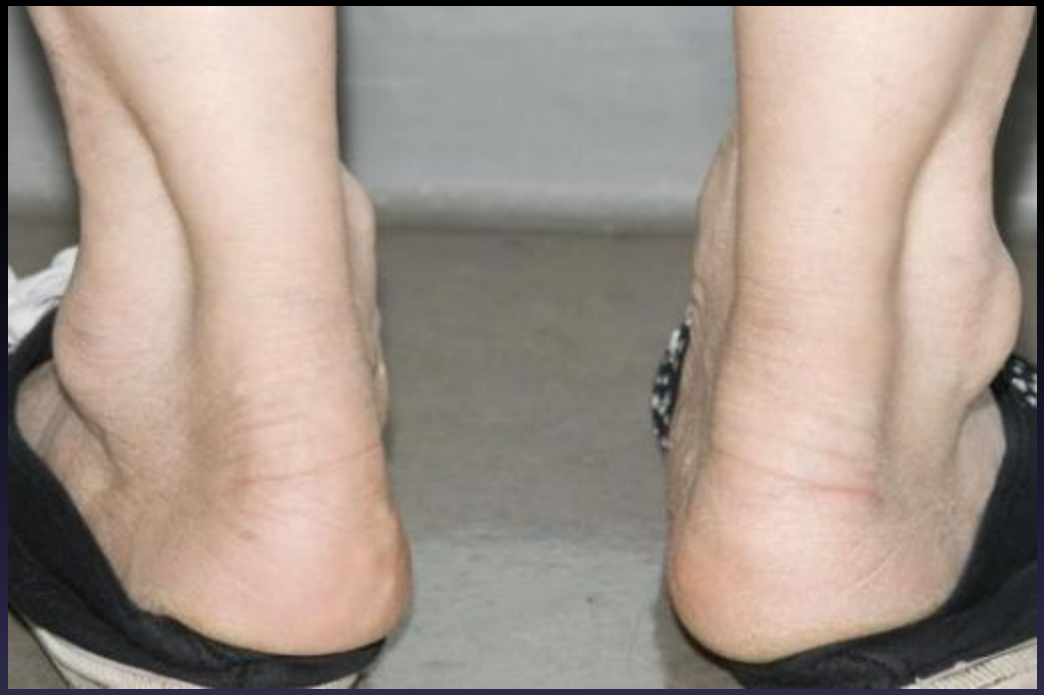
Clinical finding

FH mutation detection rate by quartile of TC & TG



Futema M et al. Atherosclerosis 2013

Achilles tendinopathy in patient with familial hypercholesterolaemia



Schofield J et al. BMJ 2013;346:bmj.f2171

In a study of patients with definite HeFH, 26.3% had consulted a doctor about symptoms of Achilles tendinopathy, but none of these consultations had led to a diagnosis of FH*

***Beeharry D *et al.* 2006;65:312–5**

Familial Hypercholesterolemia: Japanese criteria

Diagnostic criteria for adult (15 years or older) heterozygous FH

1. LDL-C before treatment ≥ 180 mg/dL
2. Tendon xanthoma or nodular xanthoma on the skin
3. Family history within the second-degree relatives FH or premature CAD

Ruling out the possibility of secondary hyperlipidemia

⇨ **Patients meeting 2 items should be regarded as having FH.**

Nodular xanthoma on the skin does not include palpebral xanthoma. Patients with Achilles tendon thickening (9 mm or more) on radiography should be regarded as having xanthoma. When LDL-C ≥ 250 mg/dL, FH should be strongly suspected. During drug therapy, the pretreatment lipid level should be employed as a reference value
CAD in males younger than 55 years old and females younger than 65 years old is defined as premature CAD.

Harada-Shiba M et al. J Atheroscler Thromb 2012

Familial Hypercholesterolemia: Simon Broome criteria

A diagnosis of definite FH requires:

Cholesterol > 7.5 mmol/l or LDL-C > 4.9 mmol/l in an adult (resp. > 6.7mmol/l or > 4 mmol/l in a child under 16)

PLUS

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

OR

DNA-based evidence of an LDL-r, apoB-100, or a PCSK9 mutation.

A diagnosis of possible FH requires:

Cholesterol > 7.5mmol/l or LDL-C > 4.9 mmol/l in an adult (resp. > 6.7mmol/l or > 4 mmol/l in a child under 16

PLUS

Family history of MI before 50 years in a 2nd degree relative or below age 60 in a 1st degree relative.

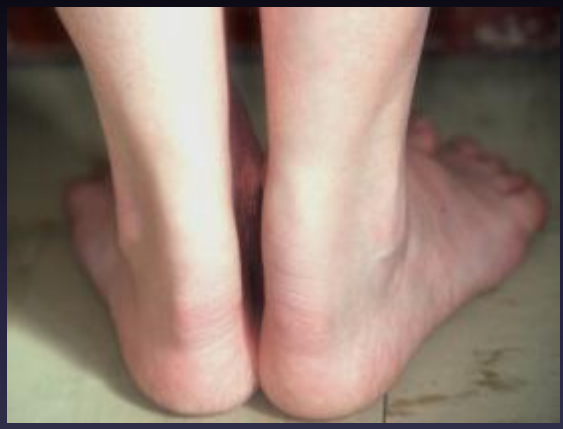
OR

Family history of raised CT: > 7.5mmol/l in adult 1st or 2nd degree relative or > 6.7mmol/l in a child or sibling aged under 16 years.

Familial Hypercholesterolaemia: Dutch criteria

	Score
Family history	
I. First-degree with premature coronary or vascular disease	1
II. First-degree relative to LDL-C levels >95th percentile, and/or	1
I. First-degree relative to tendon xanthomas and/or arcus cornealis	2
II. Children <18 years old with LDL-C levels >95th percentile	2
Personal history	
I. Coronary heart disease	2
II. Premature peripheral or cerebrovascular disease	1
Physical signs	
I. Tendon xanthomas	6
II. Arcus cornealis (<45 years old)	4
Blood analysis (with triglyceride levels <200 mg/dl, <2.3 mmol/l)	
I. LDL-C >330 mg/dl (8.5 mmol/l)	8
II. LDL-C 250–329 mg/dl (6.5–8.5 mmol/l)	5
III. LDL-C 190–249 mg/dl (4.9–6.5 mmol/l)	3
IV. LDL-C 155–189 mg/dl (4.0–4.9 mmol/l)	1
DNA analysis	
Functional mutation in LDL-receptor gene present	8

- **Diagnostic total score**
  - **Certain: ≥8**
  - **Probable: 6–7**
  - **Possible: 3–5**



- **For example: xanthomas with LDL-C >190 mg/dl, give a score of 8 (i.e. a certain diagnosis of HeFH)**

Marks D *et al. Atherosclerosis* 2003;168:1

Familial Hypercholesterolemia: limitations of clinical and biological criteria

	Score
Family history	
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II. First-degree relative to LDL-C levels >95th percentile, and/or	1
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IV. LDL-C 155–189 mg/dl (4.0–4.9 mmol/l)	1
DNA analysis	
Functional mutation in LDL-receptor gene present	8

Might be absent in individuals with young parents (especially if treated)

Might be absent in statin treated individuals

Frequently overlooked or absent in young individuals

Threshold values vary according to age. Not known in most treated patients

Marks D *et al. Atherosclerosis* 2003;168:1

Diagnosis with genetic testing

Autosomal dominant
- Over 1200 mutations of the LDL-r
- One mutation of apoB
- Few mutations of PCSK9
- One mutation of apo EE (apoE P.Leu 167del)

Autosomal recessive
- Rare mutation LDLRAP1
- Rare mutation of cholesterol 7alpha hydroxylase

The spectrum of mutations varies between countries

More than 80% of FH patients have LDL-r mutation

Why Genetic Testing is recommended?

Diagnosis

Clinical diagnosis identifies only 50% of patients using genetic testing as the gold standard*

Possible and definite FH have mutation in 20-30% and 60-80% of cases

Prognosis

Patients with positive genetic testing have a higher CV risk

Impact on medical care

Despite availability of clinical scores for years the number of patients with FH treated with statin is impressively low

Family screening

Genetic testing is useful for family screening

* Leren TP et al. Community Genet 2008

Patients with positive genetic testing have a higher CVD risk

- Patients in the Simon Broome British Heart foundation study
- Genetic testing in 409 patients
- 251 CHD negative and 158 CHD positive patients

- After adjusting for classical RFs and lipid parameters, having a LDL-r mutation was an independent predictor of CHD :
  RR=1.84 (95%CI 1.10 to 3.06, p=0.02)
- Interpretation: a single measurement of cholesterol underestimates the « true » lifelong exposure to elevated cholesterol

Humphries SE et al. J Med Genet 2006

Impact of genetic testing for FH

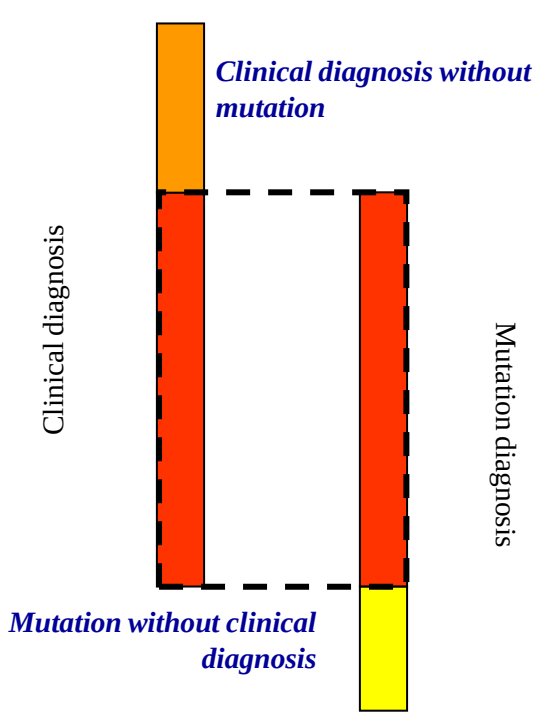
The genetic diagnosis

- Did not seem to have a great impact on patients' lives
- Reduced the uncertainty that surrounded health status
- Motivated patients to maintain healthy lifestyles*
- Changed the social status in as much as their strict life-style regimen was now based on a formal medical category rather than a general motivation to keep healthy**

*particularly salient for those receiving a positive diagnosis
**Several patients described difficulty explaining to others their dietary choices in social situations. This caused embarressment as they had to explain their behaviour in terms of having a medical condition rather than being fussy or needlessly watchful

Hollands et al BMC Medicam Genetics 2012

Overlap of clinical and mutation diagnosis of heterozygous FH



Patient: treat LDL
Family: monitor LDL and consider treatment

Patient: treat LDL
Family: mutation test, monitor LDL and consider treatment

Patient: monitor LAD and consider treatment
Family: monitor LDL and consider treatment

LDL = low-density lipoprotein cholesterol, Nordestgaard B et al. Eur Heart J 2013

Diagnosis with genetic testing and cascade screening

- Cascade screening identifies people with FH by a process of family screening. It is less costly and more efficient than systematic screening in the population
- It can be done with or without genetic testing but genetic testing is the best approach to identify patients
- It needs dedicated staff, storage facilities, electronic database
- Cascade screening in the Netherlands was associated with a dramatic increase in the number of patients treated with statin (from 38% to 90%)

Conclusion

- **Identifying patients with FH allows identification of high risk subjects and thus treatment with appropriate LDL-C target**
- **Clinical scores are useful to identify those patients but genetic testing may have several advantages**
- **Genetic testing is key for cascade screening and for improving patients' care**