Familial hypercholesterolaemia in children and adolescents

Rationale and recommendations for

early identification and treatment

European Atherosclerosis Society Consensus Panel

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REVIEW

Prevention

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

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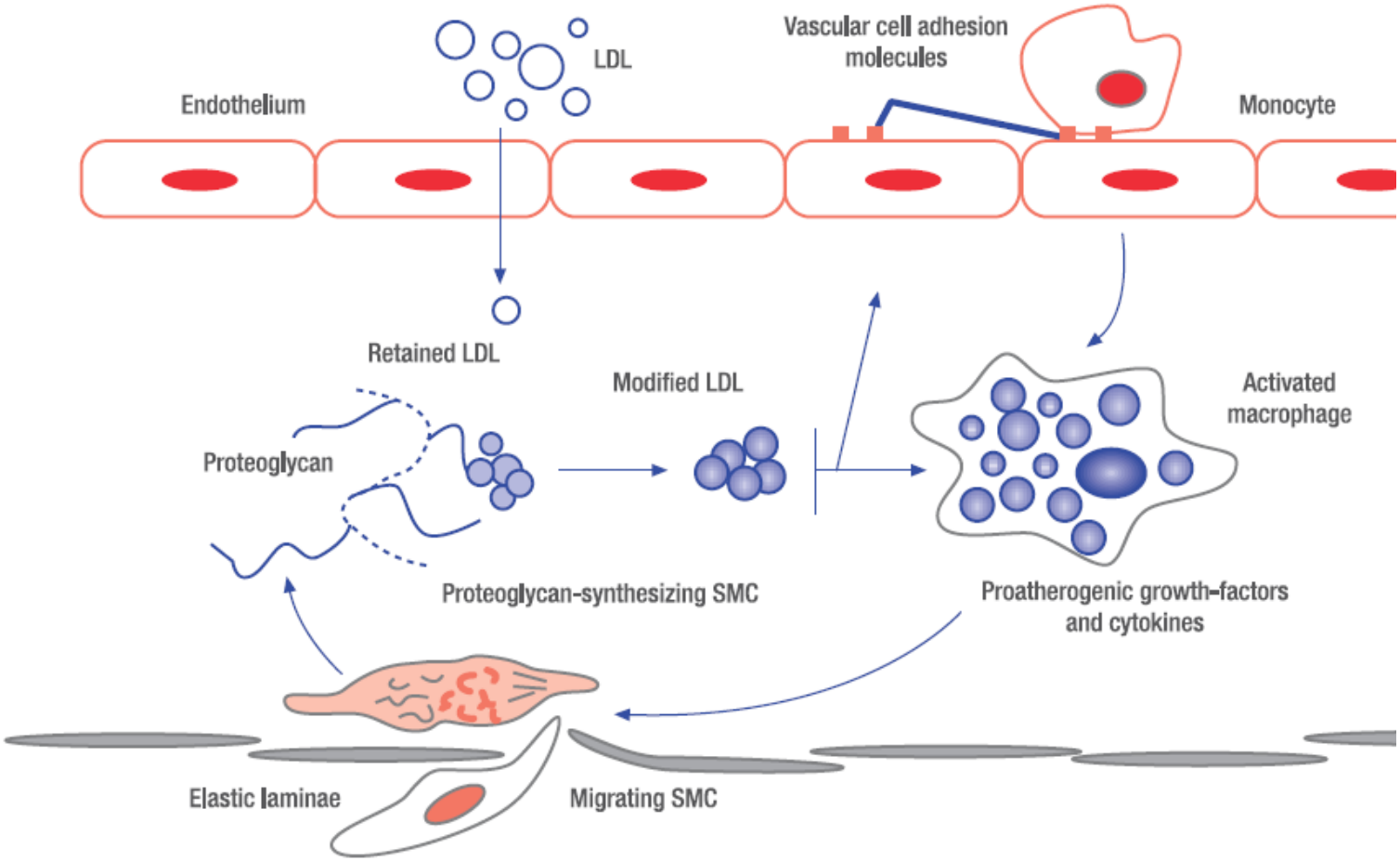
Elevated LDL-C: one of the major risk factors for cardiovascular disease

LDL and atherosclerosis

- Retention of atherogenic apolipoprotein B-containing lipoproteins in the arterial wall is the key initiating event in atherosclerosis.
- LDL retained in the artery wall undergo modification and are taken up by macrophages, which ultimately become foam cells.



Genetic studies reaffirm the role of elevated LDL-C in atherosclerosis

Mendelian randomisation studies, a type of ‘natural’ randomisation have proven the case for LDL-C and CVD

- Genetic variation identifies risk status; polymorphisms in multiple different genes are associated with both lower LDL-C and a lower risk of CVD
- Provides the rationale for the benefit of lifelong low LDL-C levels
- Consistent with clinical trial data suggesting greater effect with longer LDL lowering interventions

Lower LDL-C: lower CVD risk Independent of how LDL-C is lowered

- There was a log-linear association between genetically mediated lower LDL-C and the risk of CVD
- The lower the LDL-C, the lower CVD risk
- The benefit from LDL-C lowering does not depend on how LDL-C is lowered

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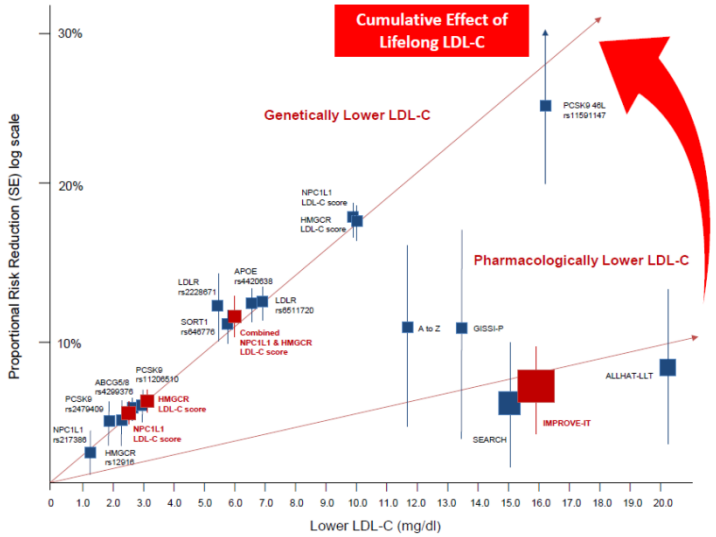
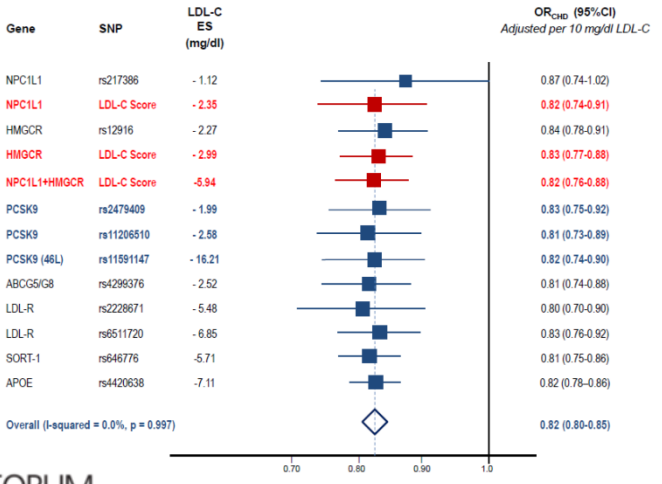
Figure

Part A: Log-linear effect of genetically and pharmacologically mediated lower LDL-C



Part B: Effect of 0.25 mmol/L (10 mg/dl) lower LDL-C on risk of CVD



Ference BA et al. J Am Coll Cardiol 2015;65:1552–61

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Higher LDL-C: higher CVD risk

Familial hypercholesterolaemia (FH): exposure to elevated LDL-C from birth markedly increases CVD risk

- Severity of atherosclerosis is proportional to both extent and duration of elevated LDL-C – the “Cholesterol -Year- Score”

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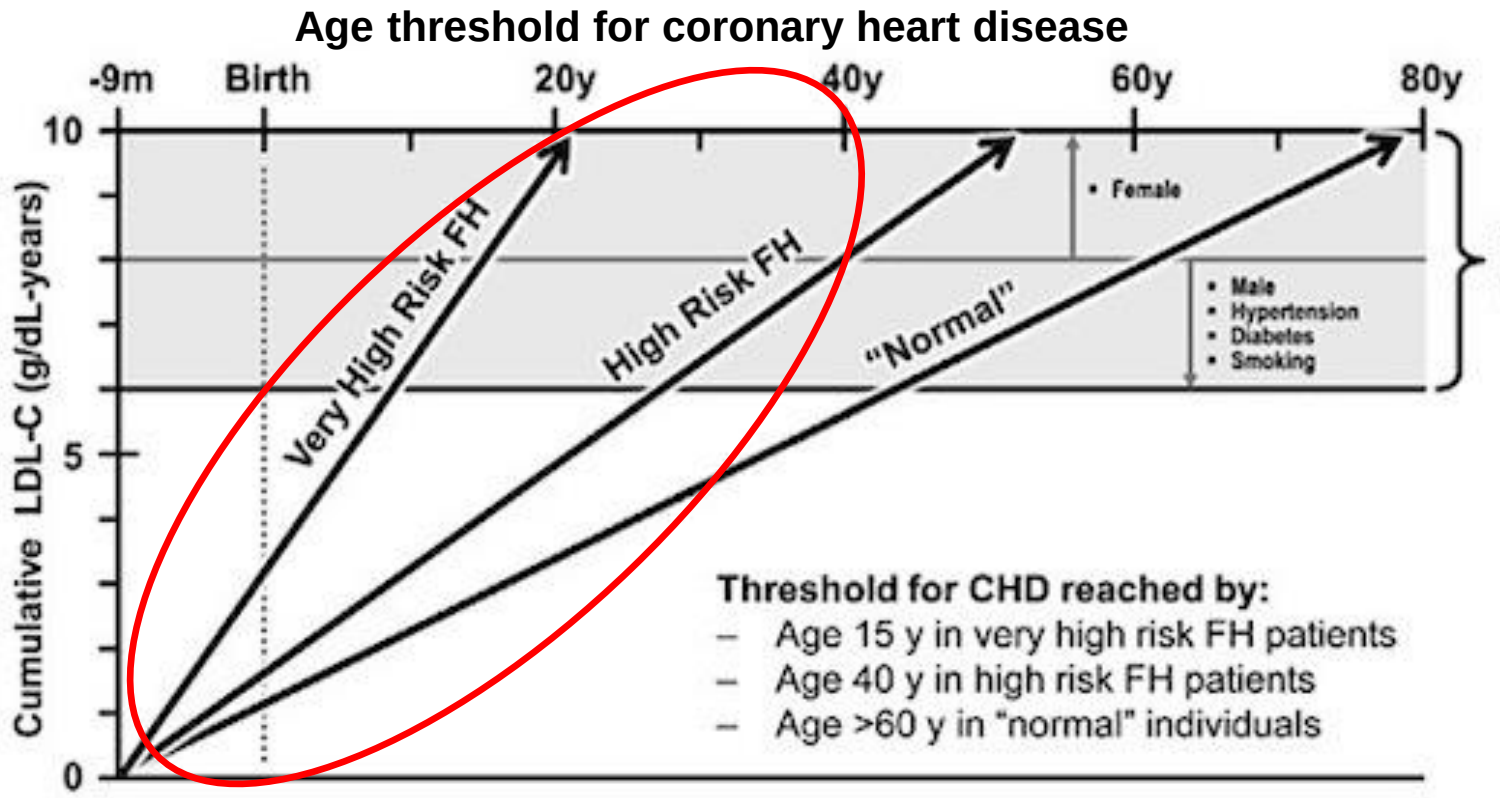

Schmidt HH et al. Am J Cardiol 1996;77:575-80

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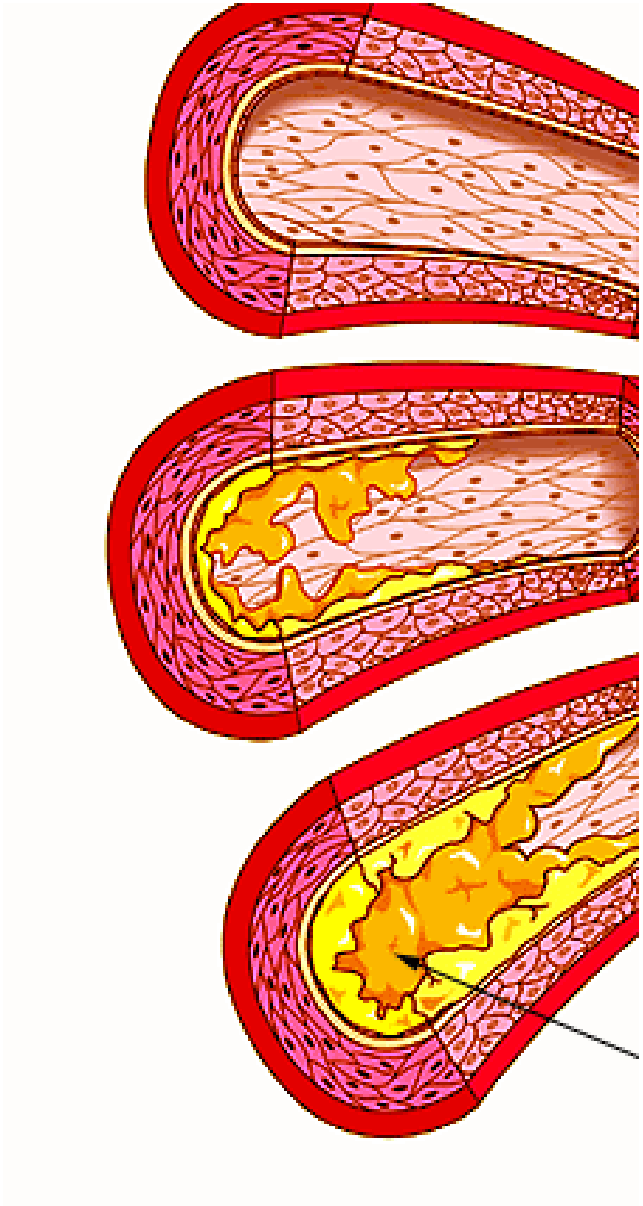
Why we need to identify and treat children with FH early

Untreated FH leads to accelerated atherosclerosis and early coronary events

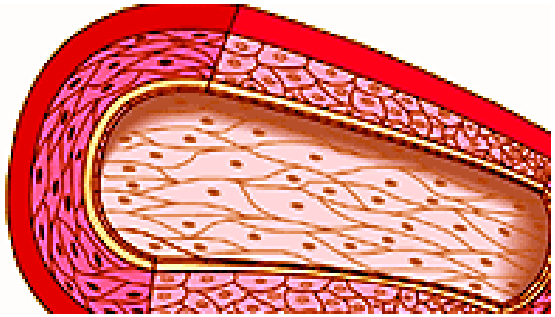


Newborn:
- **Foetal exposure to cholesterol leads to disturbed flow**

Child at risk
- **Risk factor exposure leads to early atherogenesis**

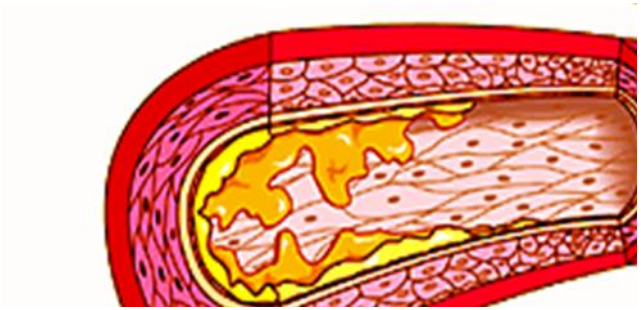
Young adult
- **Plaque build-up**
- **Early plaque rupture and thrombosis leading to coronary events**
- **Impacts mortality, morbidity and quality of life**

Treating FH early will prevent early coronary events



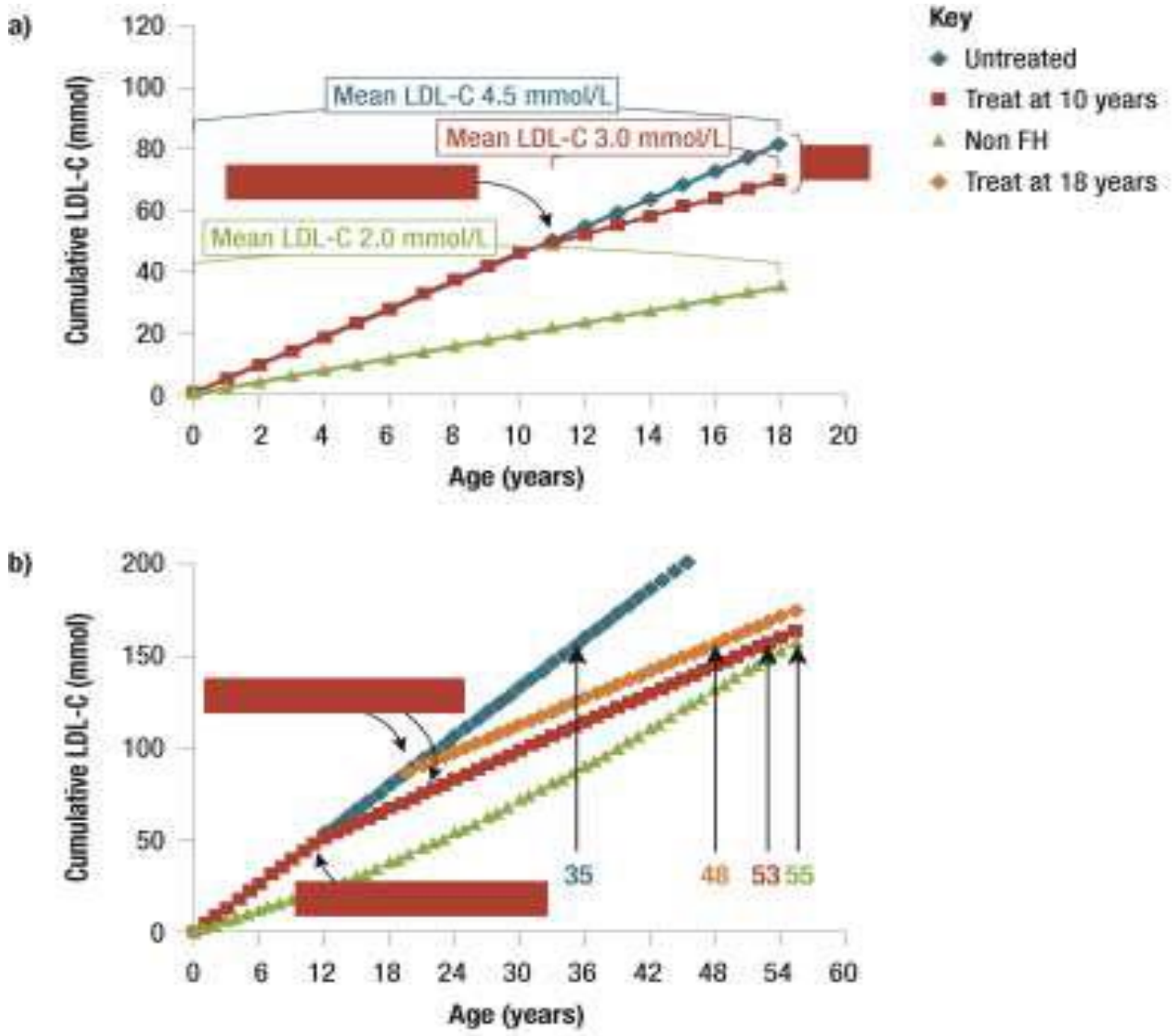
Newborn:
- **Foetal exposure to cholesterol leads to disturbed flow**

Identification of FH in childhood
- **Targeted risk factor management**
- **Lifestyle counselling**
- **Early initiation of lipid-lowering treatment**
- **Monitoring of subclinical atherosclerosis**



Young adult
- **Prevention of early coronary events?**

Impact of early treatment on LDL-C burden



Vuorio A et al. Atherosclerosis 2013;226:315-20

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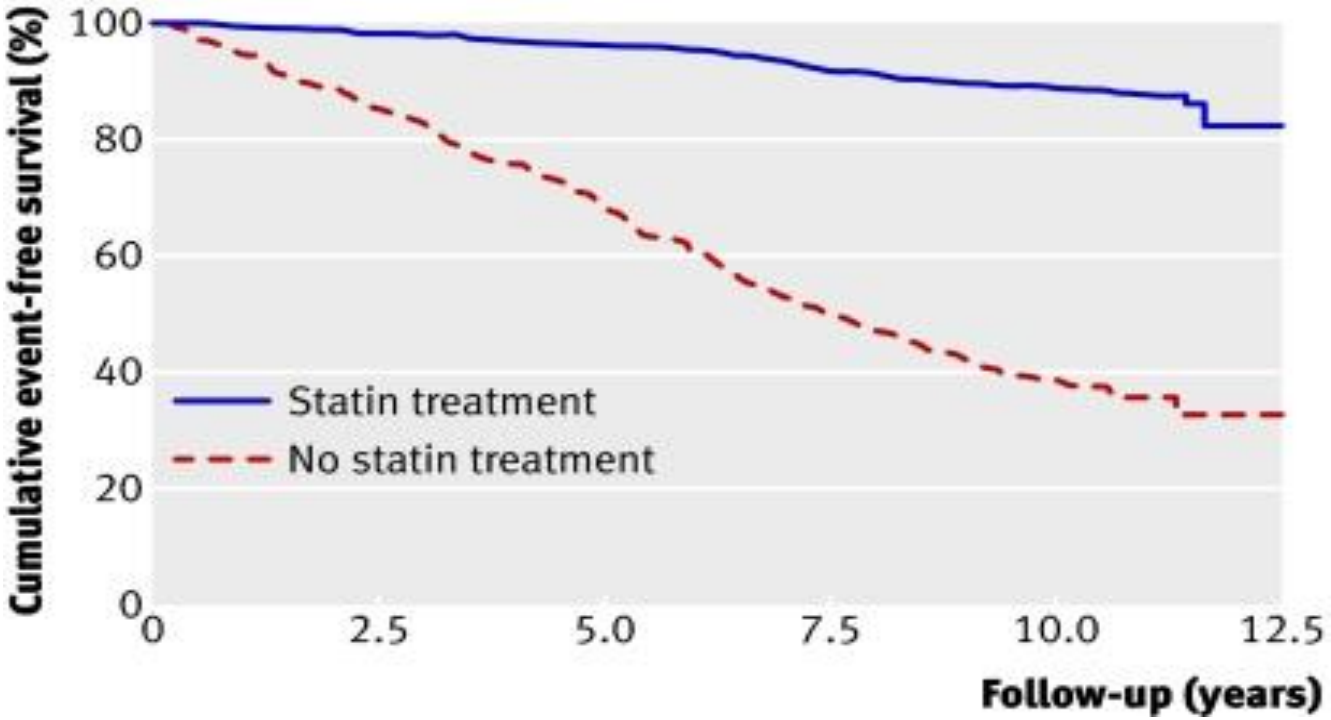
Statin treatment improves event-free survival in adults with FH



Kaplan-Meier curve estimates of cumulative coronary heart disease-free survival among patients with FH according to statin treatment ($p<0.001$ for difference)

Versmissen J et al. BMJ 2008 1;337:a2423.

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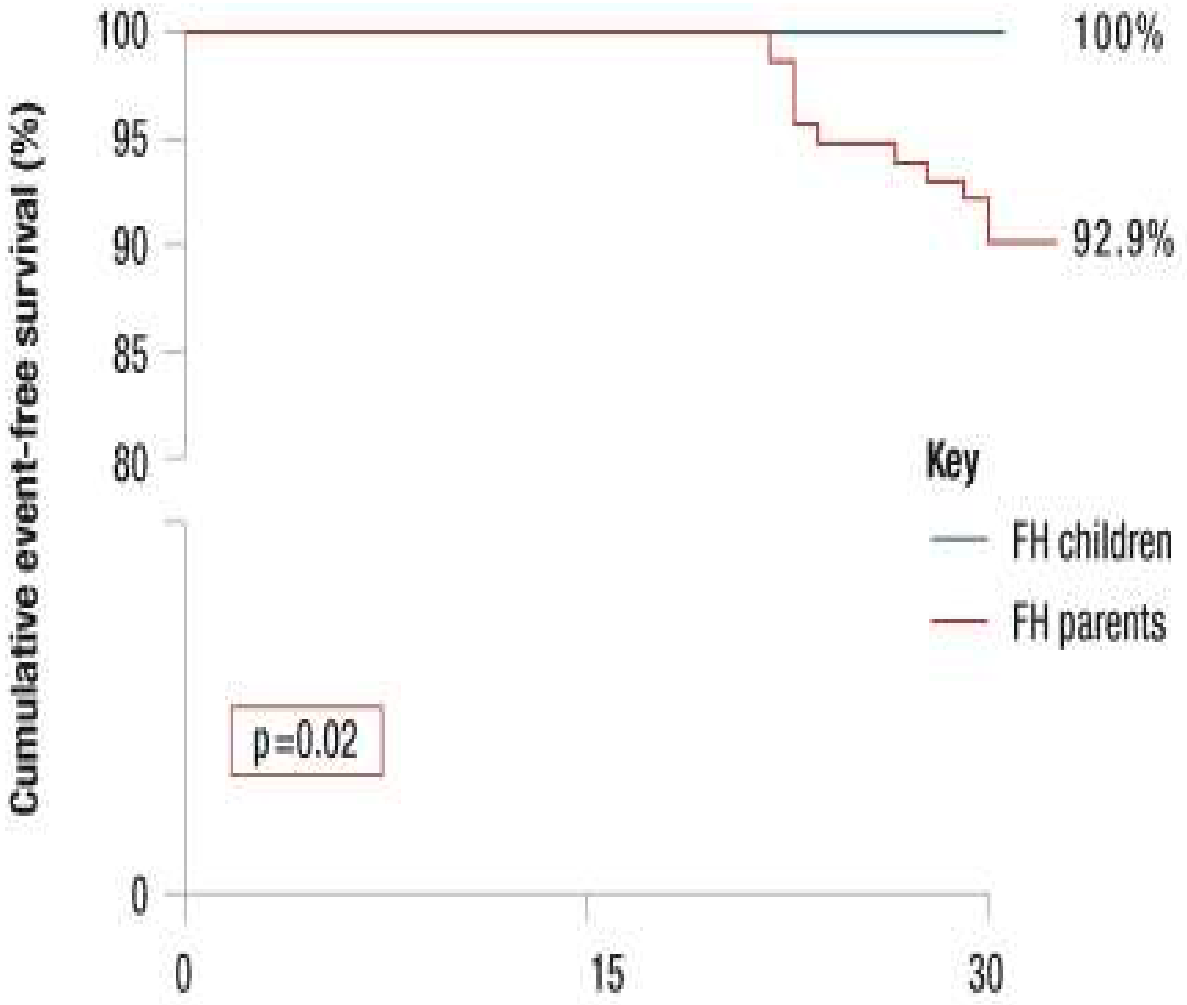
Impact of statins: Treated FH children vs treated FH parents



Braamskamp MJ et al. Circulation 2013;128:A17837,

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How to identify children with FH

Video: Dr Samuel Gidding, Nemours Cardiac Center, Wilmington, Delaware, USA discusses how to identify children with FH

http://www.pcsk9forum.org/how-to-identify-children-with-fh/

FH diagnosis is driven by phenotypic criteria

Family History + Hypercholesterolemia
= FH in Children*

*FH Foundation
http://thefhfoundation.org/

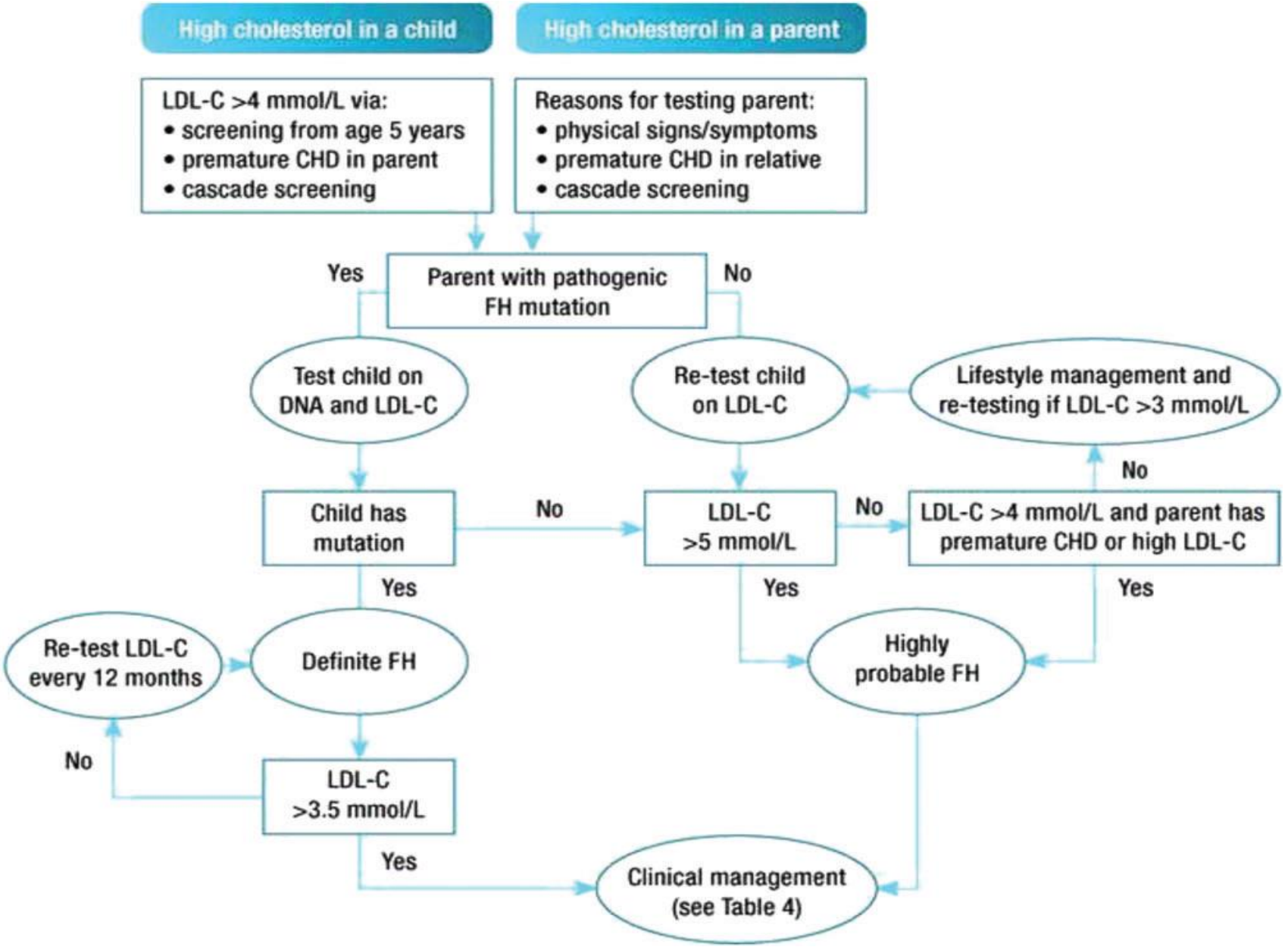
EAS Consensus Panel Recommendations Diagnosis of FH in Children

- Cholesterol testing should be used to make a phenotypic diagnosis

  ≥ 5 mmol/L (190 mg/dL) on two successive occasions over 3 months

  ≥ 4 mmol/L (160 mg/dL) and positive family history of premature cardiovascular disease

  ≥ 3.5 mmol/L (130 mg/dL) and positive genetic diagnosis in the family
- Rule out secondary causes (thyroid, liver or renal dysfunction, concomitant medication, obesity)
- Genetic testing confirms the diagnosis (after parental testing)



Wiegman A et al. Eur Heart J 2015 Epub ahead of print

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Reverse CASCADE Screening

- Identify children with FH
  - LDL cholesterol can be used to discriminate those with FH and those without in childhood
- Identify first degree family members with high LDL cholesterol
- Genotype the parents

Barriers to implementing cholesterol screening

- Awareness about FH
- Clinician
  - Belief in preventing early atherogenesis
  - Time/skill/reimbursement
- Family
  - Competing health issues
  - Education
  - Financial resources
  - Privacy concerns
- Society
  - Cost, relative importance, publicity, guideline support

How to manage children with FH

EAS Consensus Panel Recommendations Management: Diet and Lifestyle

- Assess CVD risk factors including Lp(a)
- No Smoking
- Encourage Exercise
- Diet
  - < 30% of calories from fat
  - < 7% of calories from saturated fat
  - < 200 mg cholesterol/day
  - appropriate energy for normal growth
  - sufficient in micronutrients

Wiegman A et al. Eur Heart J 2015 Epub ahead of print

EAS Consensus Panel Recommendations Treatment

- **Homozygous FH: start treatment at diagnosis**

- For children aged 8-10 years, LDL-C is ideally reduced by 50% from pre-treatment levels.

- For children aged ≥ 10 years, especially if there are additional cardiovascular risk factors, including elevated Lp(a), target LDL-C should be<3.5 mmol/L (130 mg/dL).

- Adherence should be checked if heterozygous FH children fail to achieve LDL-C targets with combination lipid-lowering treatment.

Wiegman A et al. Eur Heart J 2015 Epub ahead of print

Safety monitoring

- Check weight, growth, physical and sexual development, and well-being
- Hepatic aminotransferases: at least every 3 months if there is a history of liver disease; more frequently if levels increase >3-fold x ULN.
- Plasma CK levels: measure if musculoskeletal symptoms are reported.
- Fasting plasma glucose and/or random HbA1c: measure every 6 months in children on higher doses of statins, especially if obese or with impaired glucose tolerance

Safety monitoring discussed by Dr Albert Wiegman,

Academic Medical Center, Amsterdam, The Netherlands

http://www.pcsk9forum.org/safety-of-lowering-ldl-c/

Wiegman A et al. Eur Heart J 2015 Epub ahead of print

Targeting children with FH can make premature CHD history

Video: Dr Samuel Gidding, Nemours Cardiac Center, Wilmington, Delaware, USA discusses the importance of early identification and treatment of FH

http://www.pcsk9forum.org/making-premature-chd-history/