

Current and Future Therapeutic Approaches

Clinical case

*High risk patient, with FH,
in primary prevention*

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Case Study

44 year old, male patient. Married with 3 children aged 18-24

Clinical history : known to have high cholesterol since age of 17 years
father died at 45 years of age (MI)
older brother with high cholesterol

Physical status : BMI= 24 kg/m², BP 125/78 mmHg
increased thickness of Achilles tendon
non smoker, asymptomatic

Treatment : Atorvastatin 10 mg for \approx 20 years

Laboratory tests :

LDL-cholesterol	4.3 mmol/L (166 mg/dL)
HDL-cholesterol	1.0 mmol/L (39 mg/dL)
Triglycerides	0.85 mmol/L (75 mg/dL)
Blood glucose	5.4 mmol/L

Recommendations for the detection and treatment of patients with heterozygous familial hypercholesterolemia (FH)

Recommendations	Class*	Level†
It is recommended that a diagnosis of FH is considered in patients with CHD aged <55 years for men and <60 years for women, in people with relatives with premature fatal or non-fatal CVD, in people with relatives having tendon xanthomas, in people with severely elevated LDL-C levels [in adults >5 mmol/L (<190 mg/dL)], in children >4 mmol/L (>150 mg/dL)], and in first-degree relatives of FH patients	I	C
It is recommended that FH is diagnosed using clinical criteria and confirmed, when possible, with DNA analysis	I	C
Once the index case is diagnosed, family cascade screening is recommended	I	C
It is recommended that FH patients with ASCVD or who have another major risk factor are treated as very-high-risk, and those with no prior ASCVD or other risk factors as high-risk	I	C
For FH patients with ASCVD who are at very-high risk, treatment to achieve a ≥50% reduction from baseline and an LDL-C <1.4 mmol/L (<55 mg/dL) is recommended. If goals cannot be achieved, a drug combination is recommended	I	C
Treatment with a PCSK9 inhibitor is recommended in very-high risk FH patients if the treatment goal is not achieved on a maximal tolerated statin plus ezetimibe	I	C
In children, testing for FH is recommended from the age of 5 years, or earlier if HoFH is suspected	I	C

Table 12 Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia

Criteria	Points
1) Family history	
First-degree relative with known premature (men aged <55 years; women <60 years) coronary or vascular disease, or first-degree relative with known LDL-C above the 95th percentile	1
First-degree relative with tendinous xanthomata and/or arcus cornealis, or children aged <18 years with LDL-C above the 95th percentile	2
2) Clinical history	
Patient with premature (men aged <55 years; women <60 years) CAD	2
Patient with premature (men aged <55 years; women <60 years) cerebral or peripheral vascular disease	1
3) Physical examination^a	
Tendinous xanthomata	6
Arcus cornealis before age 45 years	4
4) LDL-C levels (without treatment)	
LDL-C ≥ 8.5 mmol/L (≥ 325 mg/dL)	8
LDL-C 6.5–8.4 mmol/L (251–325 mg/dL)	5
LDL-C 5.0–6.4 mmol/L (191–250 mg/dL)	3
LDL-C 4.0–4.9 mmol/L (155–190 mg/dL)	1
5) DNA analysis	
Functional mutation in the <i>LDLR</i> , <i>apoB</i> , or <i>PCSK9</i> genes	8

A 'definite' FH diagnosis requires >8 points

A 'probable' FH diagnosis requires 6–8 points

A 'possible' FH diagnosis requires 3–5 points

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Case Study : *What is the risk category for this patient ?*

Patient with FH

without other major risk factors

→ High-risk

with ASCVD or with another major risk factor

→ Very high-risk

Consensus Statement from IAS :

Factors that increase CV risk in FH patients

- > 40 years without treatment
- Male sex
- Smoking
- Low HDL-C
(< 1 mmol/L, < 40 mg/dL)
- Hypertension
- Diabetes mellitus
- BMI > 30 kg/m²
- CKD (eGFR < 60 mL/min/1.73 m²)
- Lp(a) > 50 mg/dL (75 nmol/L)
- Family history of early CVD in first-degree relatives
 - < 55 years males
 - < 60 years females

Patients with familial hypercholesterolaemia without clinically diagnosed ASCVD on maximally tolerated statin plus ezetimibe therapy

Check for additional **indices of risk severity**

- Diabetes mellitus with target organ damage (e.g. proteinuria), or with a major risk factor (e.g. marked hypertension)
- Lipoprotein(a) >50 mg/dL
- Major risk factors: smoking, marked hypertension
- >40 years of age without treatment
- Premature ASCVD (<55 years in males and <60 years in females) in first-degree relatives
- Imaging indicators (refer to text)

No additional indices of risk severity
LDL-C >4.5 mmol/L (>180 mg/dL)

Additional indices of risk severity
LDL-C >3.6 mmol/L (>140 mg/dL)*

* Confirmed on two consecutive occasions

Consider a PCSK9 inhibitor

Case Study : *What complementary exams do you propose to this patient ?*

1. Genetic diagnosis of FH
2. Measurement of Lp(a)
3. Evaluation of sub-clinical atherosclerosis
4. All of the above

Case Study : *What complementary exams do you propose to this patient ?*

✓ **Genetic analysis** :

Null mutation of exon 14 in LDL receptor gene

✓ **Lp(a)** : 124 mg/dL

✓ **CT angiography** : CAC score 435 Agatston units
(non obstructive plaques)

Case Study : *What does this patient persist at elevated ASCVD risk in spite of statin use ?*

1. Very early exposition to high cholesterol
2. Family history of early CHD
3. High Lp(a)
4. Advanced subclinical atherosclerosis
5. All of above

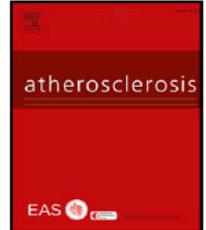


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High burden of recurrent cardiovascular events in heterozygous familial hypercholesterolemia: The French Familial Hypercholesterolemia Registry



Key findings

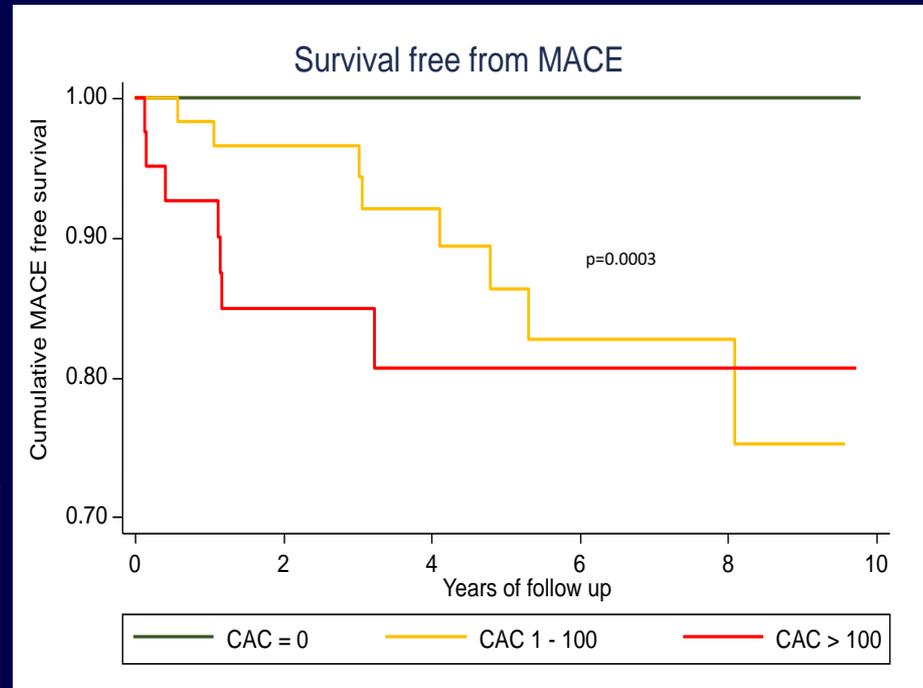
- First CV event occurred at the mean age of 47 years (72% male)
- 37% of patients had at least one recurrent CV event (mean of 1.8 events per patient)

Coronary artery calcification and cardiovascular events in statin-treated FH

206 molecularly proven HeFH individuals
Age 45±14 years
79.6% with high-dose statin
64% also with ezetimibe
On-treatment LDL-C 150±56 mg/dL

CAC present in 105 individuals
(51%)

Follow-up median of 3.7 (quartiles: 2.7–6.8) years
ASCVD events (7.2%)
Annualised event rate (1,000 patients/year)
CAC 0 = 0
CAC 1–100 = 26.4 (95% CI 12.9–51.8)
>100 = 44.1 (95% CI 26.0–104.1)



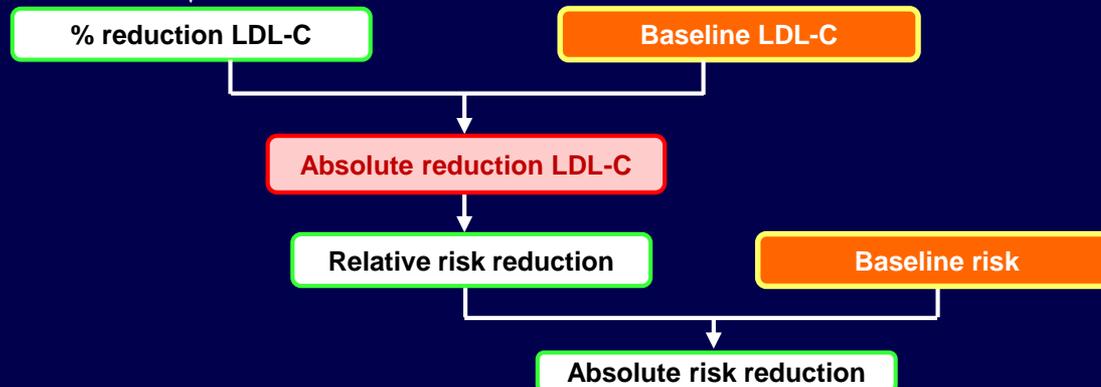
Case Study : *What would your treatment strategy be ?*

1. High intensity statin
2. High intensity statin + ezetimibe combination
3. Add PCSK9 inhibitor

Expected clinical benefits of LDL-cholesterol-lowering therapies

Intensity of lipid-lowering treatment

Treatment	Average LDL-C reduction
Moderate-intensity statin	≈ 30%
High-intensity statin	≈ 50%
High-intensity statin plus ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor plus high-intensity statin	≈ 75%
PCSK9 inhibitor plus high-intensity statin plus ezetimibe	≈ 85%



Case Study : *What would your treatment strategy be ?*

✓ Action Taken

Treatment : Rosuvastatin 20 mg + Ezetimibe 10 mg

✓ Follow-up after 8 weeks

LDL cholesterol 2.4 mmol/L (93 mg/dL)

HDL cholesterol 1.2 mmol/L (46 mg/dL)

Triglycerides 1.0 mmol/L (88 mg/dL)

Case Study : *What would your attitude be ?*

1. Switch to Atorvastatin 80 mg + Ezetimibe 10 mg
2. Up-titrate Rosuvastatin to 40 mg
3. Consider a PCSK9 inhibitor
4. Consider a bile acide sequestrant

Recommendations for the detection and treatment of patients with heterozygous familial hypercholesterolemia (FH)

In primary prevention, for individuals with FH at very-high risk, an LDL-C reduction of $\geq 50\%$ from baseline and an LDL-C goal of < 1.4 mmol/L (< 55 mg/dL) should be considered.

Treatment with a PCSK9 inhibitor is recommended in very-high-risk FH patients if the treatment goal is not achieved on maximal tolerated statin plus ezetimibe.

IIa

C

I

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Case Study : *What else to do ?*

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