



## Case 4



Jack


# Familial Hypercholesterolemia




## Learning Objectives

Upon completion of this case based session, participants will be able to:

- 01** Review the diagnostic criteria for Familial Hypercholesterolemia
- 02** Apply the newly proposed Canadian definition of Familial Hypercholesterolemia
- 03** Employ evidence-based recommendations to LDL-C targets in this population



## Case 4 Initial Visit



**Jack**  
54 years old

### Jack's History

- Jack hasn't seen a doctor in the last 15 years
- Comes in for a consult for erectile dysfunction
- He is an active smoker of 1 pack/day since 40 years
- His brother had an MI at 42 and father died suddenly at 51
- Doesn't drink alcohol but leads a sedentary lifestyle
- No chest pain on exertion


### Physical Exam

- BMI :25 kg/m<sup>2</sup>
- Waist circumference: 88 cm
- BP: 132/70 mmHg
- HR 72 BPM
- Bilateral tendon xanthoma
- Absence of peripheral pulse

### Medications

- None

## Case 4 Initial Visit



**Jack**  
54 years old


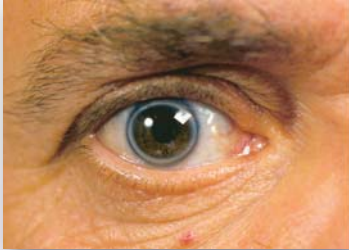


### Cholesterol Panel

- TC : 11.35 mmol/L
- TG : 2.20 mmol/L
- LDL-C: 8.72 mmol/L
- HDL-C: 1.58 mmol/L
- Non-HDL-C: 9.77 mmol/L

### Other Lab Values

- LFT: Normal
- Creatinine: 82 umol/L
- TSH: 2.4 mIU/L
- A1C: 5.3%
- No proteinuria

## Physical Exam in FH Patient

FH: Familial Hypercholesterolemia

Photos credit: Mx. Watts GF. Drugs. 2015;75:1715-24. Monreal JM. Br J Cardiol. 2008;15:76-81; Roshan B, et al. J Clin Lipidol. 2011;5:493-9. Varghese MJ. Ann Pediatr Cardiol. 2014;7:107-17. Yuan G, et al. CMAJ. 2006;174:1124-9.

## Simon Broome Diagnostic Criteria For Familial Hypercholesterolemia (FH) In Adults

**01** A plasma measurement of either:

- Total cholesterol > 7.5 mmol/L (adult patient) or > 6.7 mmol/L (child aged < 16 years)
- Low-density lipoprotein cholesterol > 4.9 mmol/L (adult patient) or > 4.0 mmol/L (child aged < 16 years)

Definite FH

**02 PLUS**  
Tendon xanthomas in the patient or any of the patient's first- or second degree relatives

**03 OR**  
DNA-based evidence in the patient of mutation in LDLR or other FH related gene

Possible FH

**04 PLUS**  
Family history of myocardial infarction before the age of:

- 50 Years, in any first- or second-degree relative
- 60 Years, in any first-degree relative

**05 OR**  
Family history of plasma total cholesterol > 7.5 mmol/L in any first- or second-degree relative

Genest J. et al. Canadian Cardiovascular Society Position Statement on Familial Hypercholesterolemia Canadian Journal of Cardiology 30 (2014) 1471e1481

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LDL-C &gt; 5.0 mmol/L – not on treatment: Consider FH



LDL-C &gt; 3.0 mmol/L – on statin therapy: Suspect FH



Review the family history

03

OR

DNA-based evidence in the patient of mutation in LDLR or other FH related gene

05

OR

Family history of plasma total cholesterol > 7.5 mmol/L in any first- or second-degree relative

Genest J. et al. Canadian Cardiovascular Society Position Statement on Familial Hypercholesterolemia. Canadian Journal of Cardiology 30 (2014) 1471e1481



## Newly Proposed Canadian Definition Of Familial Hypercholesterolemia (FH) Based On The Simon-Broome Criteria

LDL-C  $\geq$  5.0 mmol/L  
( $\geq$  4.0 mmol/L in <18 yo;  $\geq$  4.5 mmol/L in 18-40 years)



Known DNA Mutation  
OR  
Xanthomas

YES

Definite FH

NO

1st degree relative with  $\uparrow$  LDL-C  
OR  
1st degree relative with early onset ACVD

YES

Probable FH

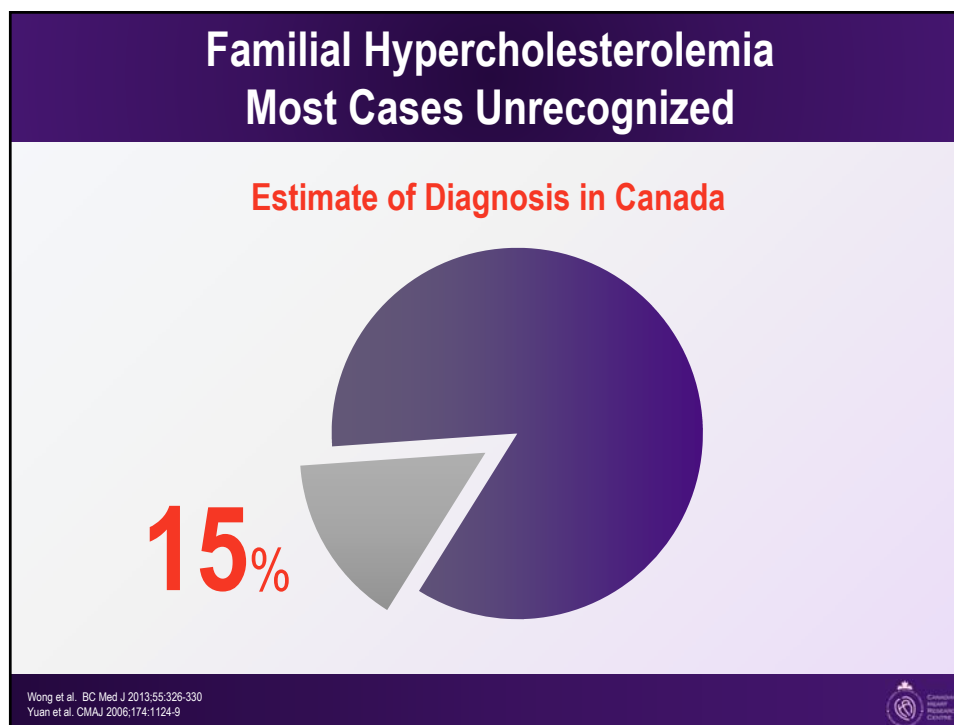
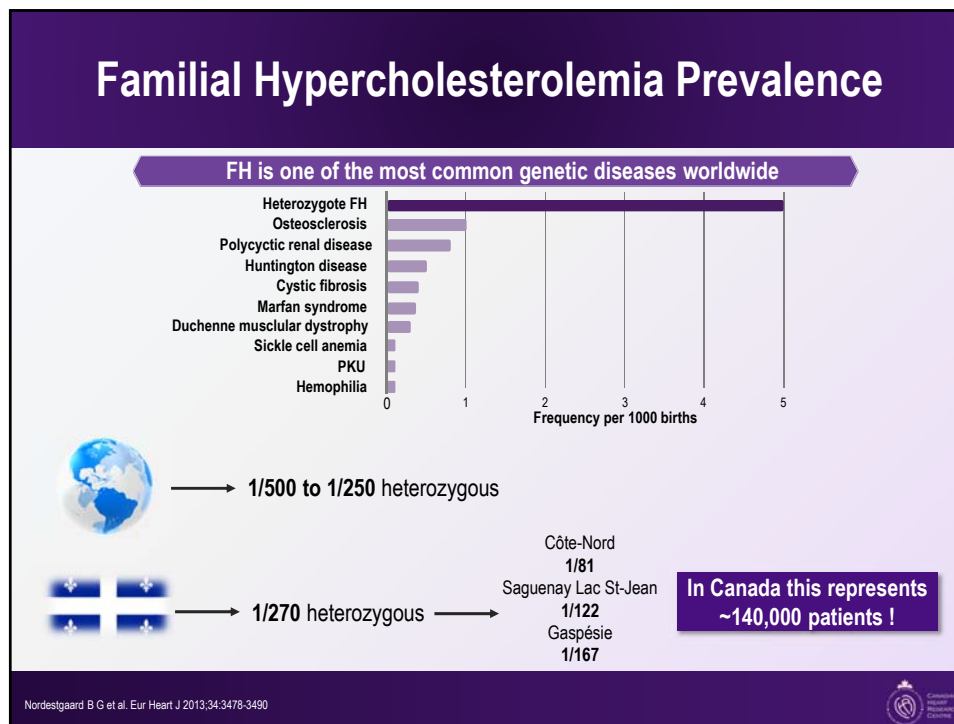
NO

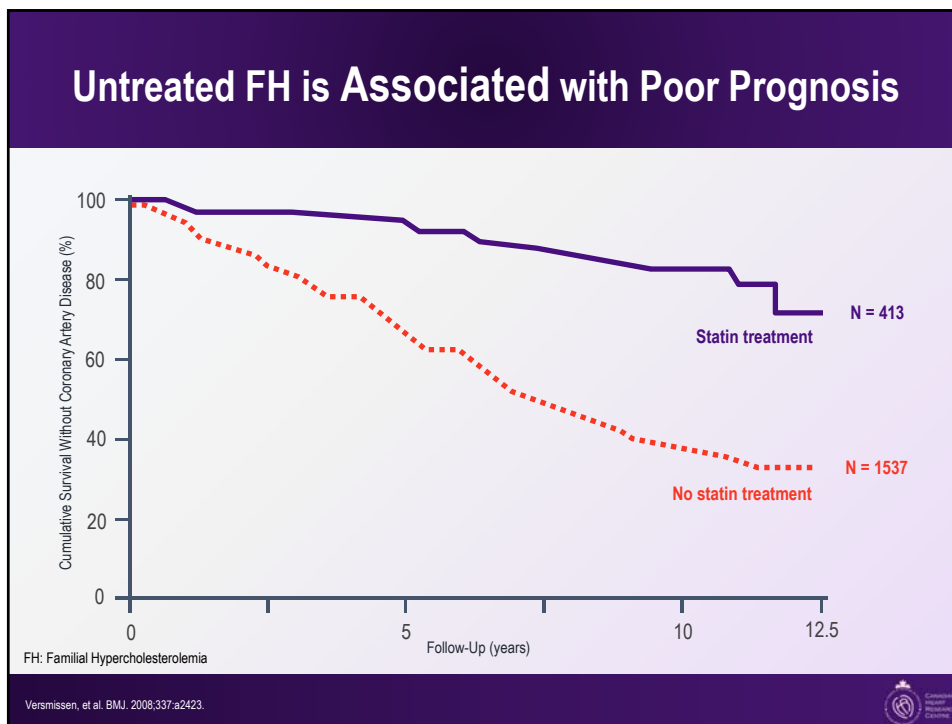
Hypercholesterolemia  
(Consider DNA testing)

\* Secondary causes ruled out (nephrotic syndrome, obstructive jaundice and hypothyroidism)

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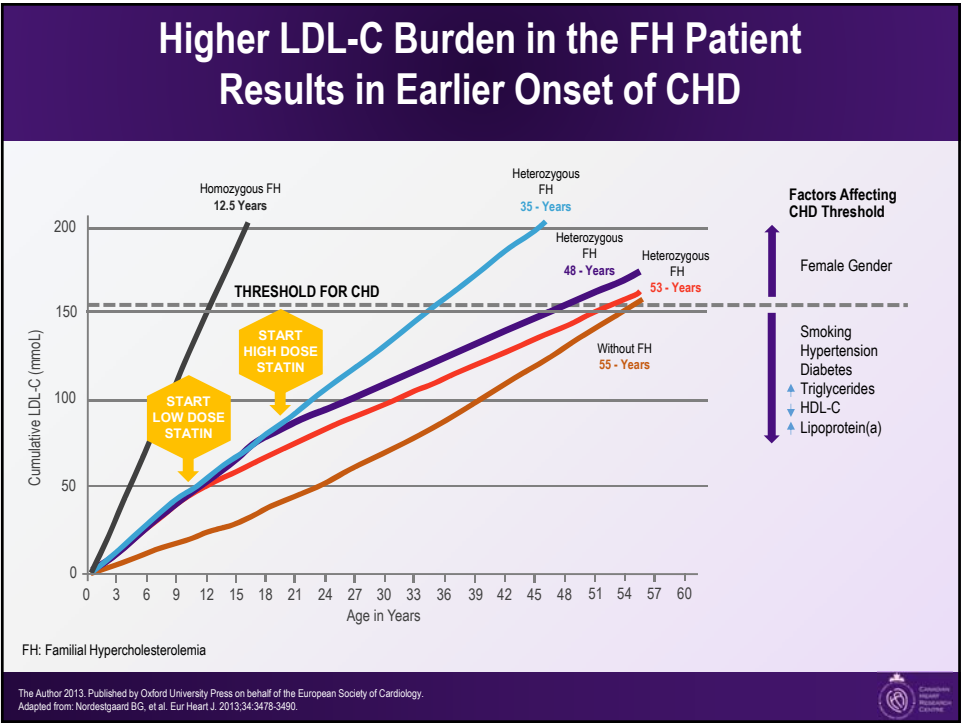
### Homozygous vs Heterozygous FH

Homozygous FH	Heterozygous FH
1 out of 160,000 to 1 million people	1 out of 250 people
LDL-C > 13 mmol/L	LDL-C > 5 mmol/L
Little or no functional LDL receptors	LDL receptors 2 times less numerous
Plasma LDL-C levels 6 to 10 times higher	Plasma LDL-C levels 2 times higher
Severe and extensive atherosclerosis	Risk of coronary artery disease ~ 20X higher in untreated patients
Frequent cases of heart attack during childhood	5% of all cases of heart attacks in people <60 years

FH: Familial Hypercholesterolemia

Cuchel M, et al. Eur Heart J. 2014;35:2146-57; Genest J, et al. Can J Cardiol. 2014;30:1471-81. Goldstein JL, Brown MS. Arterioscler Thromb Vasc Biol. 2009;29:431-8. Moorkjani S, et al. Arteriosclerosis 1989;9:211-6; Nordestgaard BG, et al. Eur Heart J. 2013;34:3478-90. Vallejo-Vaz AJ, et al. Atherosclerosis. 2015;243:257-9. Watts GF, et al. J Clin Lipidol. 2014;8:148-72.

Canadian Cardiovascular Society Pharmacological Treatment Indications and Targets			
Category	Consider Initiating pharmaco-therapy if:	Target	NNT
Primary Prevention	High (FRS ≥20%)	LDL-C <2.0 mmol/L or >50% ↓  Or  Apo B <0.8 g/L  OR  non-HDL-C <2.6 mmol/L	35
	Intermediate (FRS 10-19%) LDL-C ≥3.5 mmol/L or Non-HDL-C ≥4.3 mmol/L or Apo B ≥1.2 g/L or Men ≥50 and women ≥60 yrs and one additional CVD RF		40
Statin Indicated Conditions**	Clinical atherosclerosis*		20
	Abdominal aortic aneurysm		
	Diabetes mellitus ≥40 yrs 15 yrs duration for age ≥30 yrs (DM1) Microvascular disease		
	Chronic kidney disease (age ≥50 y) eGFR <60 mL/min/1.73 m2 or ACR > 3 mg/mmol		
	LDL-C ≥5.0 mmol/L	>50% ↓ in LDL-C	
<small>NNT: number needed to treat to prevent one CVD event for 5 years of treatment per 1 mmol/L reduction in LDL-C. NNT of &lt;50 are generally regarded as desirable by physicians with some patients wishing to see NNT &lt;30 to deem an intervention as acceptable. FRS - modified Framingham Risk Score; ACR - albumin:creatinine ratio; * consider LDL-C &lt;1.8 mmol/L for subjects with ACS within last 3 months ** statins indicated as initial therapy</small>			
<small>Anderson et al. 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult Canadian Journal of Cardiology 2016;32:1263-1282</small>			



**Case 4**  
 Visit 2 - 3 months follow-up




**Jack**  
54 years old

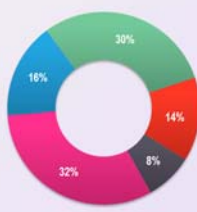
You prescribed atorvastatin 80 mg plus lifestyle modifications to Jack 3 months ago and he returns for a follow-up appointment

His most recent LDL-C is **4.01** mmol/L

- Initial Visit LDL-C: 8.72 mmol/L

## There Is a Need for More Robust Lipid Lowering in HeFH

- 
**Netherlands study of 1,249 patients with HeFH**
  - 96% were on statins
  - 79% of these did not achieve LDL-C target of < 2.5 mmol/L
  - Only 27% were using maximum therapy\*
- 47% of patients achieved 50% LDL-C reduction but were still  $\geq 2.5$  mmol/L
- Maximum lipid-lowering therapy is defined as maximum statin dose in combination with ezetimibe.
- The mean LDL-C for all patients was  $3.2 \pm 1.1$  mmol/L.




Reason	Percentage	n
Unknown	16%	48
Dosing Phase	30%	67
Adverse Events	14%	41
Reluctance of Patients	8%	25
Physician Satisfied	32%	93

HeFH: Heterozygous Familial Hypercholesterolemia

Pijlman AH, et al. Atherosclerosis. 2010;209:189–194.



**Case 4**  
 Visit 3 - 3 months follow-up



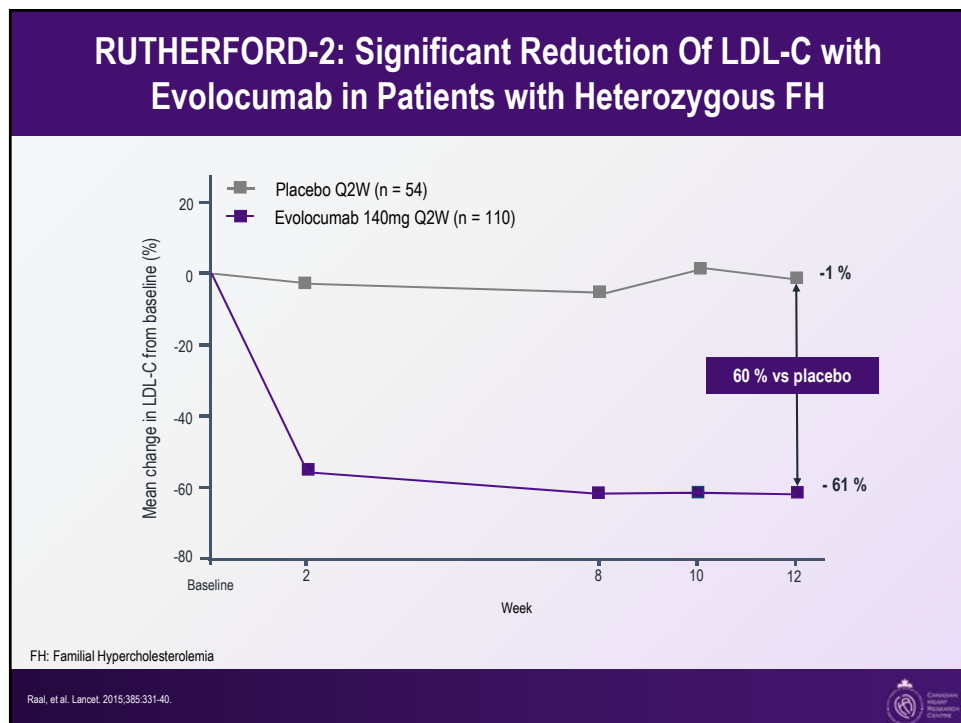
**Jack**  
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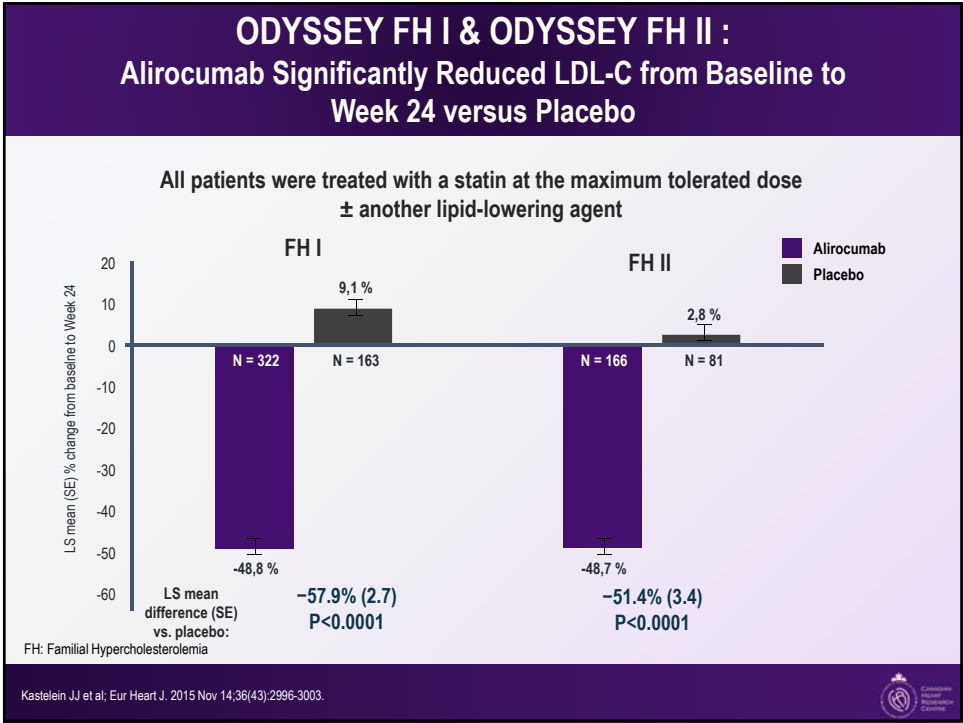
You added ezetimibe 10 mg to atorvastatin 80 mg at Jack's previous visit. Jack comes in for his follow-up appointment after 3 months.

His most recent LDL-C is **3.2 mmol/L**

- Visit 2 LDL-C: 4.01 mmol/L
- Initial Visit LDL-C: 8.72 mmol/L

You decide to prescribe Evolocumab 140mg SC q 2 w





**Case 4**  
**Visit 4 - 3 months follow-up**

**Jack**  
54 years old

**Jack's Lipid Lowering Therapy**

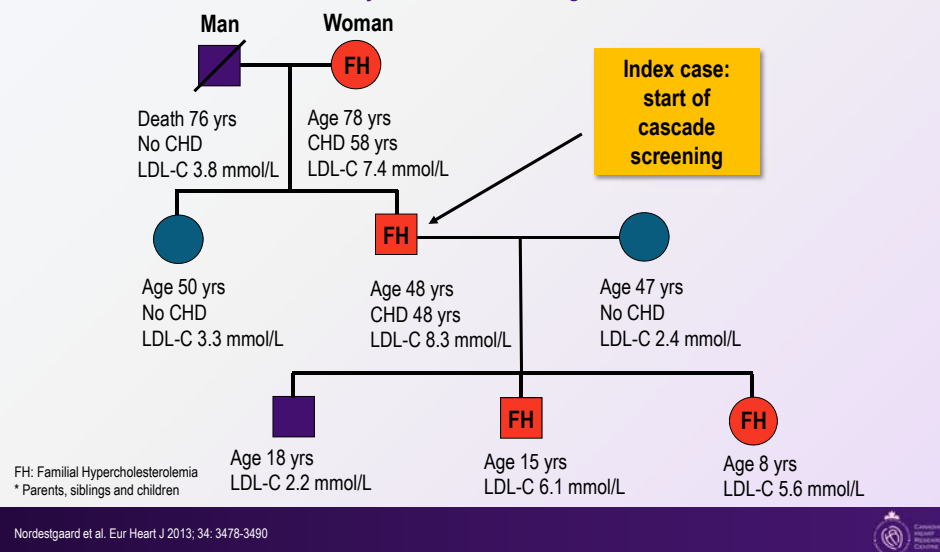
- Atorvastatin 80 mg
- Ezetimibe 10 mg
- Evolocumab 140mg SC q 2 w

His most recent LDL-C is **1.12 mmol/L**

- Visit 3 LDL-C: 3.2 mmol/L
- Visit 2 LDL-C: 4.01 mmol/L
- Initial Visit LDL-C: 8.72 mmol/L

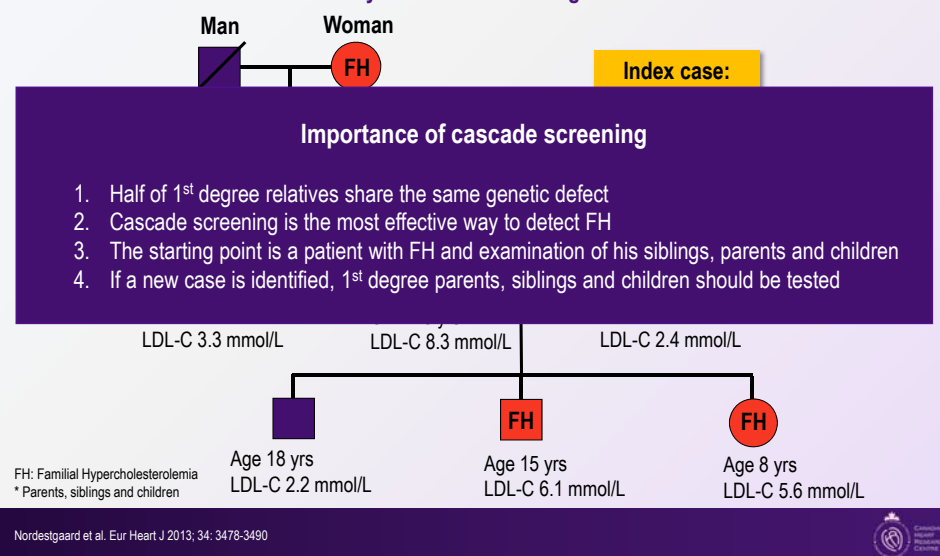
## Importance of Cascade Screening in FH

The presence of high cholesterol and early onset of coronary heart disease in some immediate family members\* are strong indicators of FH



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The presence of high cholesterol and early onset of coronary heart disease in some immediate family members\* are strong indicators of FH



## Summary

- Most FH cases are unrecognized
- A systematic approach should be used to detect the FH patient
- A robust lipid lowering treatment plan is required, including the addition of a PCSK9 inhibitor, to achieve the LDL-C target in this population

