European Heart Journal
doi:10.1093/eurheartj/eht273

CURRENT OPINION

Eur Heart J 2013; 34: 3478-3490

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

Heterozygous familial hypercholesterolaemia (FH)

Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

EAS

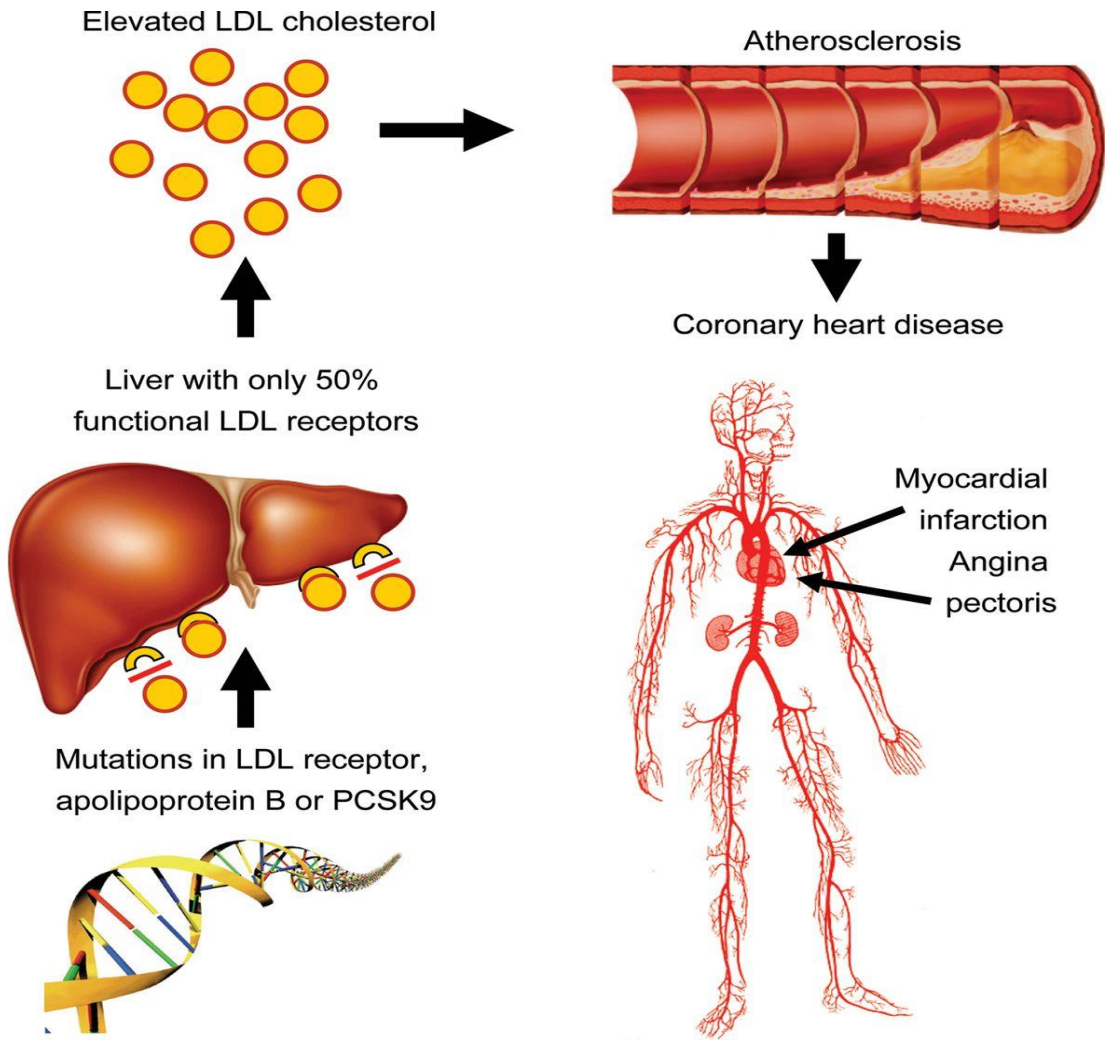
Pathophysiology & genetics

Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

EAS

Pathophysiology of heterozygous familial hypercholesterolaemia.

European Heart Journal

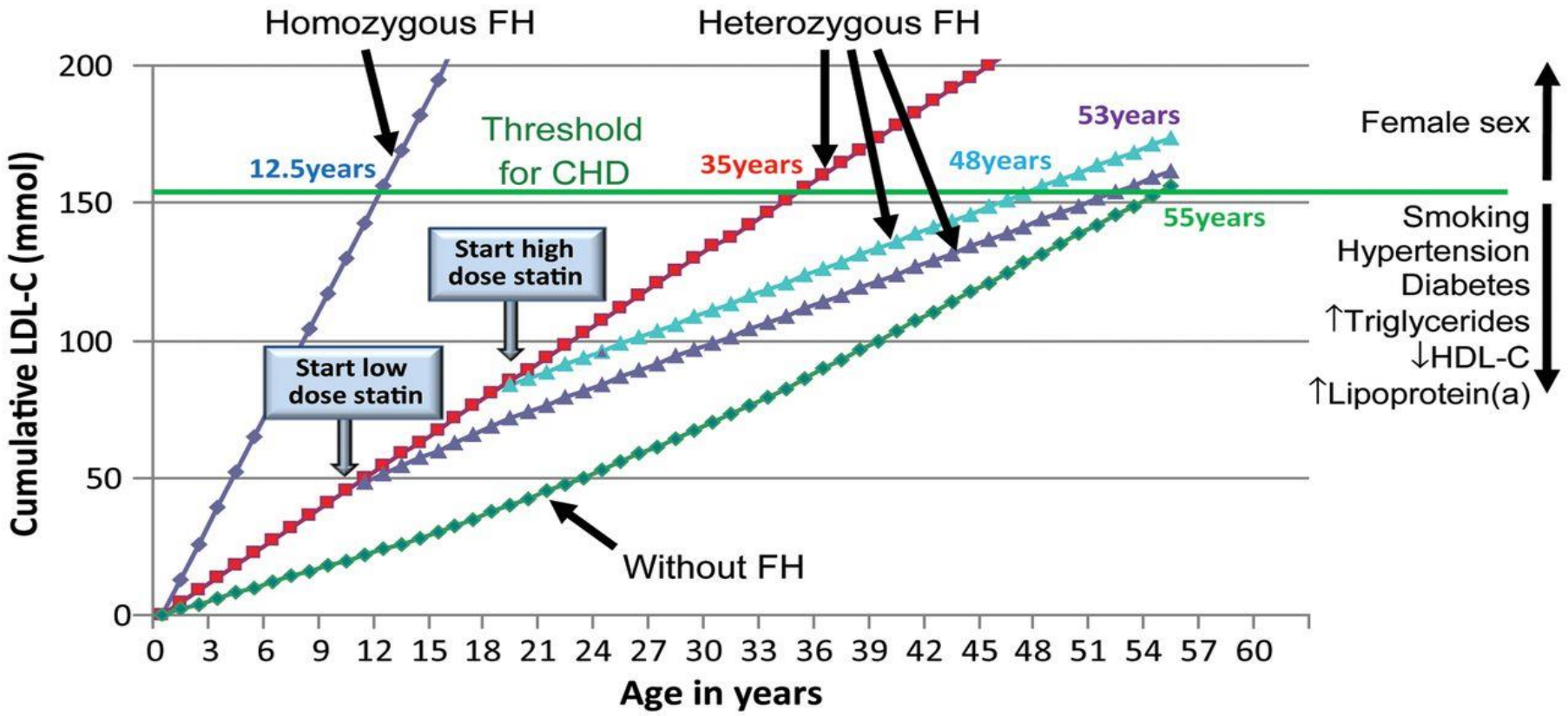


Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

EAS

LDL cholesterol burden in individuals with or without familial hypercholesterolaemia as a function of the age of initiation of statin therapy.

European Heart Journal



Adapted from Steve Humphries 2013

Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

EAS

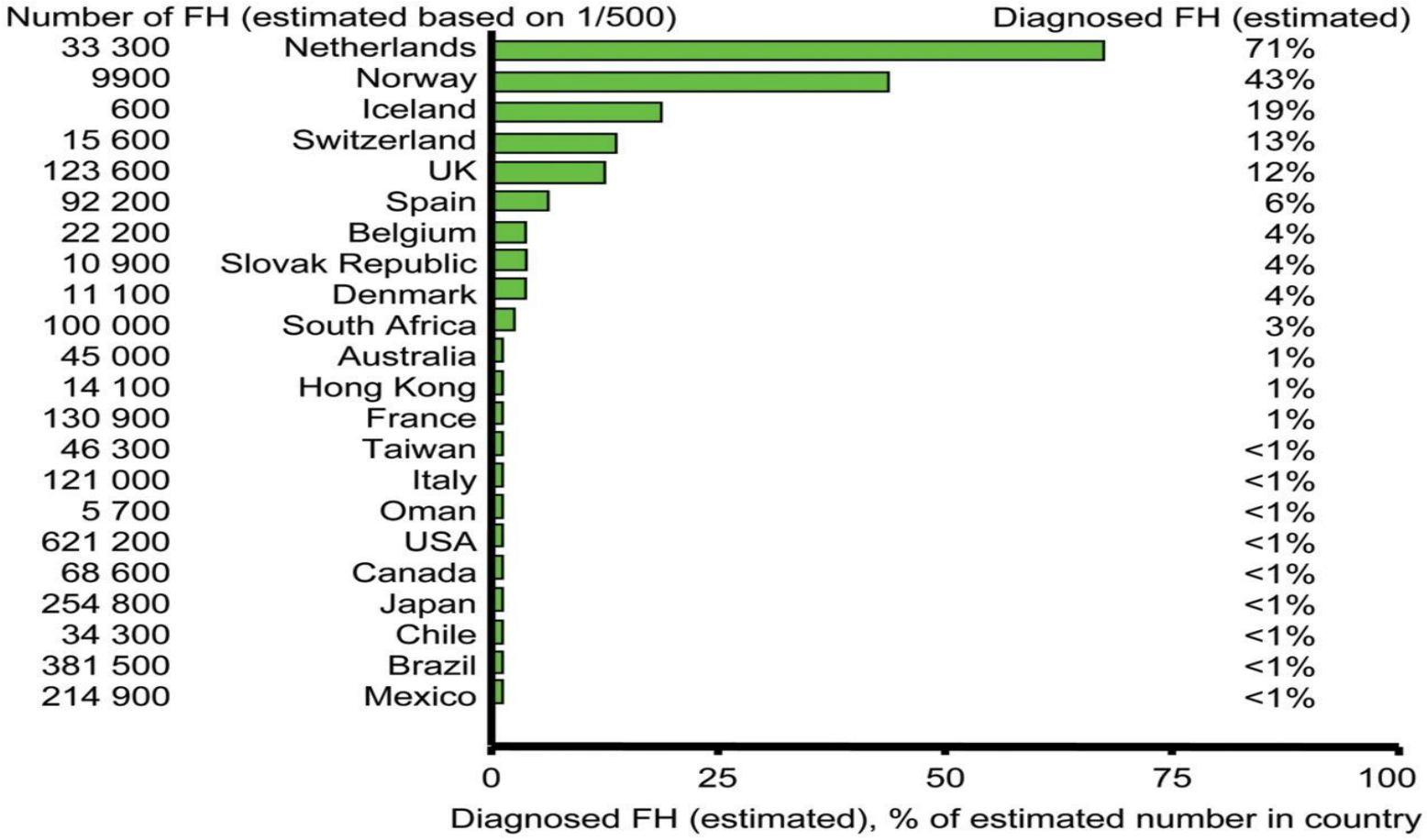
Underdiagnosis & undertreatment

Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

EAS

Estimated per cent of individuals diagnosed with familial hypercholesterolaemia in different countries/territories, as a fraction of those theoretically predicted based on a frequency of 1/500 in the general population.

European Heart Journal



~ 200 countries or territories in the World

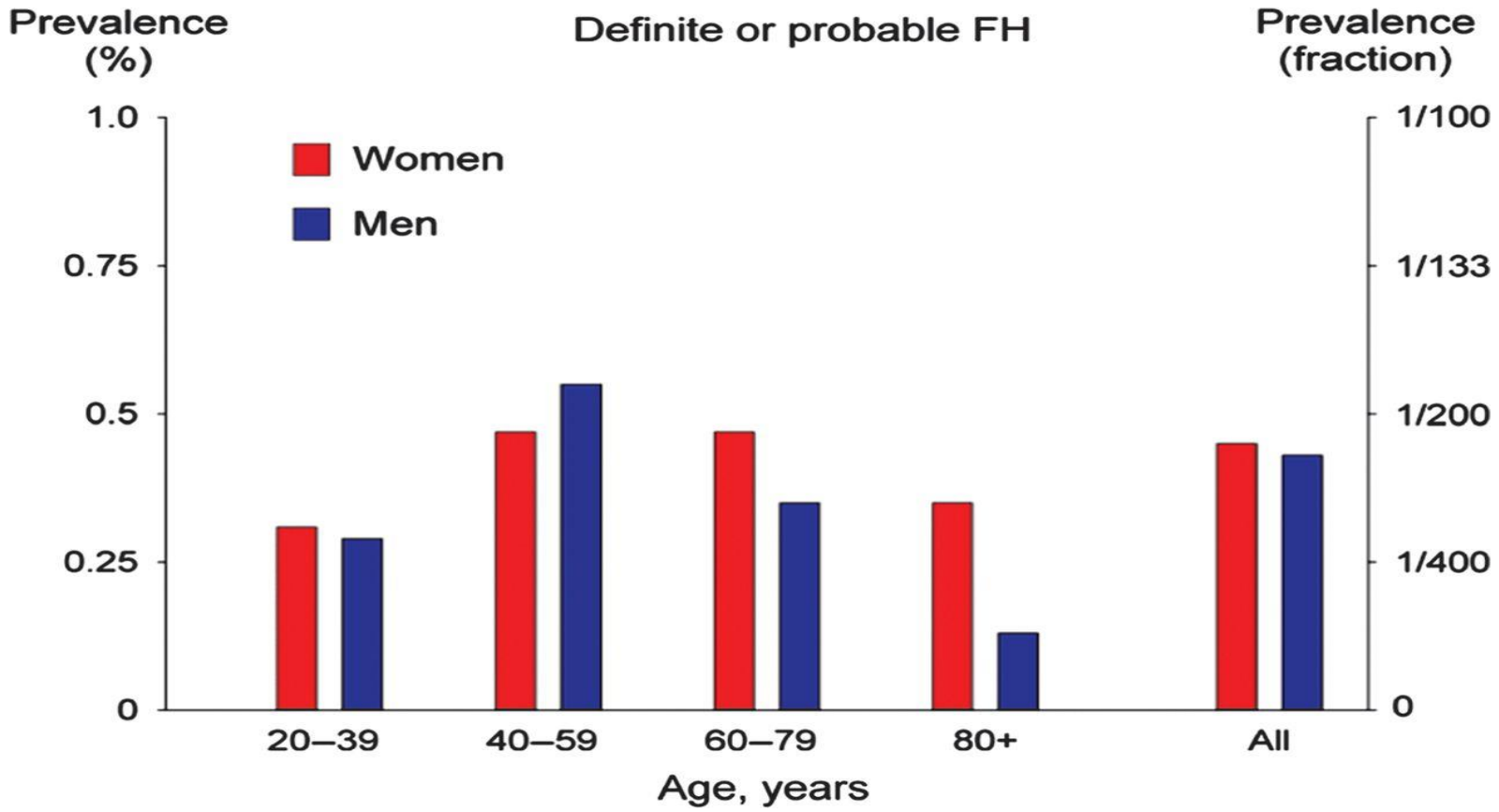
Numbers from Livingston, Descamps & Humphries

Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

EAS

Prevalence of definite or probable familial hypercholesterolaemia according to Dutch Lipid Clinic Network Criteria in the Copenhagen General Population Study by 20-year age groups and by gender.

European Heart Journal



Screening 69,000 persons from the Copenhagen General Population Study

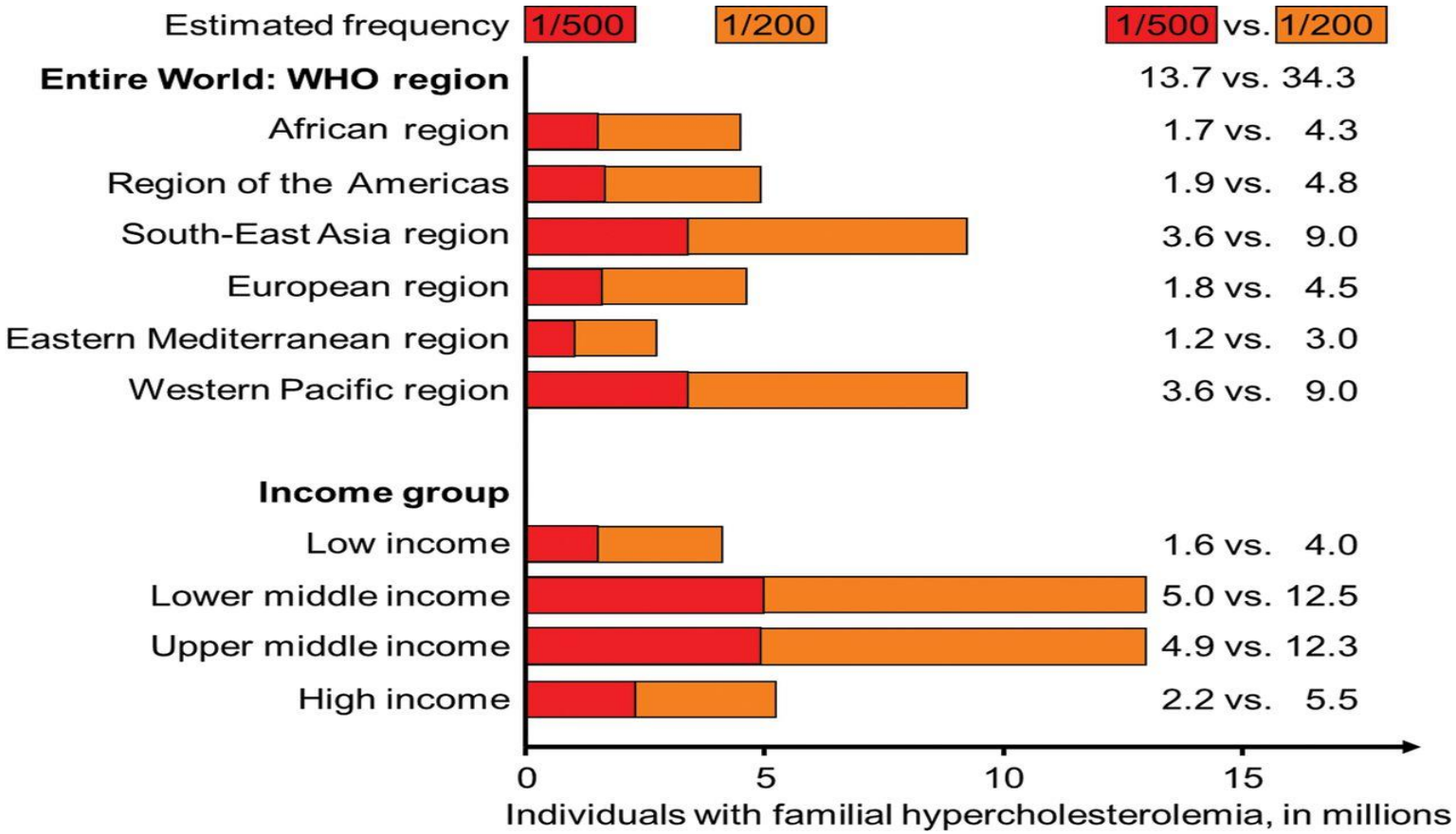
Adapted from Benn et al J Clin Endocrin Metab 2012; 97: 3956-3964

Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

EAS

Estimated millions of individuals worldwide with familial hypercholesterolaemia by WHO regions and by income groups.

European Heart Journal



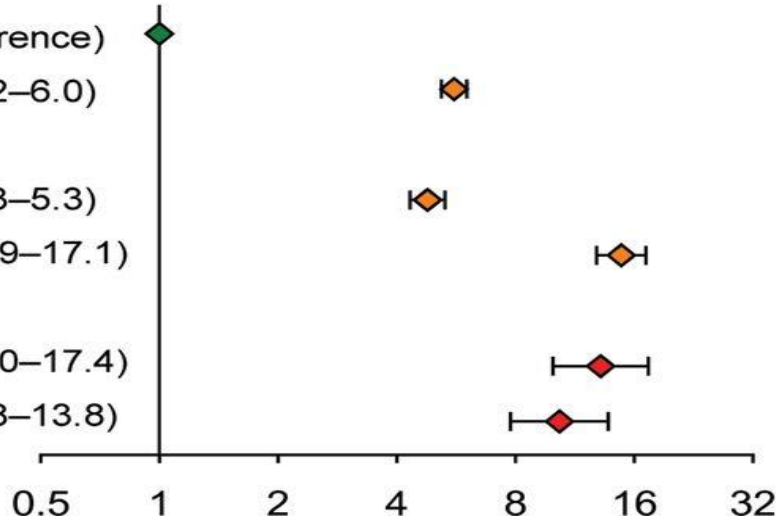
Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

EAS

Risk of coronary heart disease as a function of the Dutch Lipid Clinic Network Criteria for a diagnosis of familial hypercholesterolaemia in individuals on or off statin from the general population.

European Heart Journal

	Statin	No. of participants	No. of CHDs	Odds ratio (95% CI)
Unlikely FH	Off	58 158	2592	1 (Reference)
	On	6061	1884	5.6 (5.2–6.0)
Possible FH	Off	3380	604	4.8 (4.3–5.3)
	On	915	406	14.8 (12.9–17.1)
Definite or probable FH	Off	260	84	13.2 (10.0–17.4)
	On	242	84	10.3 (7.8–13.8)



Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

EAS

Whom to screen: how to find index cases?

Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

EAS

We recommend:

European Heart Journal

children, adults, and families
should be screened for FH if

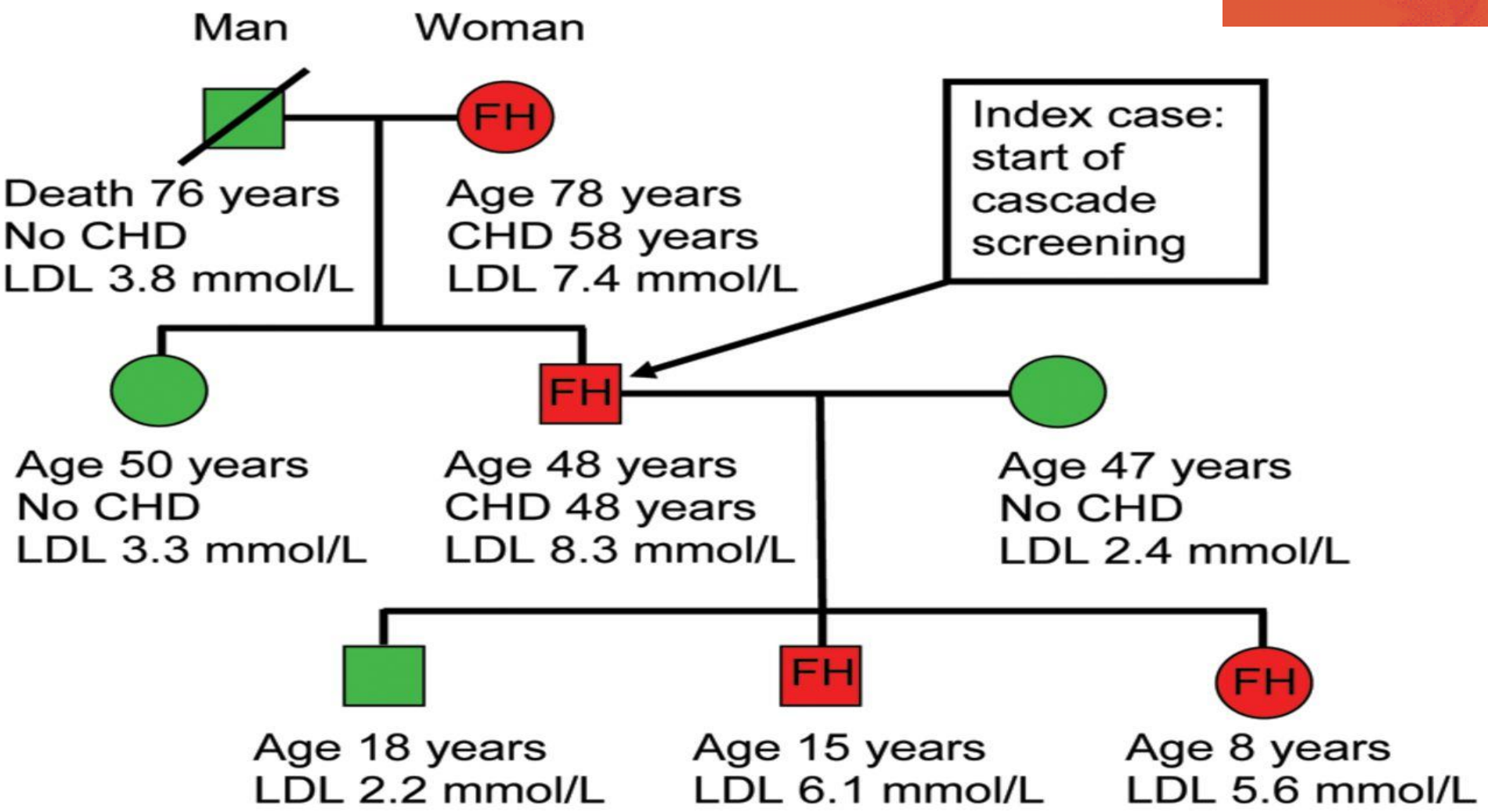
- Family member presents with FH
- P-cholesterol in adult ≥8mmol/L (≥310mg/dL)
- P-cholesterol in child ≥6mmol/L (≥230mg/dL)
- Premature CHD
- Tendon xanthomas
- Sudden premature cardiac death

Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

EAS

Pedigree of a family with familial hypercholesterolaemia

European Heart Journal



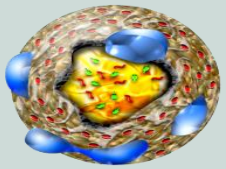
Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

EAS

European Heart Journal

DUTCH FH CRITERIA

Feature	Score
Family history	
First-degree relative with known premature coronary and/or vascular disease (men <55 years, females <60 years) OR First-degree relative with known LDL-C above the 95th percentile for age and sex	1
First-degree relative with tendinous xanthomata and/or arcus cornealis OR Children aged less than 18 years with LDL-C above the 95th percentile for age and sex	2
Clinical history	
Premature coronary artery disease (men <55 years, females < 60 years)	2
Premature cerebral or peripheral vascular disease (men <55 years, females <60 years)	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis prior to age 45 years	4
LDL-C (mmol/L) – 8.5 or higher – 6.5 to 8.4 – 5.0 to 6.4 – 4.0 to 4.9	 8 5 3 1
DNA analysis: functional mutation in the *LDLR*, *APOB* or *PCSK9* gene	8



Stratification of familial hypercholesterolaemia (FH), as determined by total score using the Dutch Lipid Clinic Network Criteria:

- **Definite FH = total score greater than 8**
- **Probable FH = total score between 6 and 8**
- **Possible FH = total score between 3 and 5**
- **Unlikely FH = total score of less than 3**

EAS

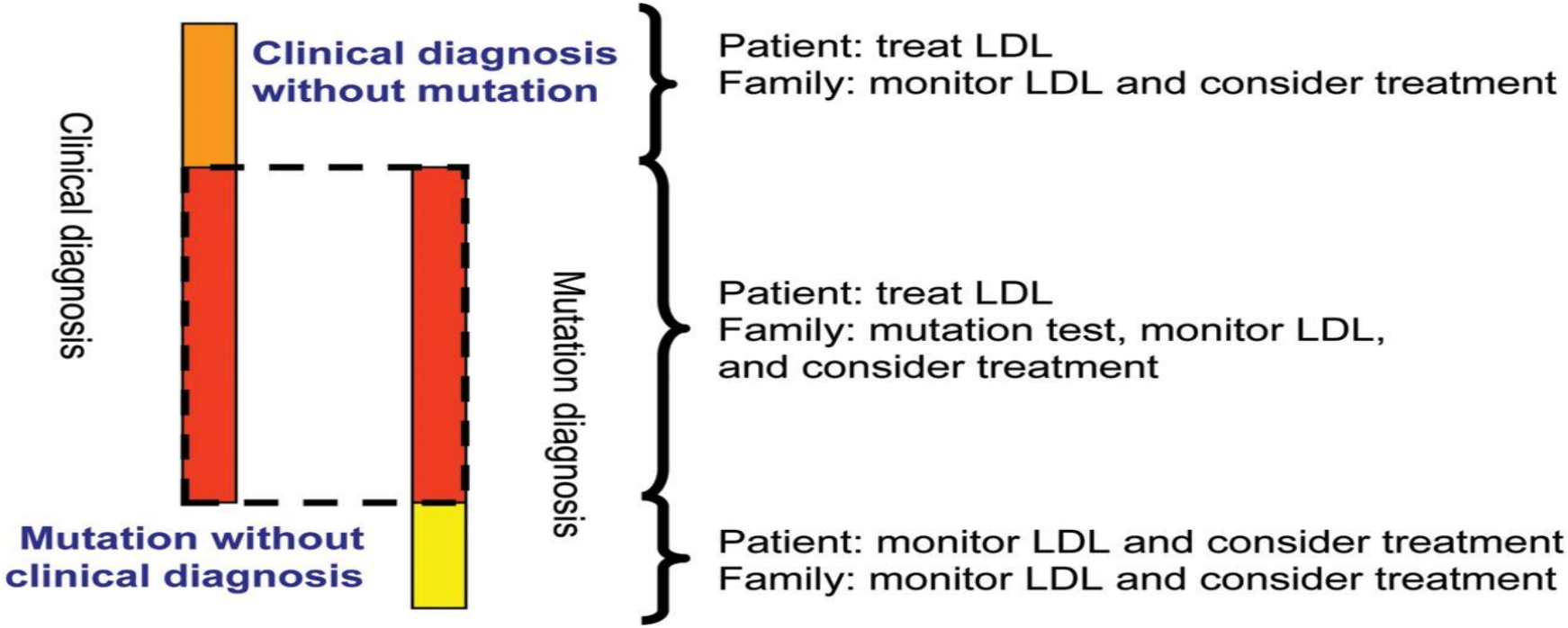
Clinical diagnosis versus mutation diagnosis

Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

EAS

Overlap of clinical and mutation diagnosis of heterozygous familial hypercholesterolaemia.

European Heart Journal



Adapted from Luis Masana

Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

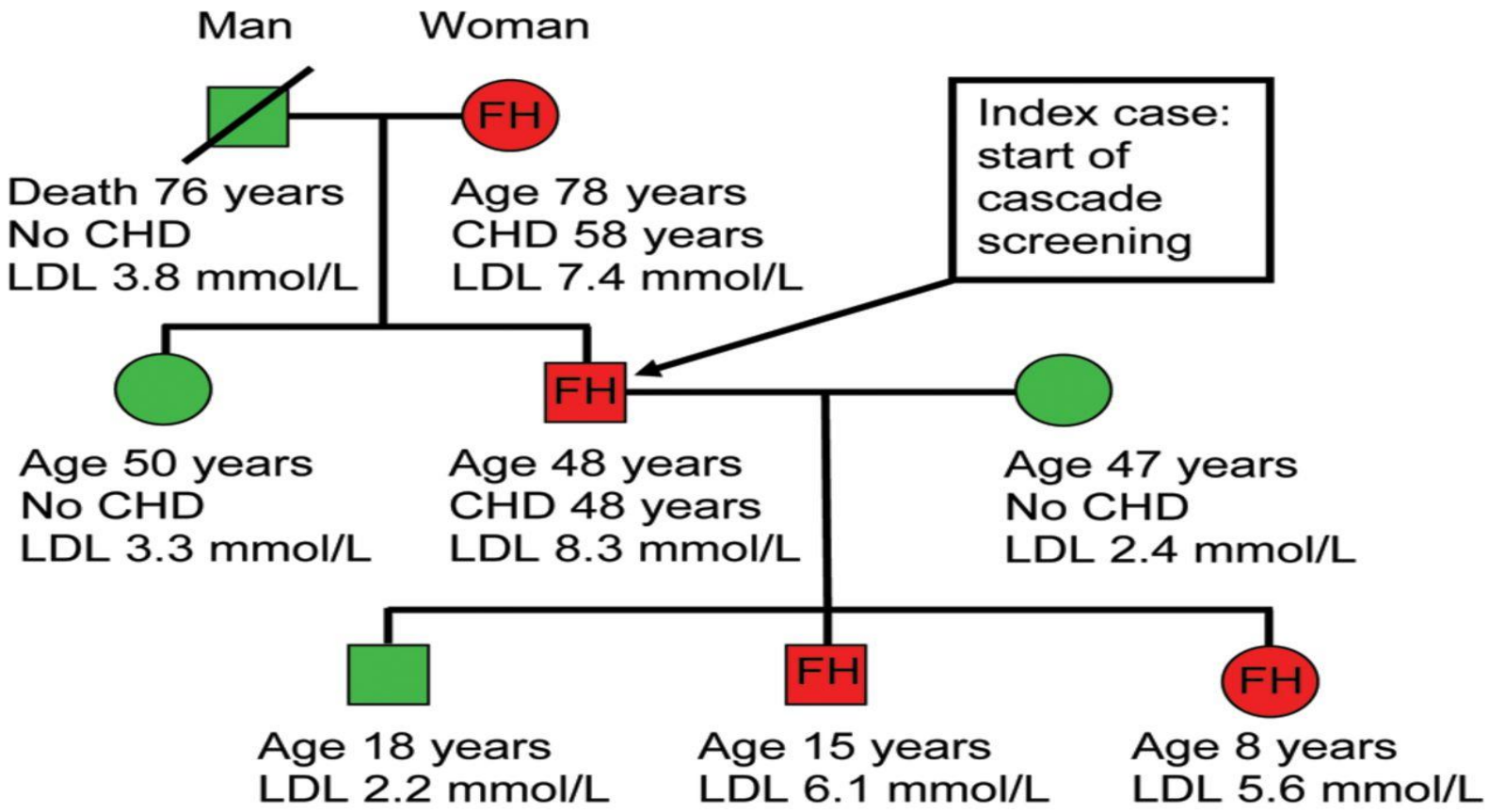
Cascade screening preferred method

Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

EAS

Pedigree of a family with Familial Hypercholesterolaemia

European Heart Journal



Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

EAS

European Heart Journal

LDL cholesterol targets: (heterozygous & homozygous FH)

- <3.5mmol/L(<135mg/dL) for children
- <2.5mmol/L(<100mg/dL) for adults
- <1.8mmol/L(<70mg/dL) for adults with known CHD or diabetes

Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

EAS

LDL lowering treatment

Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

EAS

European Heart Journal

Based on a consensus of

- opinions of experts
- small studies, retrospective studies, and registries

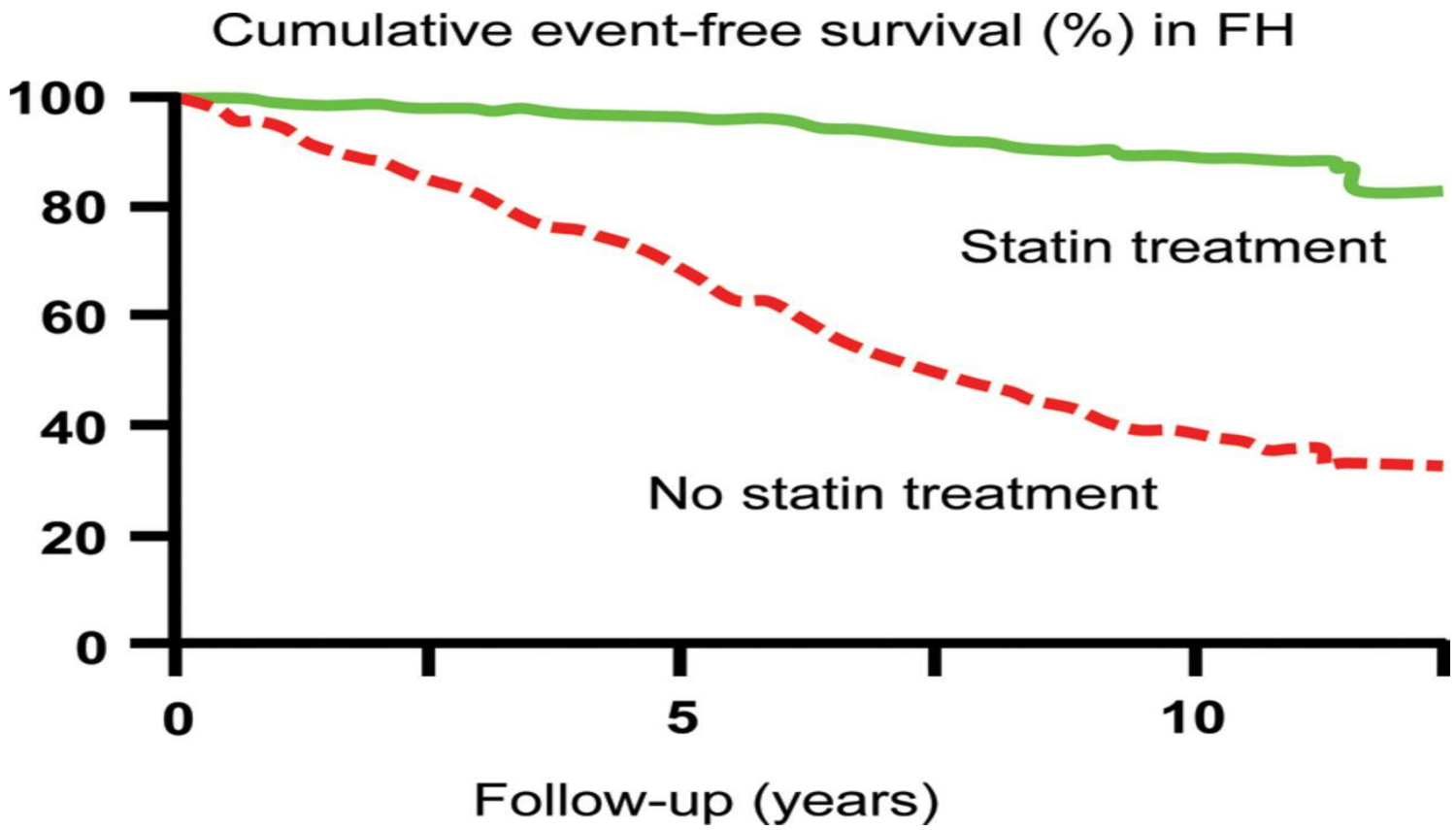
However

- effect of LDL cholesterol lowering in individuals without FH based on: randomised trials and meta-analyses

Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

Kaplan–Meier curve estimates of cumulative CHD-free survival among individuals with familial hypercholesterolaemia according to statin treatment ($P < 0.001$ for difference).

European Heart Journal



Adapted from Vermissen et al. BMJ 2008; 337: a2423

Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

EAS

In addition to lifestyle and dietary counselling, treatment priorities are

Children (from age 8-10):

1. Statin
2. Ezetimibe
3. Bile acid binding resin
4. Lipoprotein apheresis in homozygotes

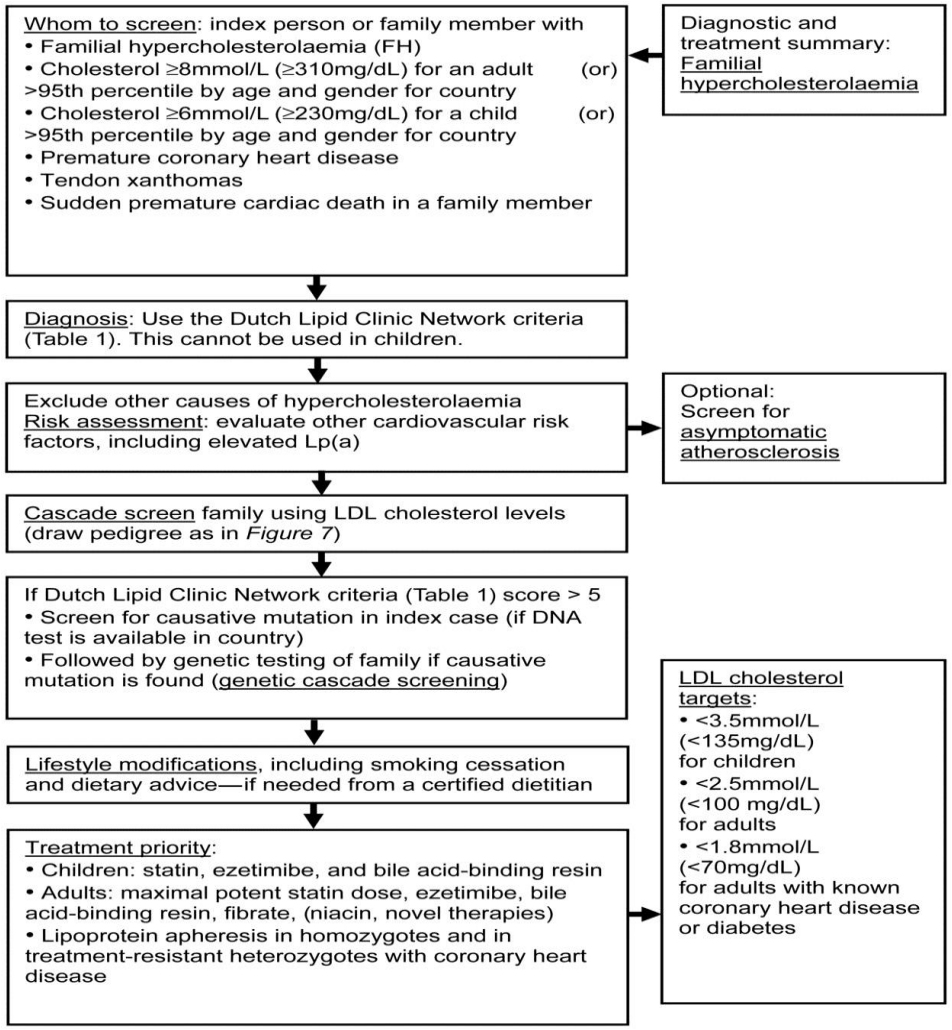
Adults:

1. Maximal potent statin dose
2. Ezetimibe
3. Bile acid binding resins
4. Lipoprotein apheresis in homozygotes & treatment-resistant heterozygotes with CHD

Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

EAS

Summary of diagnostic and treatment strategies.



Nordestgaard et al. Eur Heart J 2013; 34: 3478-3490

Disclosures

Supported by unrestricted educational grants to EAS from Amgen, Aegerion, AstraZeneca, Genzyme, Hoffman-La Roche, Kowa Europe, Novartis, and Sanofi-Aventis/Regeneron.

These companies were not present at the Consensus Panel meetings, had no role in the design or content of the Consensus Statement, and had no right to approve or disapprove the final document.

Nordestgaard B G et al. Eur Heart J 2013;34:3478-3490

EAS