European Heart Journal (2014) **35**, 2146–2157
doi:10.1093/eurheartj/ehu274

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†

Institute for Translational Medicine and Therapeutics, University of Pennsylvania, 8039 Maloney Building, 3600 Spruce Street, Philadelphia, PA 19104, USA

Received 13 March 2014; revised 19 May 2014; accepted 13 June 2014

Homozygous Familial Hypercholesterolemia (HoFH)

- Rare disease characterized by markedly elevated LDL cholesterol levels
- Poor cardiovascular prognosis
- Mandatory referral to highly specialised centers
- Treatment strategy combines available drugs including statin and ezetimibe, LDL apheresis when possible and new therapeutic options (mipomersen, lomitapide)

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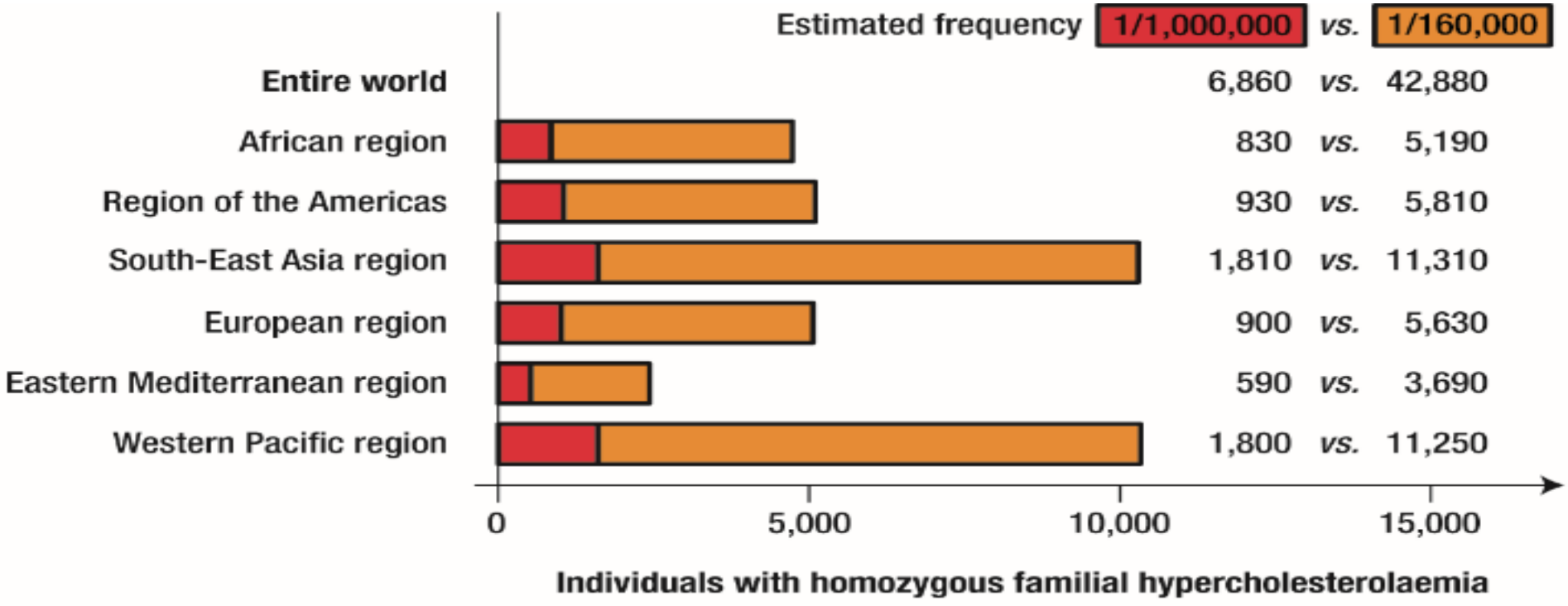
Number of individuals with HoFH worldwide
Estimates vary between 1/1,000,000 and 1/160,000



Estimates are based on historical prevalence data (1 in a million), as well as directly detected estimates of familial hypercholesterolaemia in the Danish general population (1 in 160,000)*

* Nordestgaard BG et al. *Eur Heart J* 2013;34:3478 – 3490

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

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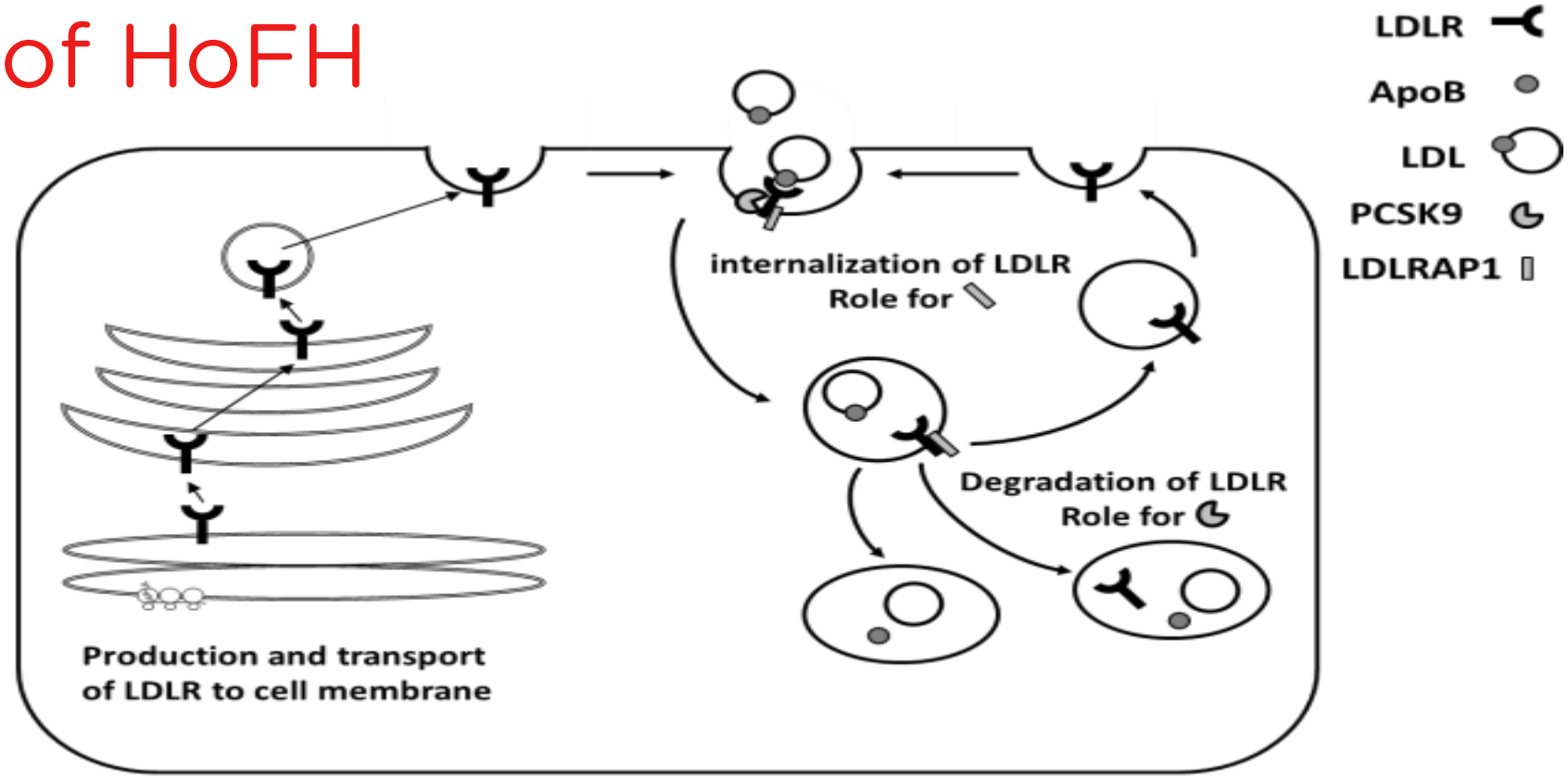
Genetics of HoFH



Panel A

- HoFH is caused by mutations in genes encoding for proteins affecting LDL receptor function
- Currently known genes are: LDLR, apoB, PCSK9 and LDLRAP1

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Genetics of HoFH

- Most patients with genetically confirmed HoFH have 2 mutant alleles of the *LDLR* gene (MIM 606945)
- Mutations in alleles of 3 other genes are identified as causal in cases with a severe phenotype resembling HoFH:
  - **APOB** (MIM 107730) encoding apolipoprotein B
  - **PCSK9** (MIM 607786) encoding proprotein convertase subtilisin/kexin type 9
  - **LDLRAP1** (MIM 695747) encoding LDL receptor adapter protein 1, which uniquely causes a recessive phenotype
- Patients can be "simple homozygotes", with the same mutation in both alleles of the same gene, "compound heterozygotes" with different mutations in each allele of the same gene, or "double heterozygotes" with mutations in two different genes affecting LDL receptor function

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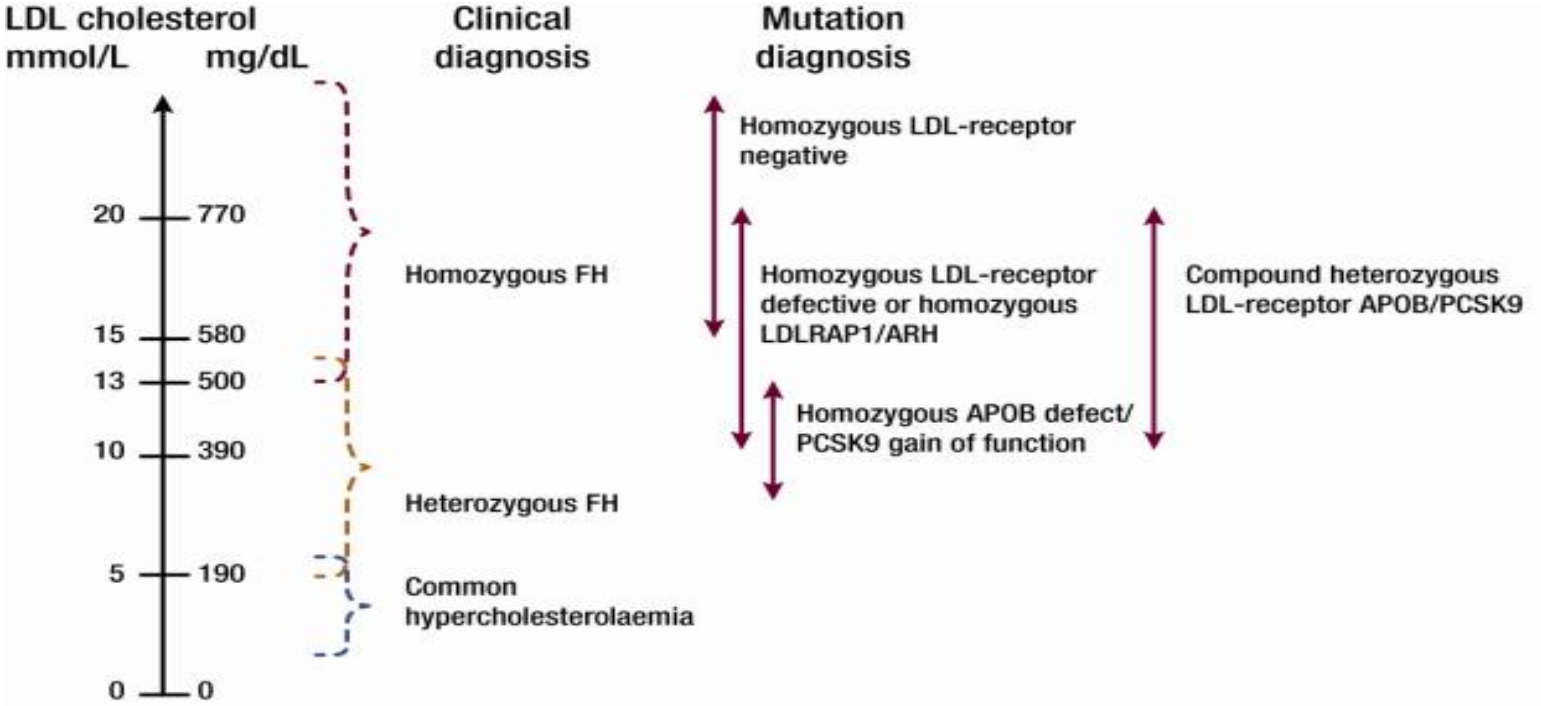
Genetic heterogeneity translates to phenotypic variability in HoFH



- HoFH patients who are LDLR-negative have higher LDL-C levels and poorer clinical prognosis than LDLR-defective patients
- HoFH patients who carry mutations on genes other than the LDLR may present a milder phenotype compared with that of LDLR-negative subjects

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Diagnosis of HoFH according to the criteria recommended by the EAS Consensus Panel

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

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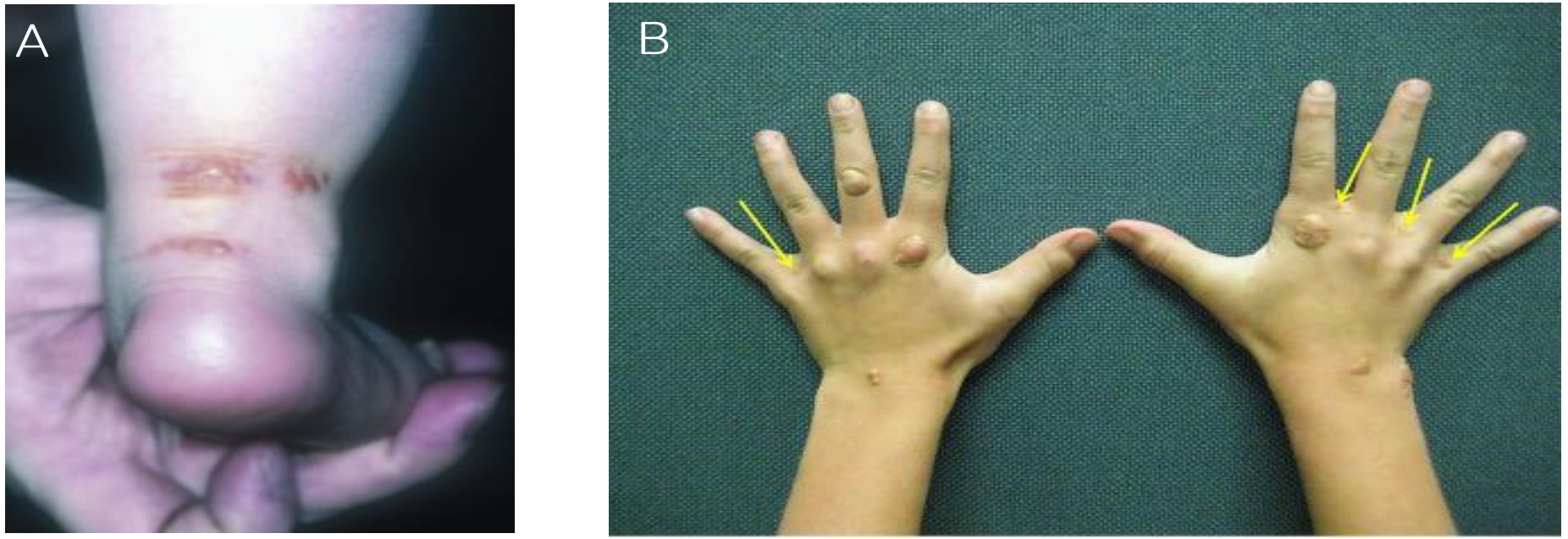
Xanthomas in HoFH



Cutaneous and tuberous xanthomas in HoFH.

Interdigital xanthomas (see B, yellow arrows) in children are highly suggestive of HoFH diagnosis.

Photograph (A) kindly provided by Prof. Eric Bruckert.
Photograph (B) kindly supplied by Prof. Frederick Raal.

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

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Differentiation from sitosterolemia

Sitosterolemia is an extremely rare disease with transient major elevation of cholesterol and clinical feature 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

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Diagnosis of HoFH: Recommendation by the EAS Consensus Panel

- Patients with suspected diagnosis (Box 1) should be referred to a specialised centre for proper comprehensive management
- Genetic analysis should be considered to:
  - Confirm the clinical diagnosis
  - Facilitate testing of family members (reverse cascade screening)
  - Assist in diagnosis where clinical presentation is borderline between that of HoFH and heterozygous FH

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Cardiovascular complication of HoFH

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.

Late referral of HoFH patients to specialised center increases the severity of CVD complications

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Screening for subclinical ACVD* recommended by the EAS Consensus Panel

- All patients with hoFH should undergo comprehensive CV evaluation at diagnosis
- Subsequent evaluation should include:
  - Annualy: Doppler echocardiography evaluation of the heart and aorta
  - Every 5 years: computed tomography coronary angiography; stress testing if CT angiography or cardiac MRI are not available
  - more frequent evaluation when clinically indicated
- Stress testing and invasive coronary angiography are indicated in the presence of clinical symptoms suggestive of ischaemia or valve malfunction, or in the presence of findings from non-invasive cardiac evaluation

* ACVD: Atherosclerotic Cardiovascular Disease

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LDL cholesterol targets recommended by the EAS Consensus Panel for HoFH

- <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

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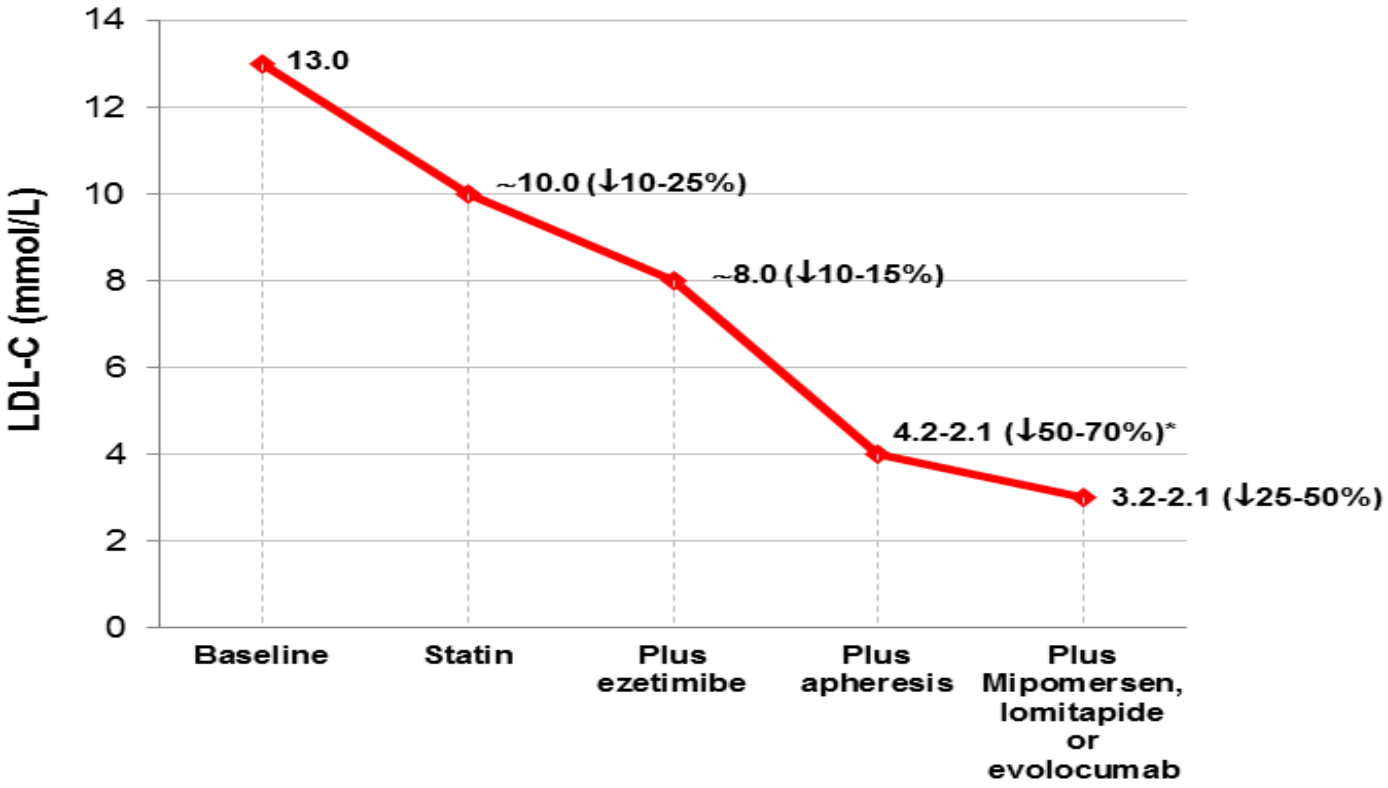
Estimated cumulative LDL-C lowering effects of current and novel treatments for HoFH



There is considerable heterogeneity in the effect of lipid lowering treatment and absolute magnitude of LDL-C reduction depending on the genetic background and the baseline LDL-C levels.

* Decrease in LDL-C after a single apheresis treatment

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New therapeutic options (1)

- **Lomitapide** is an oral inhibitor of the microsomal triglyceride transport protein (MTP)
- In an open-label trial in HoFH patients, lomitapide at maximally tolerated doses, in addition to the standard of care including LDL apheresis, reduced plasma LDL-C and apoB levels by 50% and Lp(a) by 15% at 26 weeks*
- The most frequently observed adverse events were gastrointestinal symptoms and liver fat accumulation. ALT elevation (>3 ULN were reported in 34% of patients
- Gastro- intestinal adverse events (e.g. nausea, flatulence, and diarrhoea) were reduced by a gradual dose-escalation regimen combined with adherence to a low-fat diet (below 20% of energy from fat) and dosing outside of mealtime

* Cuchel et al, Lancet 2013

New therapeutic options (2)

- **Mipomersen** is a second generation antisense oligonucleotide, administered by subcutaneous injection, that targets the messenger ribonucleic acid (mRNA) of apoB
- In a placebo-controlled double-blind trial in HoFH patients, mipomersen (weekly 200 mg, on top of standard lipid-lowering therapy), resulted in further reductions from baseline at 26 weeks in plasma levels of LDL-C (mean 25%), apoB (27%), and Lp(a) (31%)*
- The most frequently reported events were injection site reactions (76% of patients), and flu-like symptoms, typically appearing 2 days after injection. ALT elevations (>3 ULN) have been reported in 12% of patients

* Raal et al, Lancet 2010

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

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Management of HoFH: Recommendation by the EAS Consensus Panel

- Current management of HoFH focuses on a combination of lifestyle, statin treatment (with or without ezetimibe) and lipoprotein apheresis if available.
- Lipid-lowering therapy should be started as early as possible.
- Lipoprotein apheresis should be considered in all patients with HoFH, and started as soon as possible, ideally by age 5 and not later than 8 years.
- Lomitapide and mipomersen should be considered as adjunctive treatments to further lower plasma LDL-C levels in patients with HoFH.

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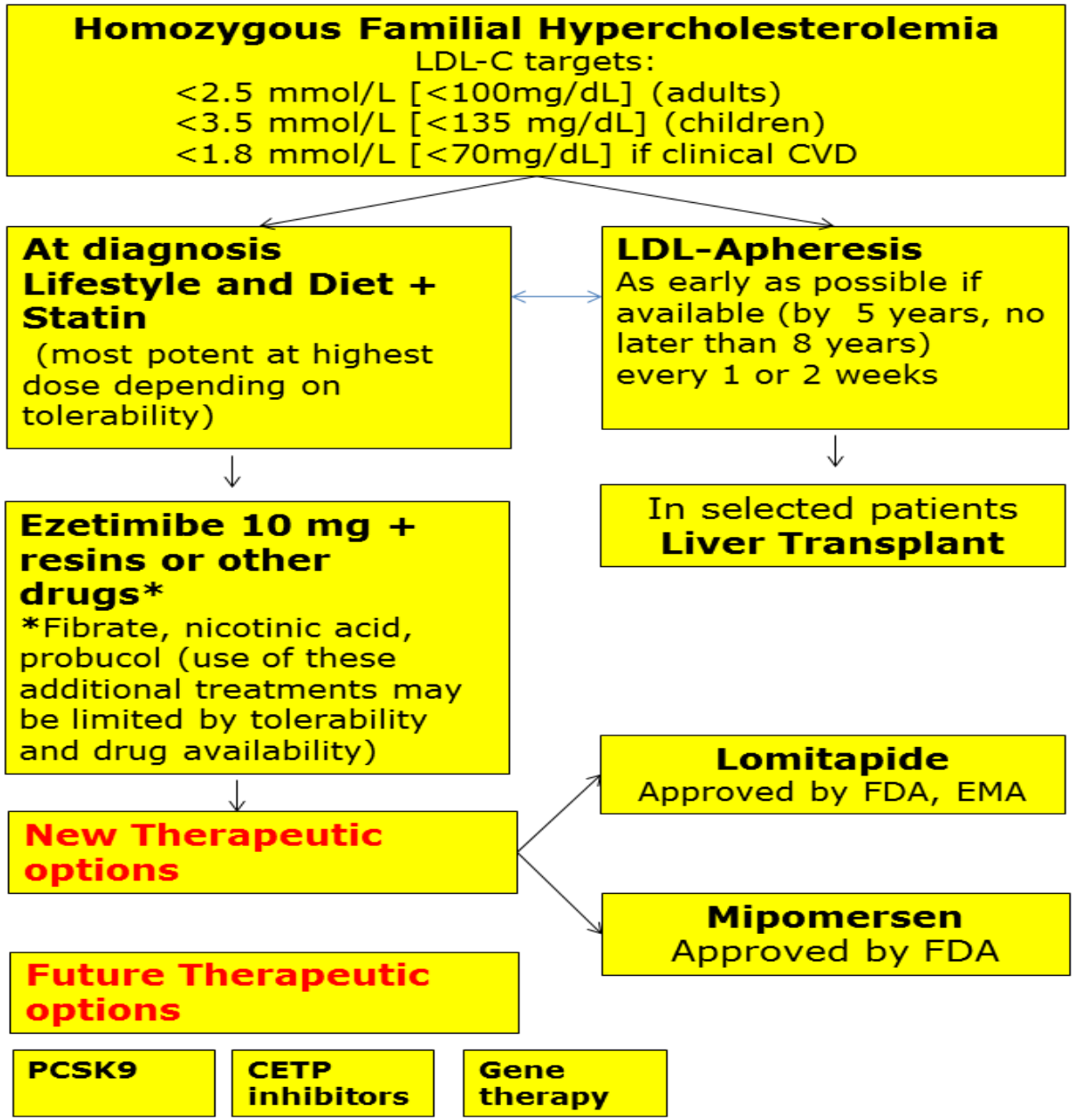
Suggested algorithm for the management of HoFH



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Other issues in HoFH management: Recommendation by the EAS Consensus Panel

- Hormonal contraception is generally contraindicated in HoFH
- Women wishing to become pregnant should be counselled and undergo detailed CV assessment. Where pregnancy is not contraindicated, women should remain on LDL apheresis
- Psychological support should be integrated into routine care. Patient and family support groups clearly have a role
- Surgery may be considered to remove large cutaneous or tuberous xanthomas for either functional or cosmetic reasons

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Disclosures

The European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolaemia is supported by unrestricted educational grants 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 manuscript, and had no right to approve or dis- approve the final document.

Funding to pay the Open Access publication charges for this article was provided by the European Atherosclerosis Society.

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