HoFH WEBINAR TRILOGY

Advancing Knowledge, Care, and Community

New Frontiers in HoFH: Expanding Treatment possibilities

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Heterozygous vs Homozygous FH

Heterozygous FH

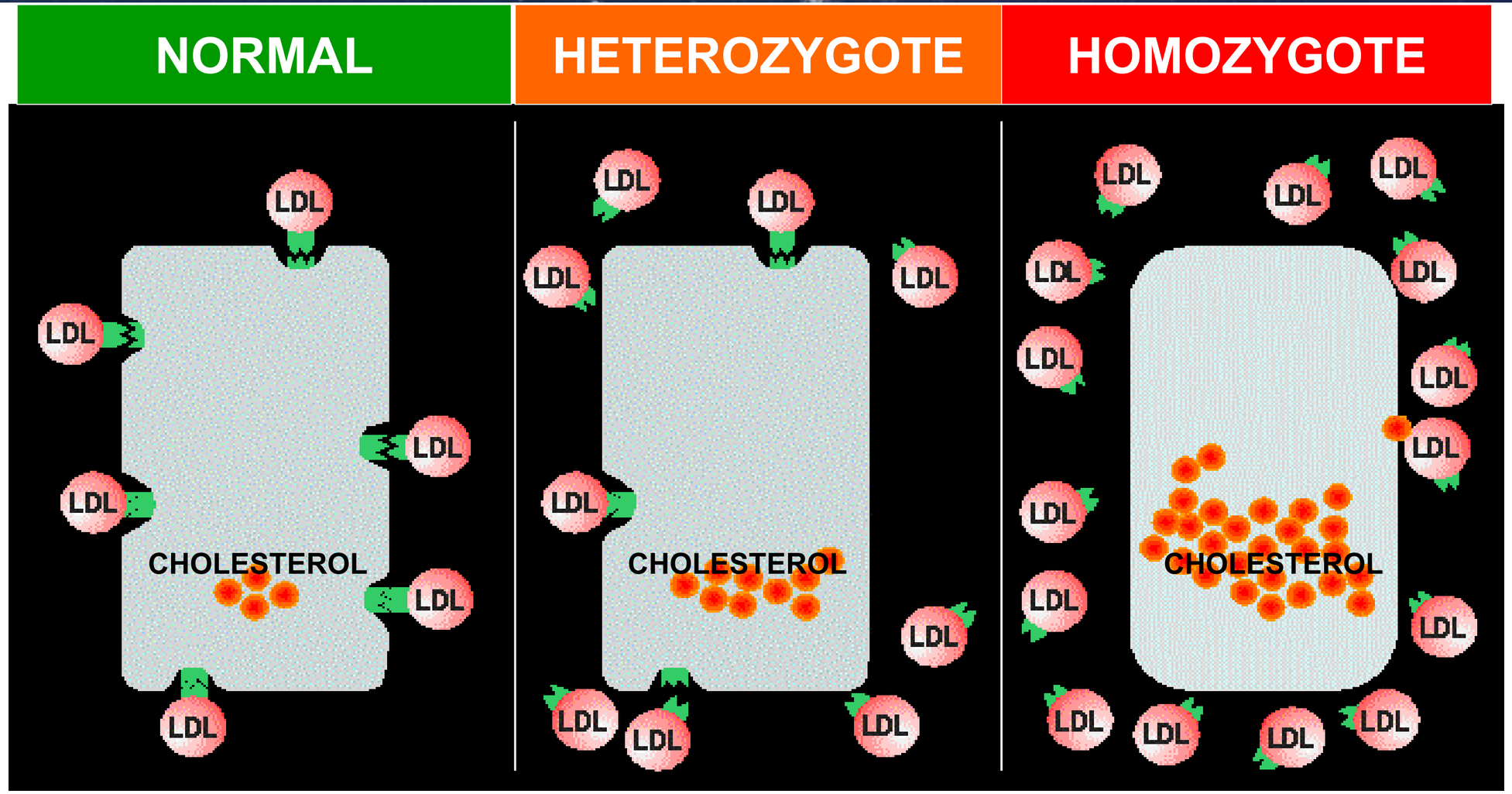
- Prevalence 1:200 – 500
- LDL –cholesterol 5 -12 mmol/L
- CHD onset usually age 30-60 yrs
- Most patients respond to drug therapy, but individual response quite variable

Homozygous FH

- Prevalence 1:300 000 -1000 000
- LDL-cholesterol 10-25 mmol/L
- CHD onset in early childhood
- **Poorly responsive to lipid-lowering drug therapy**

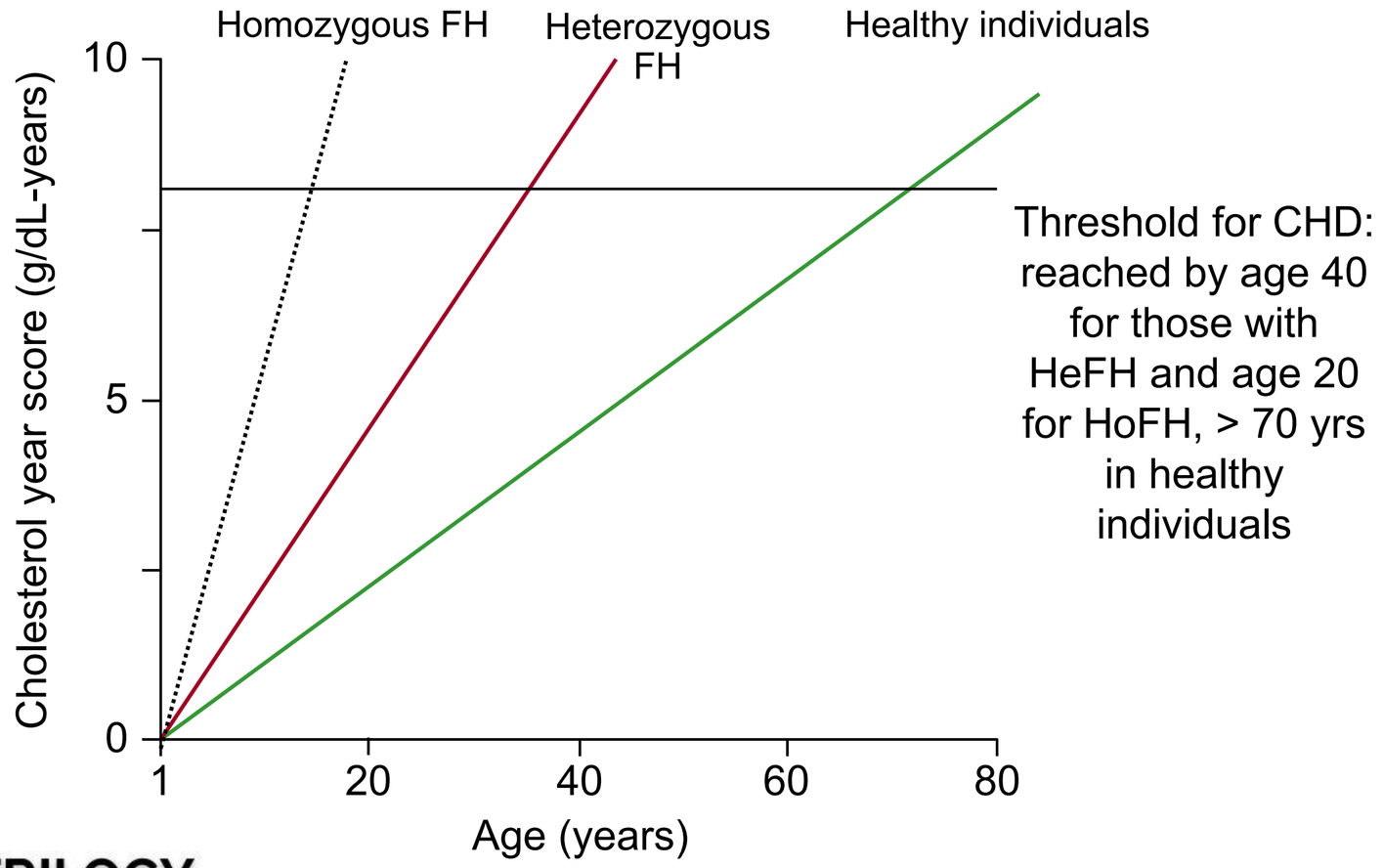
Nordestgaard B.G. et al. *Eur Heart J* 2013;34:3478-3490

Heterozygous vs Homozygous FH



FH exposes people to very high cholesterol from birth, thus reaching a threshold for CHD earlier in life

Cumulative exposure (cholesterol yrs) by age: FH vs unaffected (healthy) individuals



Threshold for CHD: reached by age 40 for those with HeFH and age 20 for HoFH, > 70 yrs in healthy individuals

Adapted from Horton et al. *J Lipid Res.* 2009;50:S172-S177

A case of severe hypercholesterolaemia

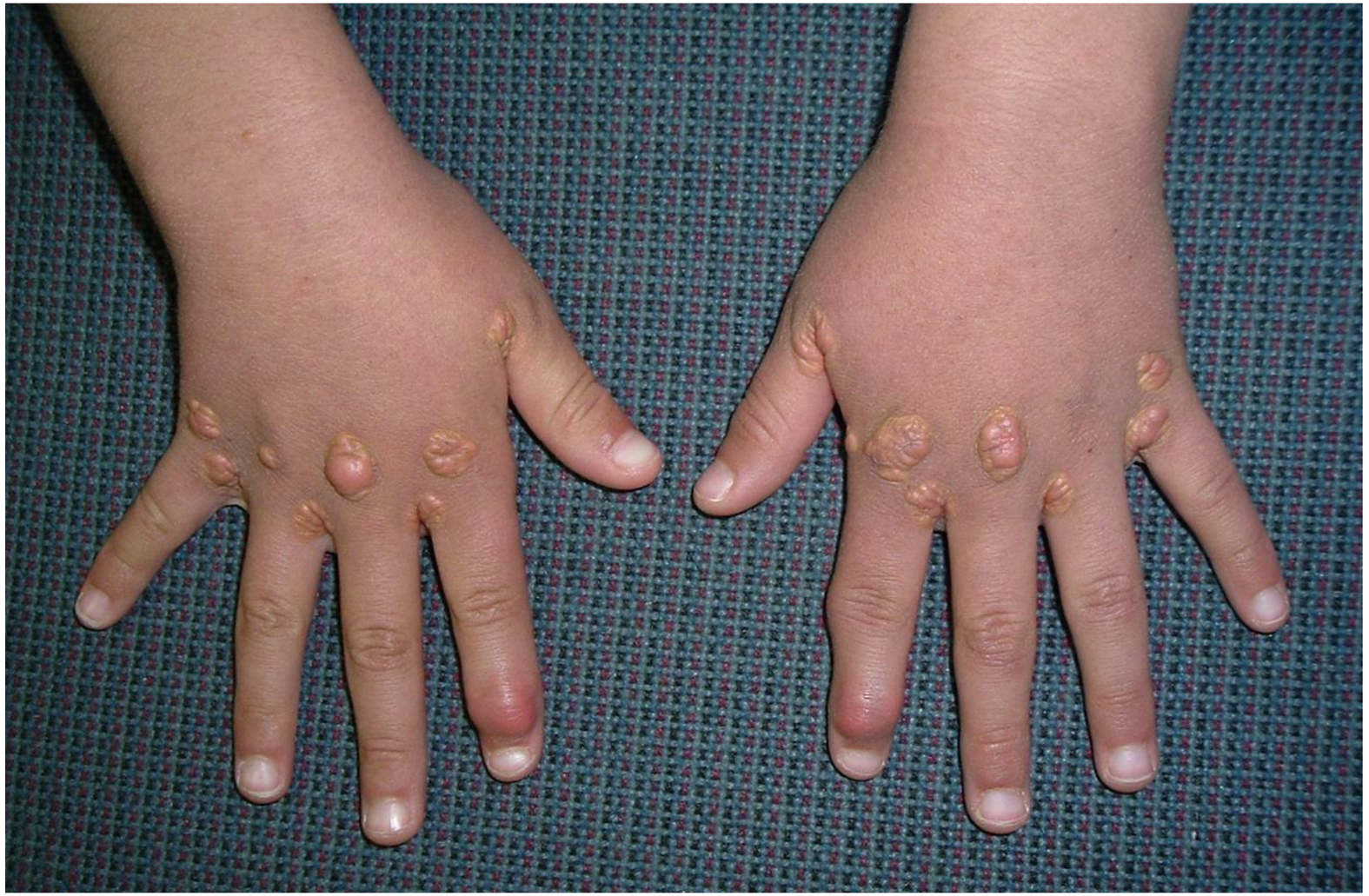
Miss A-R

16 year old female. Parents noted “yellow lumps” over hands elbows and buttocks. A lipid disorder was suspected so a lipid profile was done.

Fasting lipid profile

Total cholesterol:	16.2 mmol/L
Triglycerides:	1.7 mmol/L
HDL-cholesterol:	0.8 mmol/L
LDL-cholesterol	14.6 mmol/L

Interdigital xanthoma in a young patient with HoFH



EAS HoFH Consensus, *Eur Heart J* 2014; 35: 2146–2157

Therapy for severe FH

Pharmacotherapy:
Lipid-modifying drugs

Surgical therapy:
- portacaval shunt
- partial ileal bypass

Extracorporeal removal of LDL:
LDL apheresis

Methods to restore LDL receptor activity:
- liver transplantation
- gene therapy

Gidding S. The agenda for FH; *Circulation* 2015;132:2167-2192

Pharmacotherapy for severe FH/HoFH

Lipid-modifying drugs

- LDL-R dependent
- LDL-R independent

Statin therapy for HoFH

		% LDL-C Reduction
Rosuvastatin	40 mg/d	22.5 %
Rosuvastatin	80 mg/d	22.8%
Rosuvastatin vs Atorvastatin	80 mg/d crossover	19% 18%

Marais AD, Raal FJ et al. *Atherosclerosis* 2008;**197**:400-406

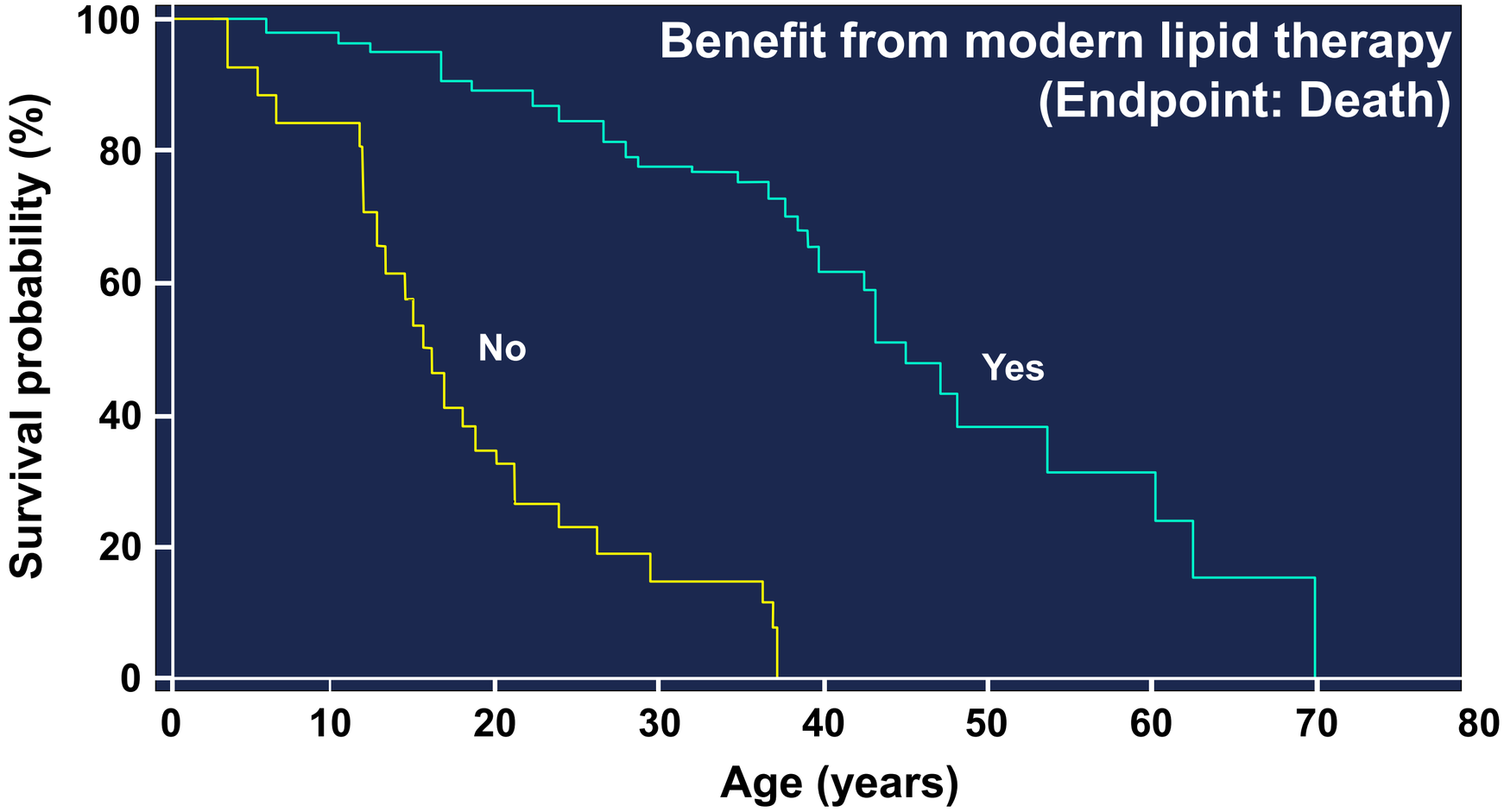
Cardiovascular mortality characteristics of patients with HoFH pre- statin(1990) and post-statin (n=149)

	pre-1990 (n=36)	post-1990 (n=113)
Females/Males	24/12	58/55
Age at death – all causes (years)	18.4 ± 10.1 (n=27)	32.9 ± 15.5 (n=38) *
Age at death – CV (years)	17.7 ± 10.1 (n=22)	31.7 ± 13.3 (n=28) #

Results are expressed as mean ± SD
* *P*<0.0001 #*P*<0.001

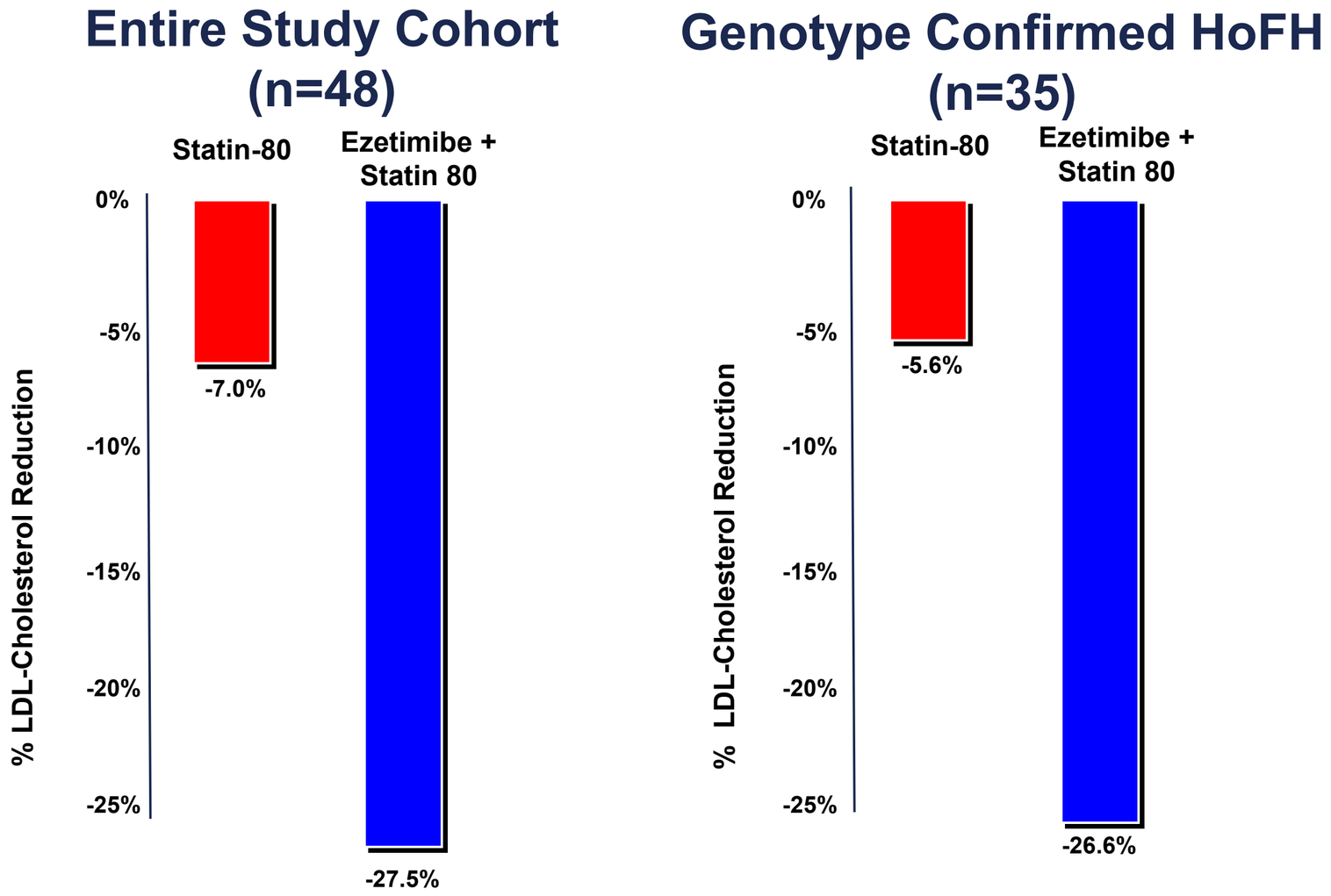
Raal FJ *Circulation* 2011;124:2202-2207

Kaplan-Meier probability estimates of survival among HoFH patients before and after the introduction of modern lipid-lowering therapy



Raal FJ *Circulation* 2011;124:2202-2207

Mean percentage reduction in LDL-C in HoFH patients receiving ezetimibe plus statin



Gagne C. *Circulation* 2002;105:2469-2475; Mansfield B. *J Clin Lipidol* 2025;19:320-326

Miss A-R, a case of severe hypercholesterolaemia

Treated with Atorvastatin 80mg plus Ezetimibe 10mg daily x 3 months

Lipid profile

Total cholesterol:	10.3 mmol/L
Triglycerides:	1.9 mmol/L
HDL-cholesterol:	0.6 mmol/L
LDL-cholesterol	8.8 mmol/L

Current/Emerging therapies for HoFH

While statins and ezetimibe constitute first-line therapy, they provide far less than optimal LDL-C reduction in patients with HoFH

Current therapies

- PCSK9 inhibitors
  - mAbs
  - Inclisiran
- Lomitapide (MTP inhibitor)
- ANGPTL3 inhibitors
  - Evinacumab

Emerging therapies

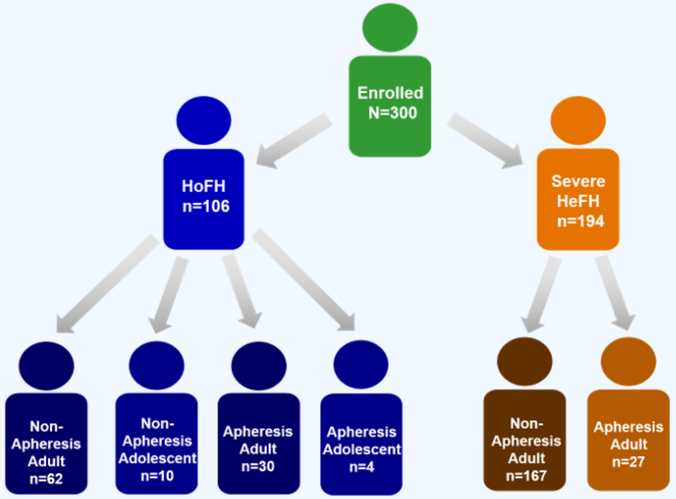
- siRNA ANGPTL3 inhibitors
- ACL/AMP kinase modulator (Bempedoic acid)
- Others e.g. CETP–inhibitors
- Gene therapy
  - AAV-8 LDLR gene replacement therapy
  - CRISPR

Modified from Stein EA, Raal FJ. *Curr Cardiol Reports* 2015;17:1-11

Inhibition of PCSK9 in FH

- How effective is PCSK9-inhibitor therapy in FH?
- In patients with HoFH with either no or minimal residual LDL-receptor function will PCSK9 inhibition be effective?

Long-term evolocumab in FH



TAUSSIG Trial
Open-label, single-arm study

300
patients with homozygous and severe heterozygous FH

4.1
year duration (median)

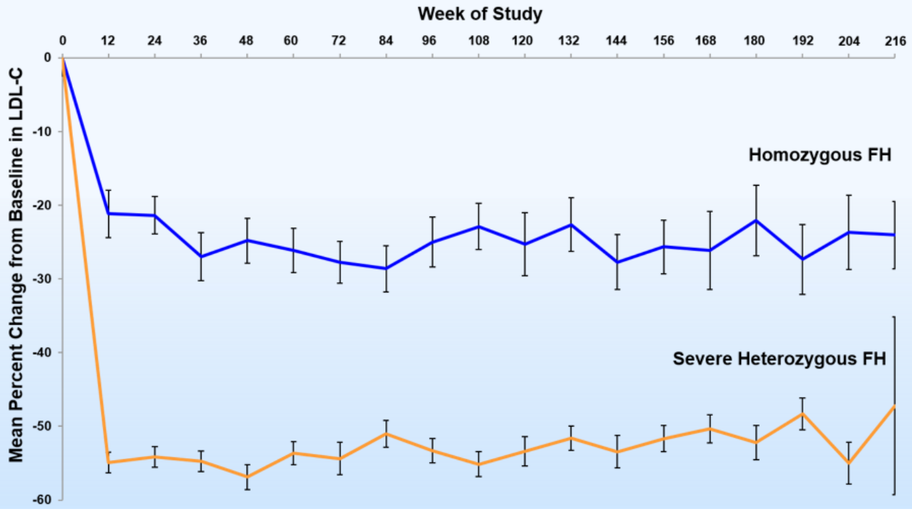
Objective: To provide long-term safety and efficacy data for evolocumab in FH

Evolocumab was well-tolerated

26% stopped apheresis

2.7% per year CV event rate

LDL-C levels were effectively reduced



Santos RD, et al. *J Am Coll Cardiol* 2020;75:565-74

Miss A-R, a case of severe hypercholesterolaemia

Atorvastatin 80mg plus Ezetimibe 10mg daily
plus a PCSK9 mAb inhibitor Q2W

Lipid profile

Total cholesterol:	7.8 mmol/L
Triglycerides:	1.6 mmol/L
HDL-cholesterol:	0.9 mmol/L
LDL-cholesterol	6.2 mmol/L

LDLR independent therapies for severe FH

Established therapies

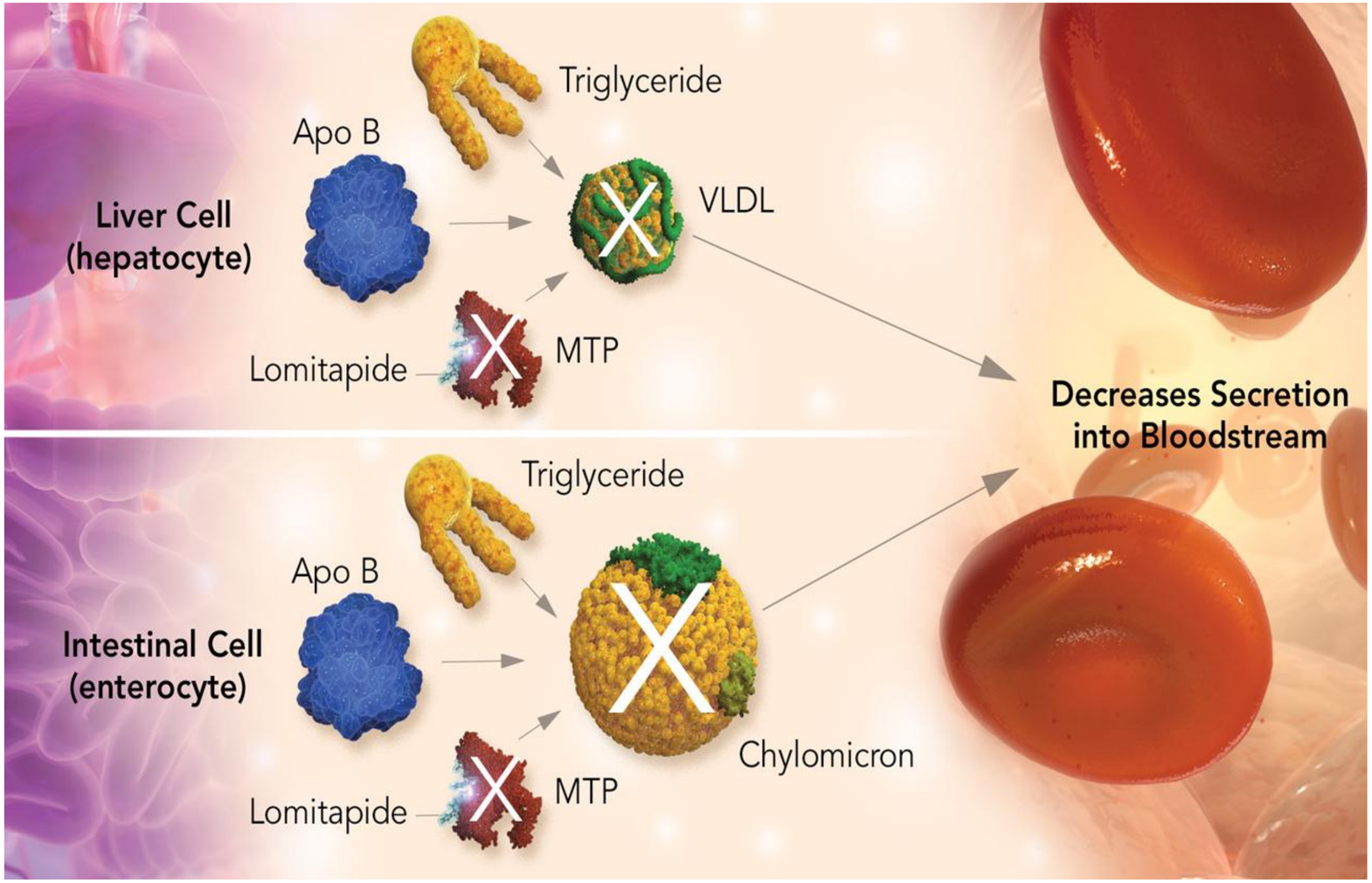
- Mipomersen (apoB inhibitor)
- Lomitapide (MTP inhibitor)
- Evinacumab (ANGPTL3 inhibitor)

Emerging therapies

- siRNA ANGPTL3 inhibitors

Stein EA, Raal FJ. *Curr Cardiol Reports* 2015;17:1-11

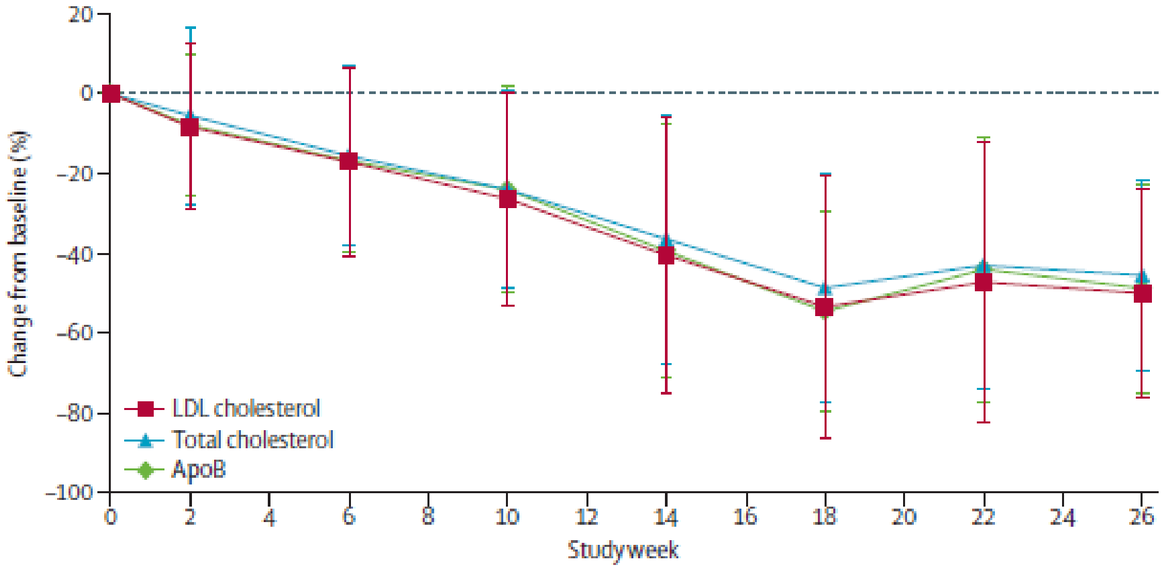
Lomitapide Mode of Action



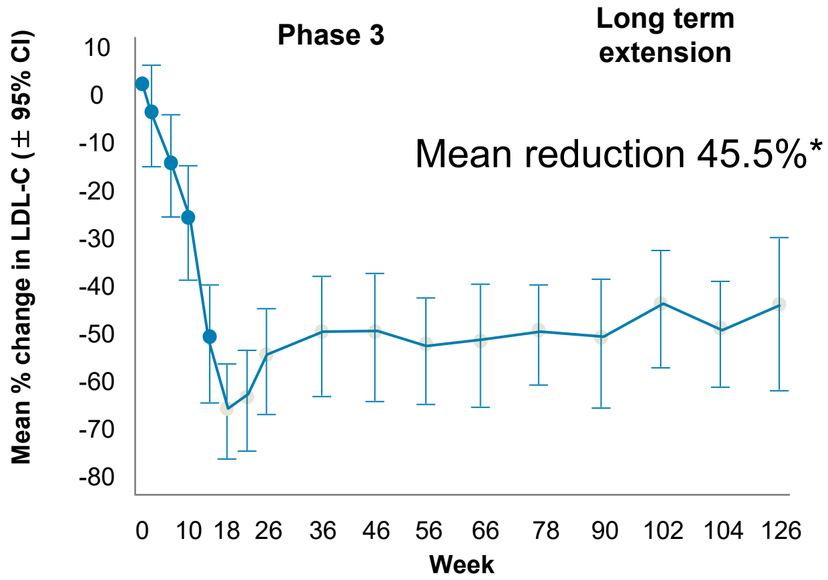
Cuchel M. *N Engl J Med* 2007;356;148-56

Clinical Trial Data - Lomitapide reduces LDL-C in HoFH

Lomitapide treatment reduced LDL-C at 26 weeks by an additional 50%[1,2]



Efficacy maintained to 126 weeks[3,4]

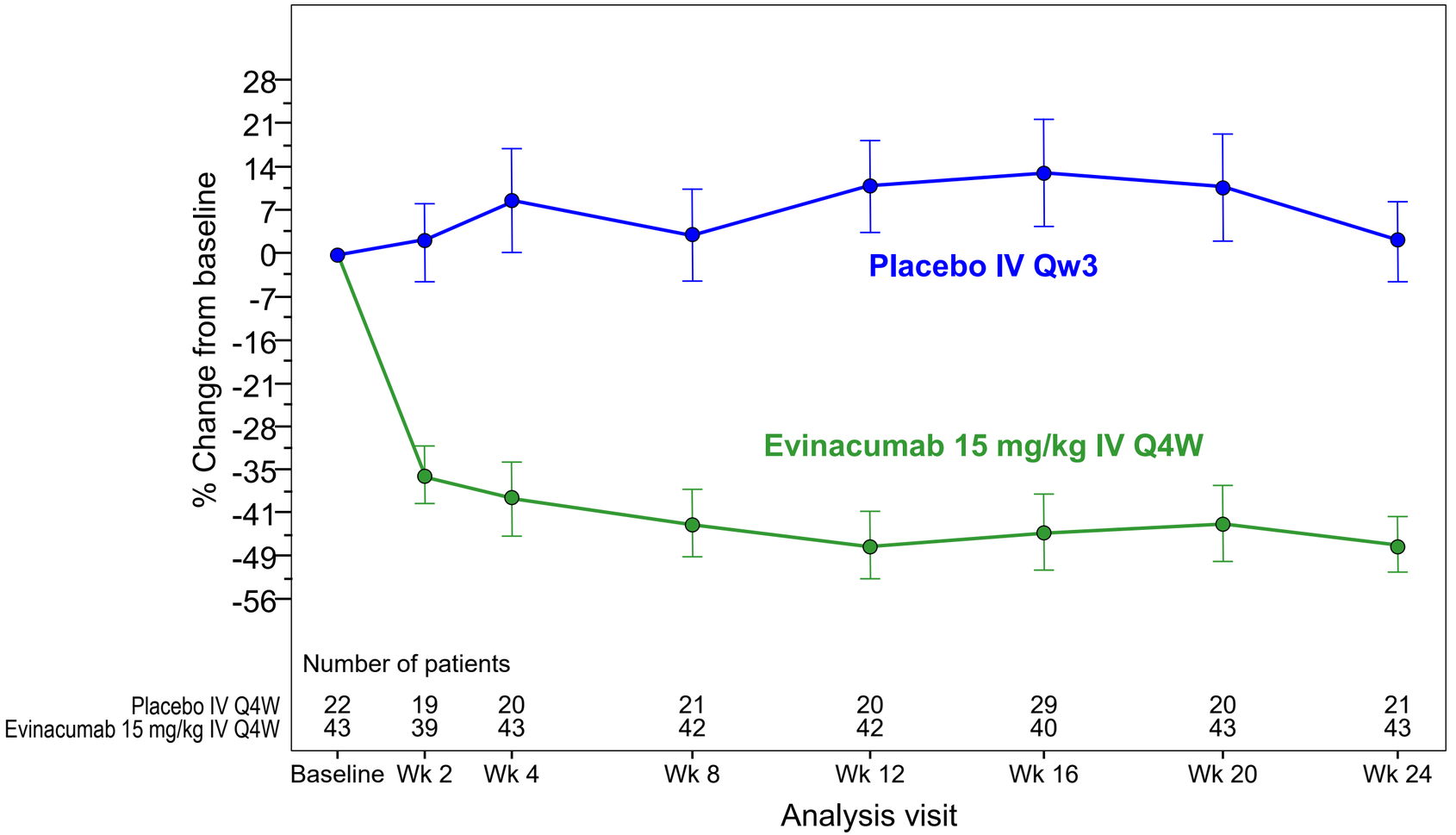


Values represent mean ± 95% confidence levels (CIs) Completers' population. n=17
* Population is those entering the long term extension trial

At any time point to week 126, 12 patients (53%) had an LDL-C < 2.6 mmol/L and 8 patients (42%) had an LDL-C < 1.8 mmol/L[5]

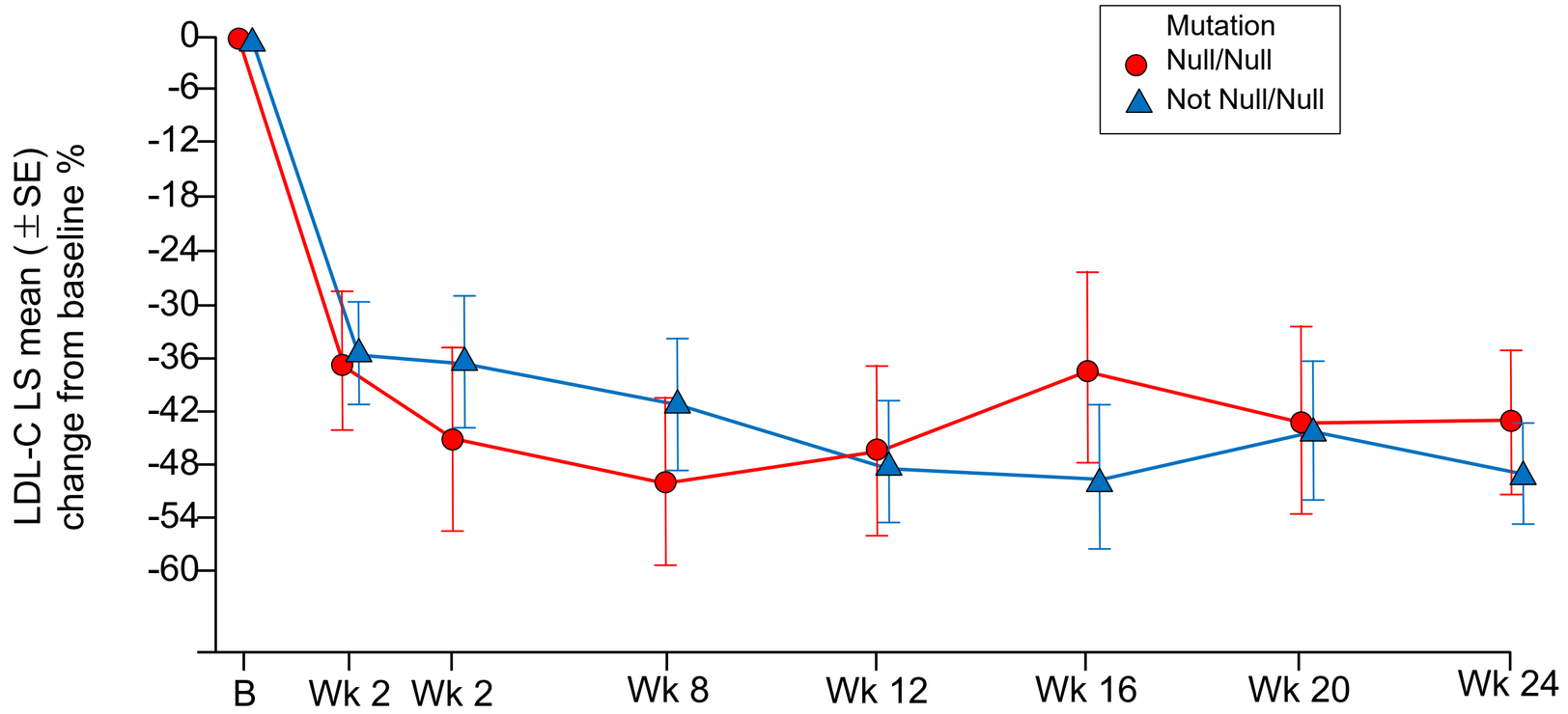
1. Cuchel M, et al. Lancet. 2013;381(9860):40-46. 2 Lojuxta Summary of Product Characteristics. 3. Blom et al. Circulation. 2017;136:332–335. 4. Cuchel et al. Presented at the 2013 American Heart Association Scientific Sessions, Dallas, Texas, USA; November 16–20, 2013. 5. Blom et al Orphanet Journal of Rare Diseases (2018) 13:96.

The addition of the ANGPTL3-inhibitor, evinacumab, for homozygous FH (n=65)



Raal FJ et al. *N Engl J Med* 2020;383:711-20

Response to evinacumab in HoFH is independent of residual LDLR function



Number of patients

Null/Null	15	14	14	15	14	15	15	15
Not Null/Null	28	24	24	27	28	25	28	28

Raal FJ et al. *N Engl J Med* 2020;383:711-20

116

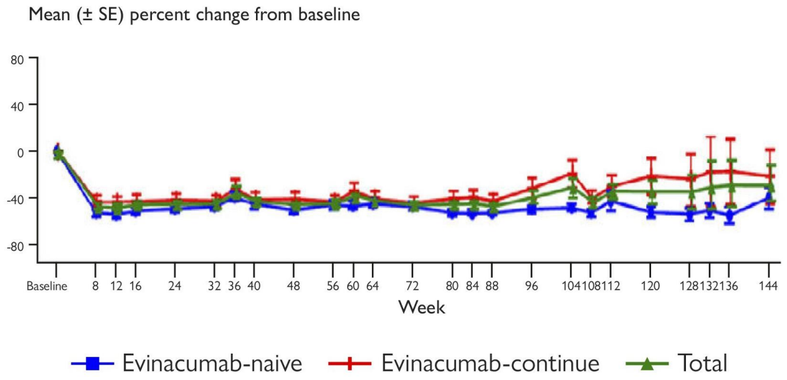
Patients aged ≥12 years with HoFH who were evinacumab-naïve (n=46) or had previously received evinacumab in other trials (n =70, evinacumab-continue) were enrolled

Open-label treatment period (≤ 192 weeks)

Evinacumab 15 mg/kg IV Q4W

Follow-up (24 weeks)

Substantial long-term LDL-C reduction of ~44%



- TEAEs and serious TEAEs occurred in 93 (80.2%) and 27 (23.3%) patients, respectively
- 3 patients (2.6%) discontinued treatment due to a TEAE (none were considered related to evinacumab treatment)
- 2 deaths (1.7%) were reported (both were considered unrelated to evinacumab treatment)

Meaningful reductions in LDL-C at week 24 irrespective of subgroups

Age	55.4% in patients aged <18 years 41.7% in patients aged ≥18 years
Sex	51.2% in female patients 37.1% in male patients
Race	41.8% in Caucasian patients 48.0% in non-Caucasian patients
LDLR activity	49.0% in patients with null-null variants 41.4% in patients with non-null variants
Apheresis	39.0% in patients receiving apheresis 46.3% in patients not receiving apheresis
PCSK9i	46.1% in patients receiving PCSK9i 39.5% in patients not receiving PCSK9i
Statin	43.3% in patients receiving statin 48.1% in patients not receiving statin
Lomitapide	52.3% in patients receiving lomitapide 41.7% in patients not receiving lomitapide
Baseline Lp(a)	45.0% in patients with Lp(a) < 75 nmol/L 42.2% in patients with Lp(a) ≥ 75 nmol/L

Gaudet D, et al. *Eur Heart J*, 2024;45:2422-2431

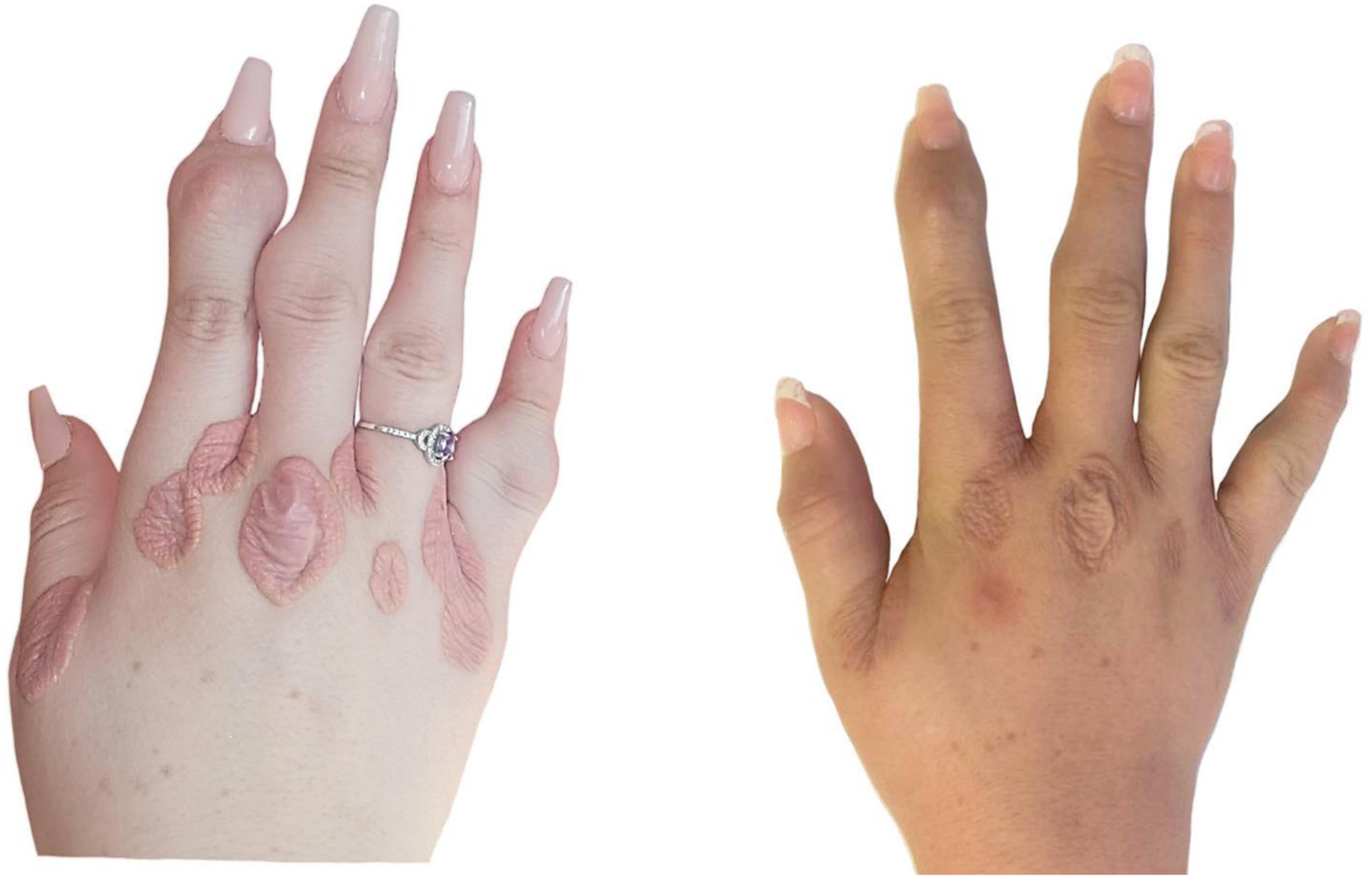
Combination of ANGPLT3-I, PCSK9-I and statin therapy?

- In animal models this combination reduced lipid levels by >93% and regresses atherosclerosis[1]

- In human studies profound plaque regression was demonstrated in two young HoFH patients with this combination[2]

1. Hurt-Camejo E,.*JLR*, *J Lipid Res*. 2020;61(3):272-274
2. Reeskamp et al. *Atherosclerosis* 2021;327:13-17

Regression of cutaneous xanthomata in patient with homozygous familial hypercholesterolaemia using novel therapies



Mansfield BS, Raal FJ. Lancet 2023; 402: e11

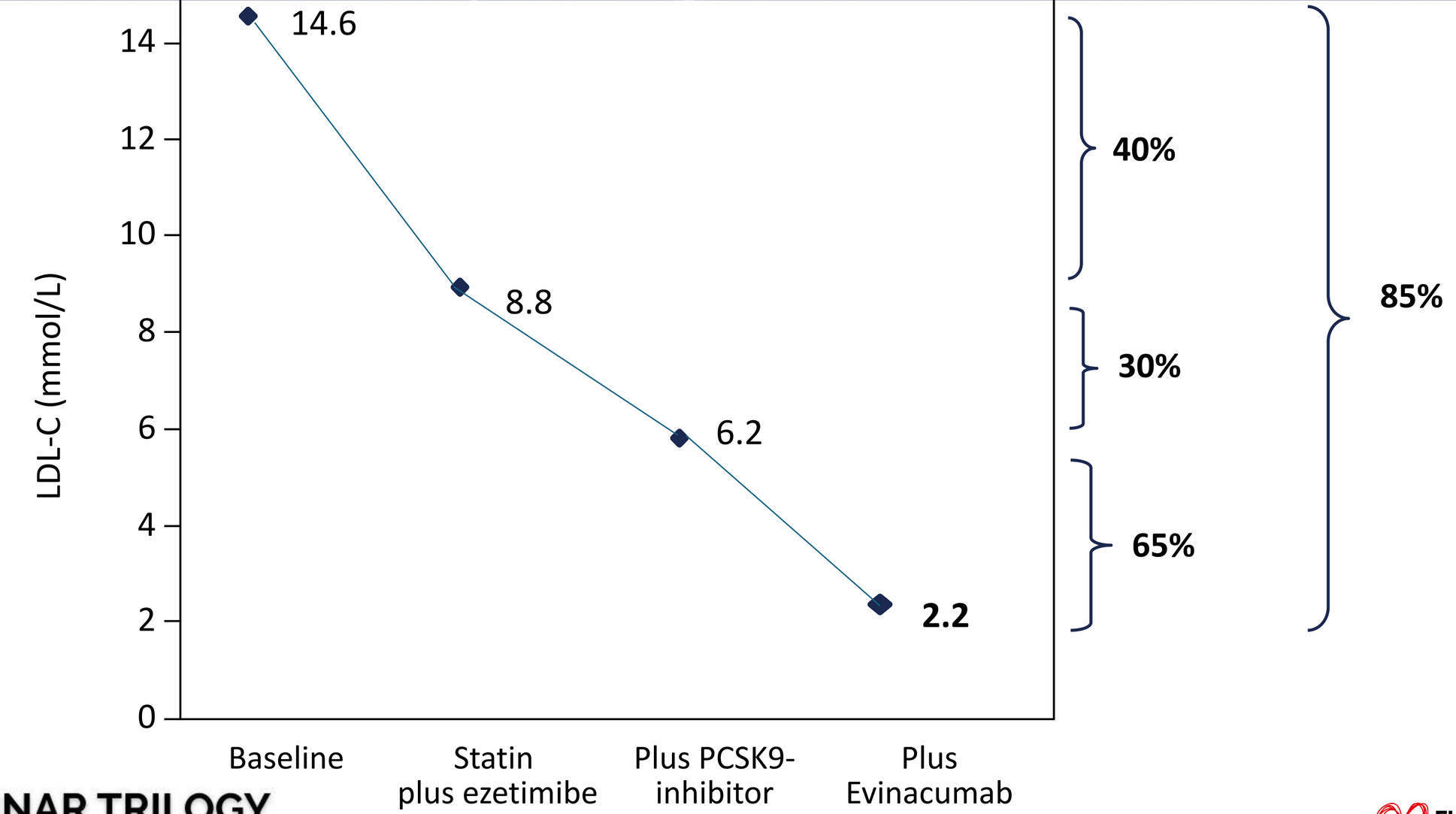
Miss A-R: A case of severe hypercholesterolaemia

With the addition of evinacumab 15mg/kg IVI monthly

<u>Lipid profile</u>

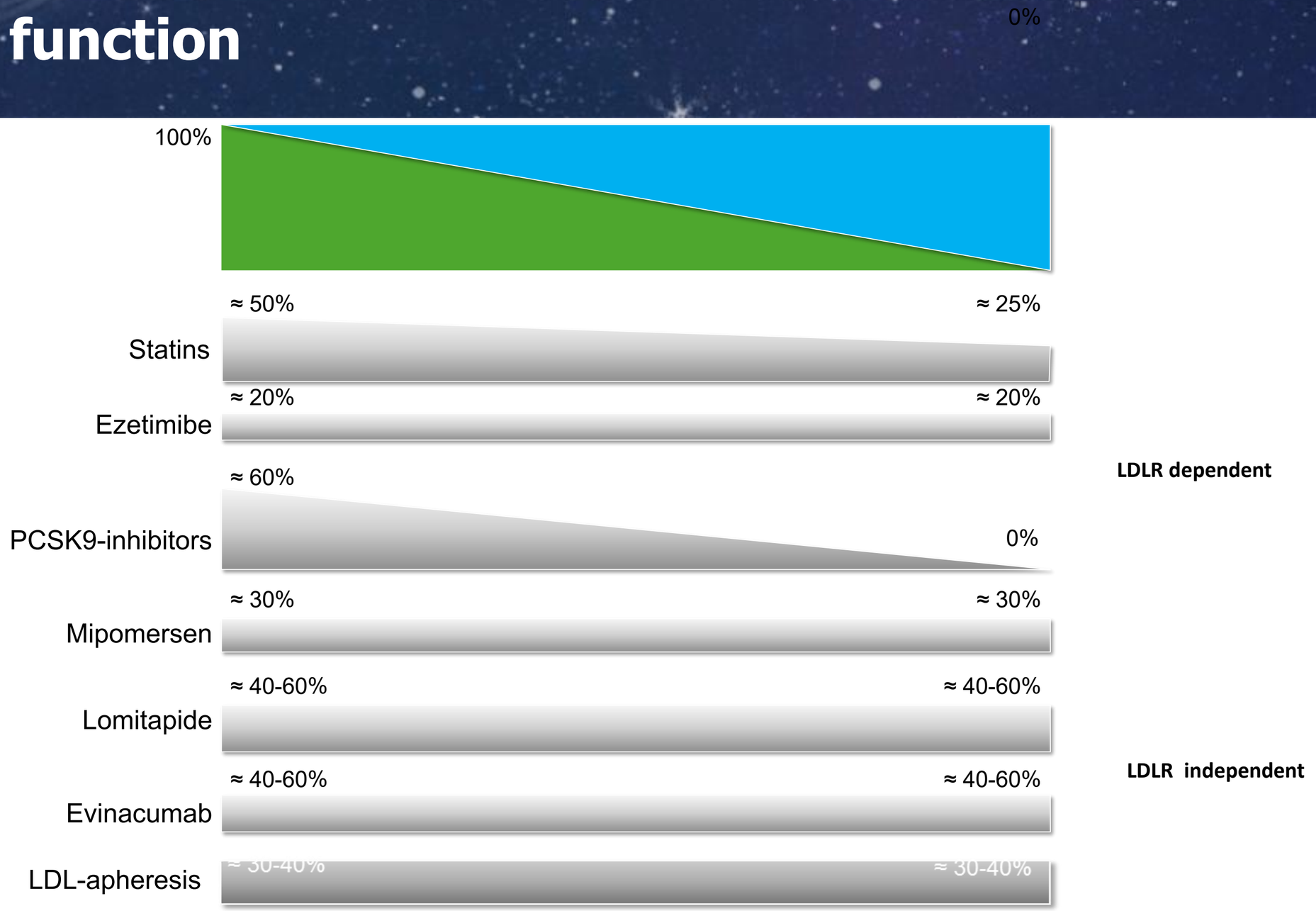
Total cholesterol:	3.1 mmol/L
Triglycerides:	0.9 mmol/L
HDL-cholesterol:	0.5 mmol/L
LDL-cholesterol	**2.2 mmol/L**

Cumulative LDL-cholesterol lowering effects of statin, ezetimibe, a PCSK9-inhibitor plus evinacumab



Adapted from Kastelein JJP. *Nat Rev Cardiol.* 2014;11:629-631
and Cuchel M et al. *Eur Heart J* 2014;35:2146-57

LDLR function



Mohammed F, et al. *Curr Opin Endocrinol, Diabetes Obes* 2021;28:188-195

FH Europe Foundation

Lipoprotein Apheresis

If lipid-modifying therapy does not achieve LDL-C goal, LDL-apheresis may be required

Can lower LDL-cholesterol by 40-50% or more depending on frequency of the procedure

Disadvantages

- Frequency of procedure
- Access – shunt often required
- Must be continued indefinitely as does not restore LDL receptor actively

Reijman MD et al. *Atherosclerosis* 2024;392:117525

Methods to Restore LDL Receptor Activity

- Liver transplantation
- Gene therapy

Liver transplantation and other surgical approaches

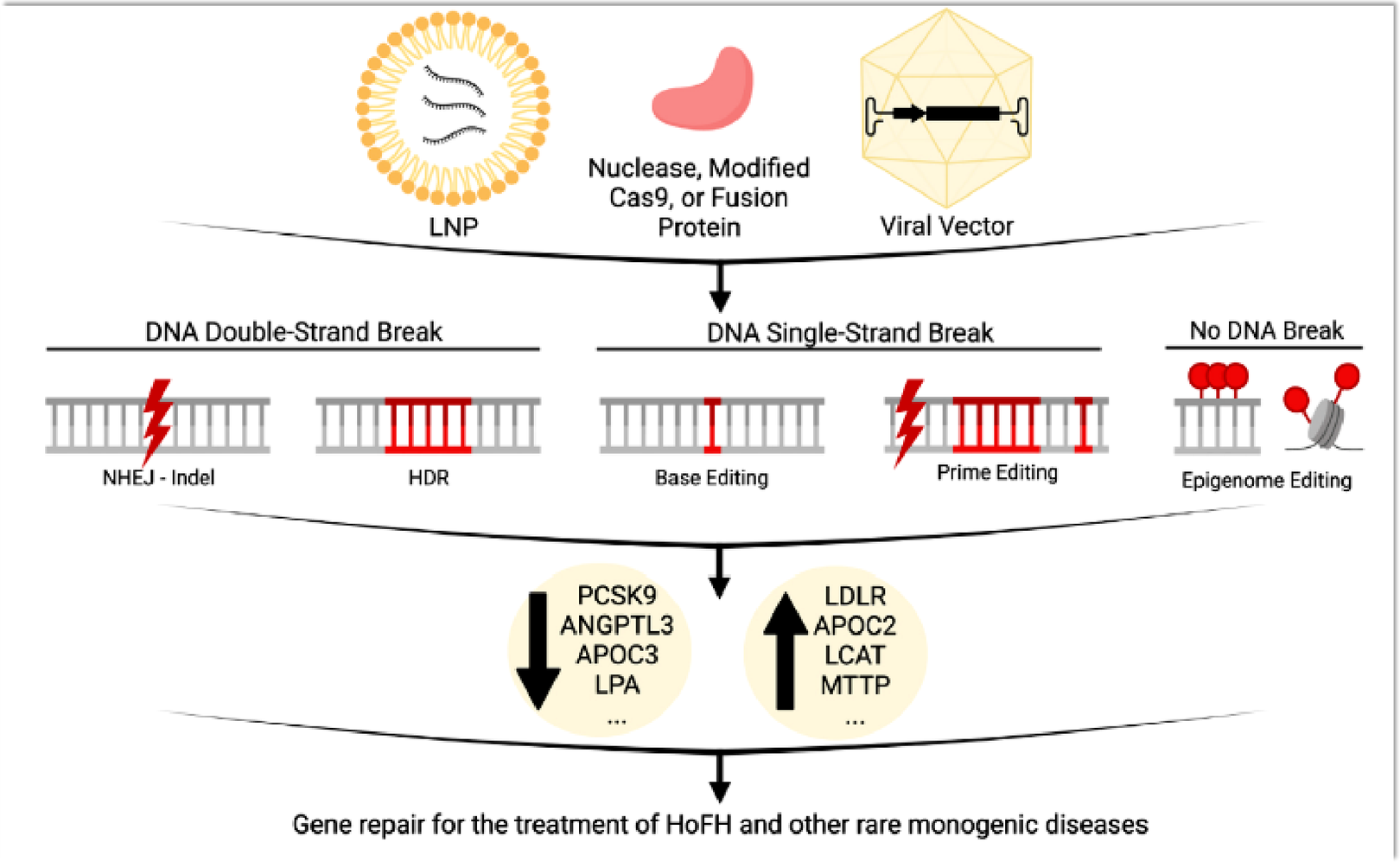
Liver transplantation corrects the molecular deficit in the organ most active in the clearance of LDL, resulting in a marked lowering of LDL-C levels

BUT

- Costly
- High risk of post-transplantation surgical complications
- Need for lifelong immunosuppressive therapy

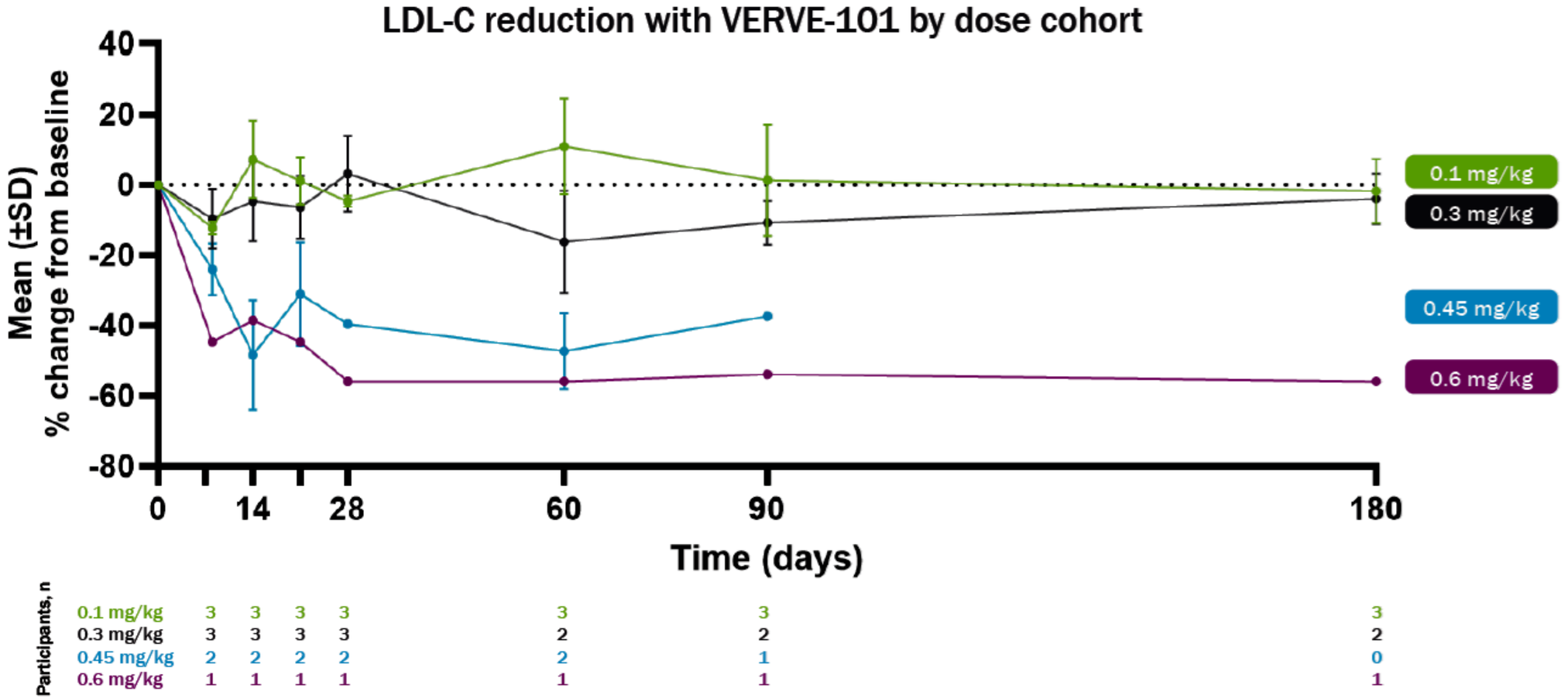
Al Dubayee M. et al. *Adv Ther* 2022;39:3042-3057

“Once and done” gene editing for the treatment of HoFH



Stankin S, et al. *Atherosclerosis* 2023;468:14-24

Durable 55% reduction in LDL-C extending up to 180 days in the single participant in the highest dose cohort with Verve-101 directed against PCSK9



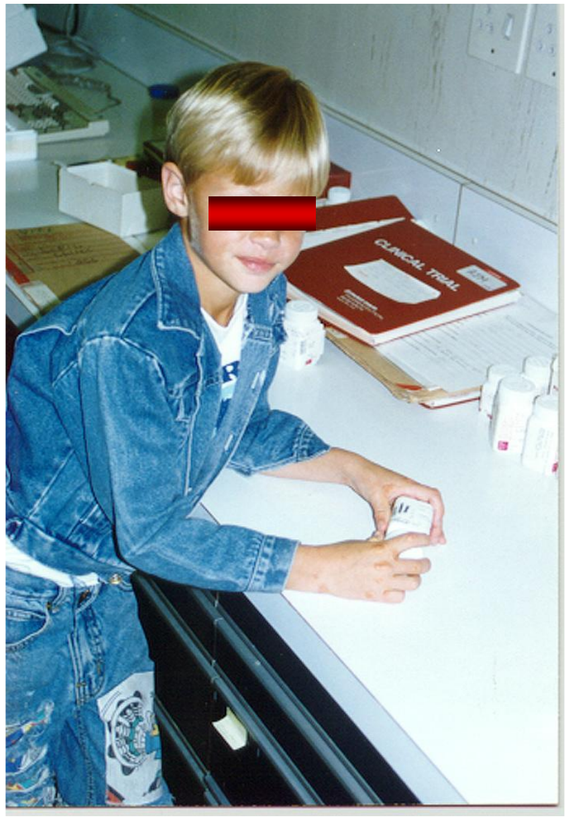
Scott Vafai et al. Presented at the AHA, Philadelphia, 11 -13 Nov 2023

A "CURE" FOR HoFH?

"Like the conquest of Mount Everest, overcoming the challenge of FH has been a long and difficult endeavour."

Gil Thompson

***Atherosclerosis* 2018;276:148-54**



BUT WITH THE ARRIVAL OF NOVEL DRUGS; GENE THERAPY ETC, I HOPE SO

TAKE HOME MESSAGE

The majority of HeFH and all HoFH children and adolescents require lipid-lowering therapy in order to reduce their life-long LDL-cholesterol burden and to delay the onset of atherosclerotic cardiovascular disease.

We now have effective therapies:

- **The earlier the better**
- **The lower the better**
- **The longer the better**