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The University of Manchester

Central Manchester University Hospitals NHS
NHS Foundation Trust

HoFH and HeFH
The Role of Lipoprotein Apheresis

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Declaration

- Received research grants from Synageva, Pfizer, Amgen, MSD

- Received personal fee from Aegerion, Amgen, Johnson & Johnson, Lilly, MSD, Pfizer, Sanofi, Synageva.

1. Introduction
2. Current medical therapy
3. Lipoprotein apheresis
    1. HoFH
    2. HeFH
    3. Guidelines and targets
    4. Challanges
4. New Therapies
5. Conclusion

HoFH

- Rare…
- Mutations effect
  - LDL receptor
  - apolipoprotein B
  - Proprotein convertase subtilisin/kexin type 9 (PCSK9) protein
  - LDL adaptor protein (LDLRAP1) (ARH)
- CHD before age of 20 years and often in childhood

HoFH

- Some now survive longer
  - with potent statins
  - other lipid modifying agents
  - extracorporeal removal of LDL and
  - heart surgery/intervention

The current standard treatment for adults and children is lipoprotein apheresis combined with maximum doses of rosuvastatin or atorvastatin, ezetimibe and bile acid sequestrants (BAS)

Durrington N, Hypercholesterolaemia Diagnosis and Management Hodder Arnold 2007

HoFH
just double trouble?

Abnormality	Notes
Decreased clearance of LDL-C	but 90% have 2-25% residual receptor function
Two- to three-fold increase in apoB–LP turnover with increase in apoB–LP assembly and secretion	
increased SRB1-mediated bulk flow of cholesterol	
Increase in cholesteryl ester production	
High LP(a)	
Delayed clearance of apoB 48 containing particles	

Sun XM et al, Atherosclerosis1998; Jeenah M et al Atherosclerosis 1993; Zelcer N et al,Science 2009; Sawamura T et al, Clin Chem 2009; Ikonen E et al Nat Rev Mol Cell Biol, 2008. Goldstein Jl et al, Cell 2006; Soufi M et al,Gene 2012; Goldberg Rb et al, Arteriosclerosis 1984; Raal F et al 2015; France M et al, Clinical Lipidology 2014

HoFH
just double trouble?

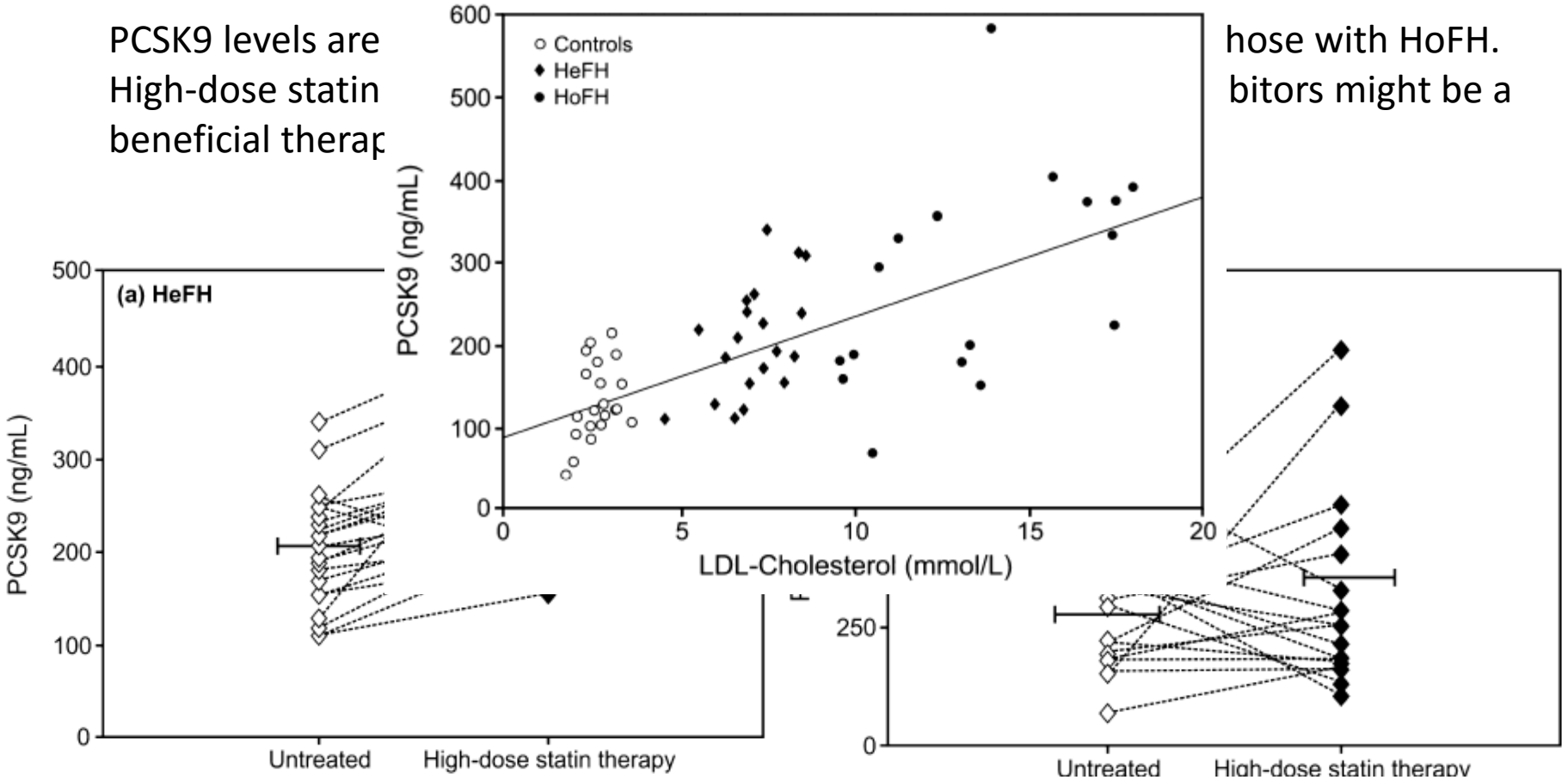
Abnormality	Notes
Low HDL Cholesterol	LXR underactivation which affect production of pre-beta HDL. Reduced ABCA1 and ABCG1 cholesterol egress
Increased PCSK9 and E3-ubiquitin ligase inducible degrader of the LDL receptor (IDOL)	IDOL acts post-translationally to reduce LDLR recycling
Biliary free cholesterol is increased	probably via SRBI
Possible decreased trans-intestinal cholesterol transport	

Sun XM et al, Atherosclerosis1998; Jeenah M et al Atherosclerosis 1993; Zelcer N et al,Science 2009; Sawamura T et al, Clin Chem 2009; Ikonen E et al Nat Rev Mol Cell Biol, 2008. Goldstein Jl et al, Cell 2006; Soufi M et al,Gene 2012; Goldberg Rb et al, Arteriosclerosis 1984; Raal F et al 2015; France M et al, Clinical Lipidology 2014

PCSK9 in HoFH and HeFH

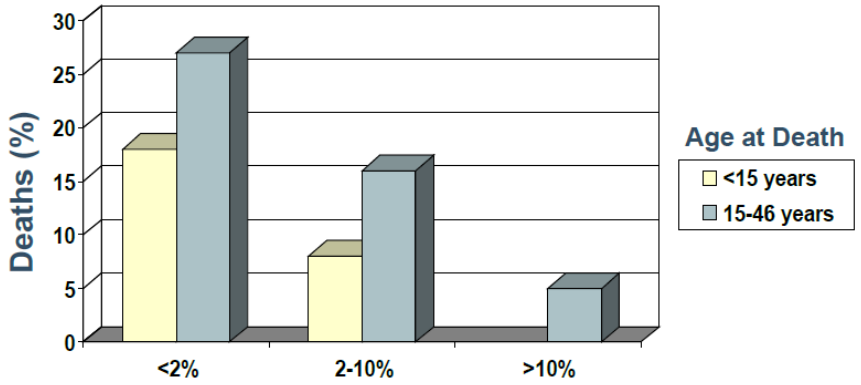
PCSK9 levels are
High-dose statin
beneficial therap

hose with HoFH.
bitors might be a



Raal et al. JAHA 2011

LDL receptor activity and prognosis



LDL receptor activity

Goldstein et al 1993

	LDLR Negative (n = 18)	LDLR Defective (n = 16)	p Value
Age at visit 1 (yrs)	11.5 (3.3–29)	28.1 (3.3–44.6)	0.0083
Age at first xanthomas (yrs)	2.0 (0.25–4)	7.0 (1–15)	0.0003
Age at FH diagnosis (yrs)	3.0 (0.5–7)	8.0 (2–17)	0.0005
Total cholesterol at diagnosis (mg/dl)	903 ± 187	715 ± 124	0.0019
Age at start of treatment (yrs)	5.0 (1.2–10)	16.0 (2–31)	0.0013
Age at CAD (yrs)	12.5 (6–16)	22.0 (16–37)	0.0039

Kalonsky et al. Am J Cardiology 2008

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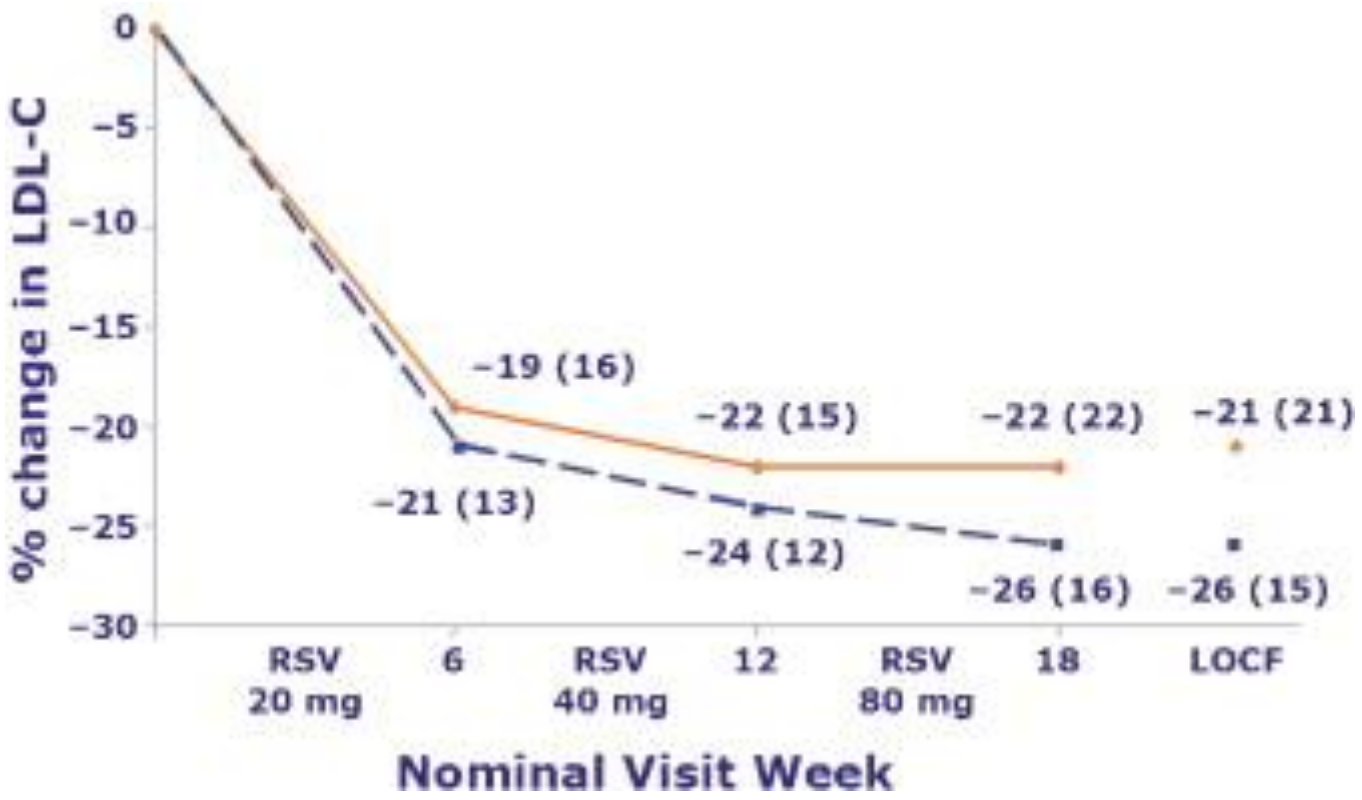
Statin therapy in HoFH



Mean (SD) percentage change in low-density lipoprotein (LDL) cholesterol by week and dose of rosuvastatin (RSV). Observed data for all patients in the intention-to-treat population are shown in the solid line for weeks 6 (*n* = 40), 12 (*n* = 36), and 18 (*n* = 35), and week 18 last observation carried forward (LOCF) (*n* = 40). Mean (SD) baseline LDL cholesterol was 13.3 (3.0) mmol/L. The data for patients who neither had portacaval shunts nor were receiving plasmapheresis are shown in the dashed line for week 6 (*n* = 28), week 12 (*n* = 27), week 18 (*n* = 26), and week 18 LOCF (*n* = 28). Mean (SD) baseline LDL cholesterol for this group of patients was 14.0 (2.9) mmol/L.

David Marais et al Atherosclerosis 2008

Statin Therapy in HoFH

- 149 patients (81 females, 68 males)
- Lipid-lowering therapy is associated with delayed cardiovascular events and prolonged survival in patients with homozygous familial hypercholesterolemia.

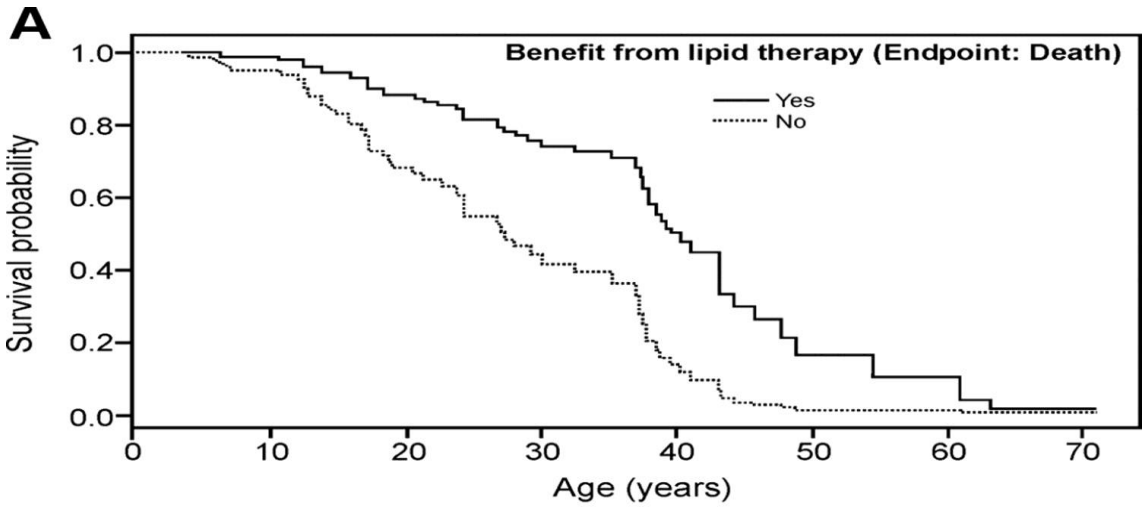
Lipid profile	Untreated	Taking Lipid-Lowering Therapy	Change, %
Total cholesterol, mmol/L	17.3±3.8	13.1±3.3*	−24.3
Triglycerides, mmol/L	1.28±0.81	1.18±0.63	−7.8
HDL-C, mmol/L	0.89±0.33	0.91±0.25	2.2
LDL-C, mmol/L	15.9±3.9	11.7±3.4*	−26.4
LDL/HDL ratio	21.4±10.9	13.5±5.9*	−36.9

•HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Results are expressed as mean±SD. ↵* P<0.0001.

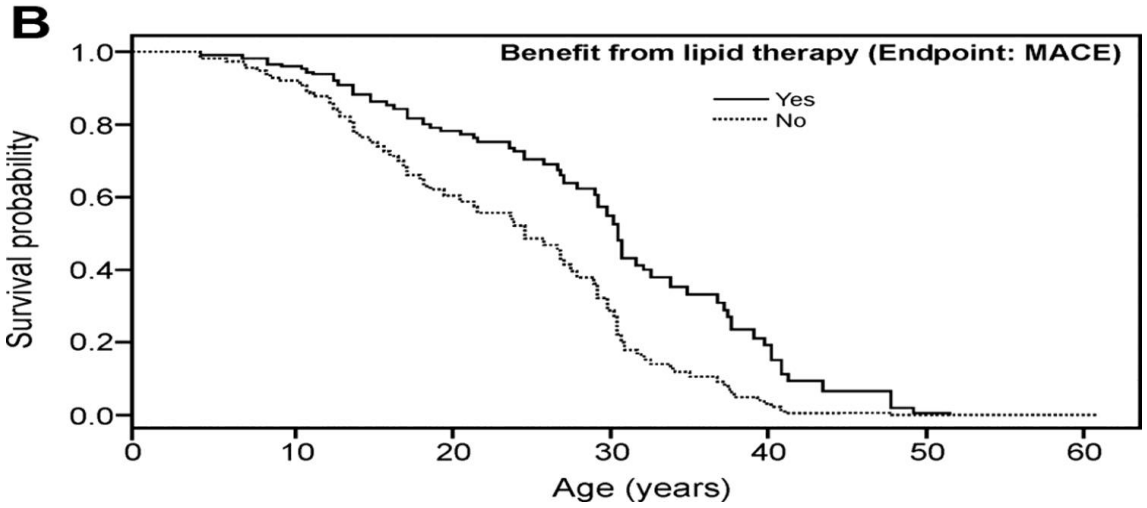
Frederick J. Raal et al. Circulation. 2011.

Cox proportional hazards model with time-varying benefit from statin therapy comparing treated and untreated in patients with homozygous familial hypercholesterolemia, with year of birth fixed as mean year of birth

A) survival



B) first major adverse cardiovascular event (MACE)



Frederick J. Raal et al. Circulation. 2011.

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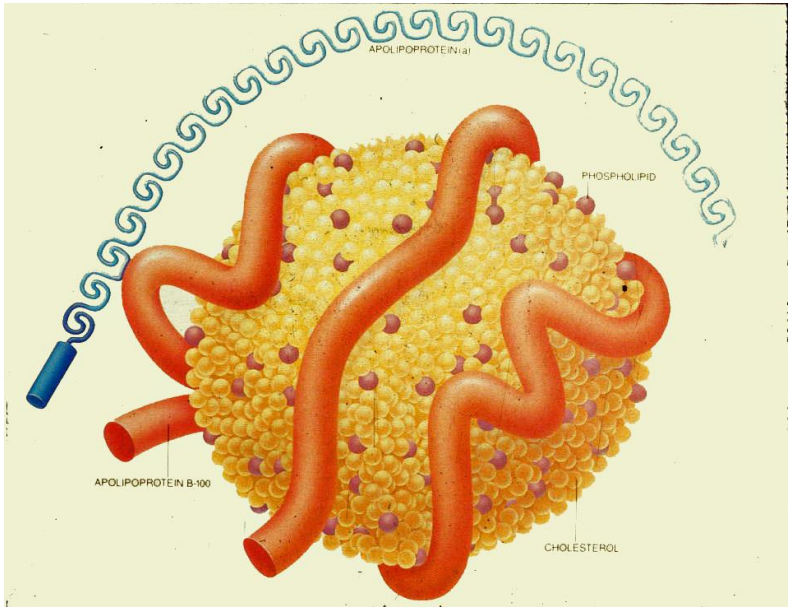
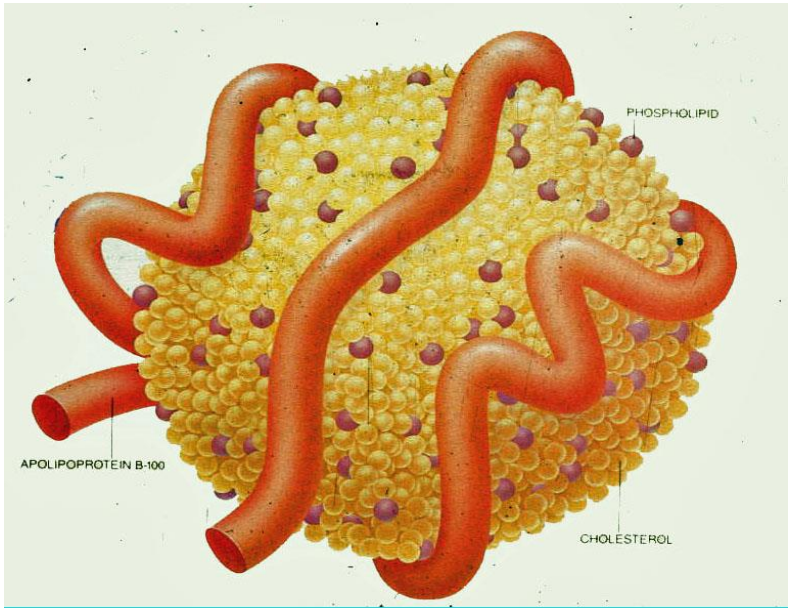
ἀφαίρεσις = to take away

ApoB containing particles
Lipoprotein (a)





Historical development of LDL apheresis

Manual plasmapheresis

- 1964 Myant & Lewis
- 1967 De Gennes et al

Continuous flow plasma exchange

- 1972 Turnberg et al
- 1975 Thompson et al

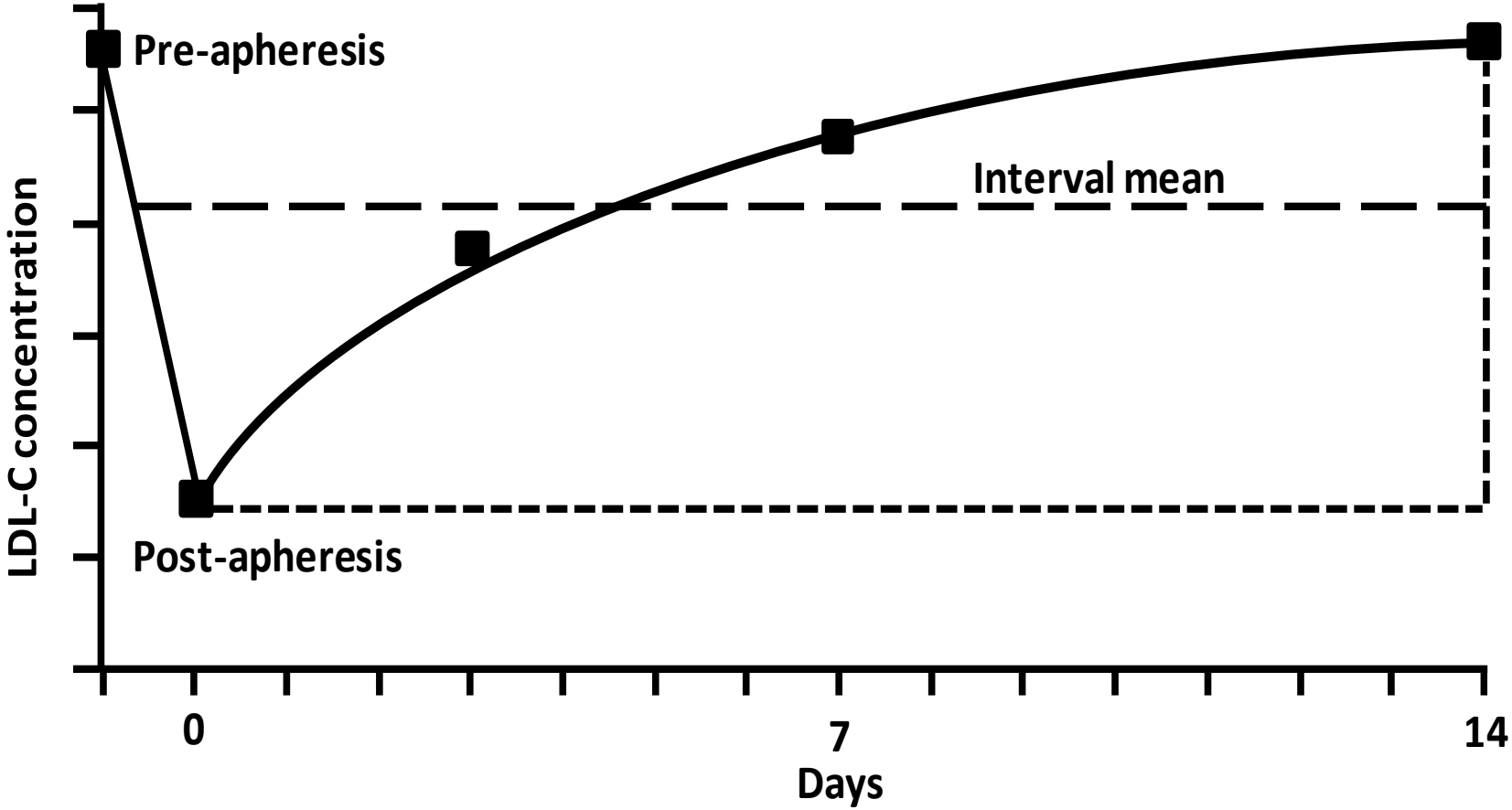
Selective LDL removal

- 1976 Lupien et al
- 1980 Agishi et al
- 1981 Stoffel et al

$$C_{mean} = C_{min} + K(C_{max} - C_{min})$$

Interval mean

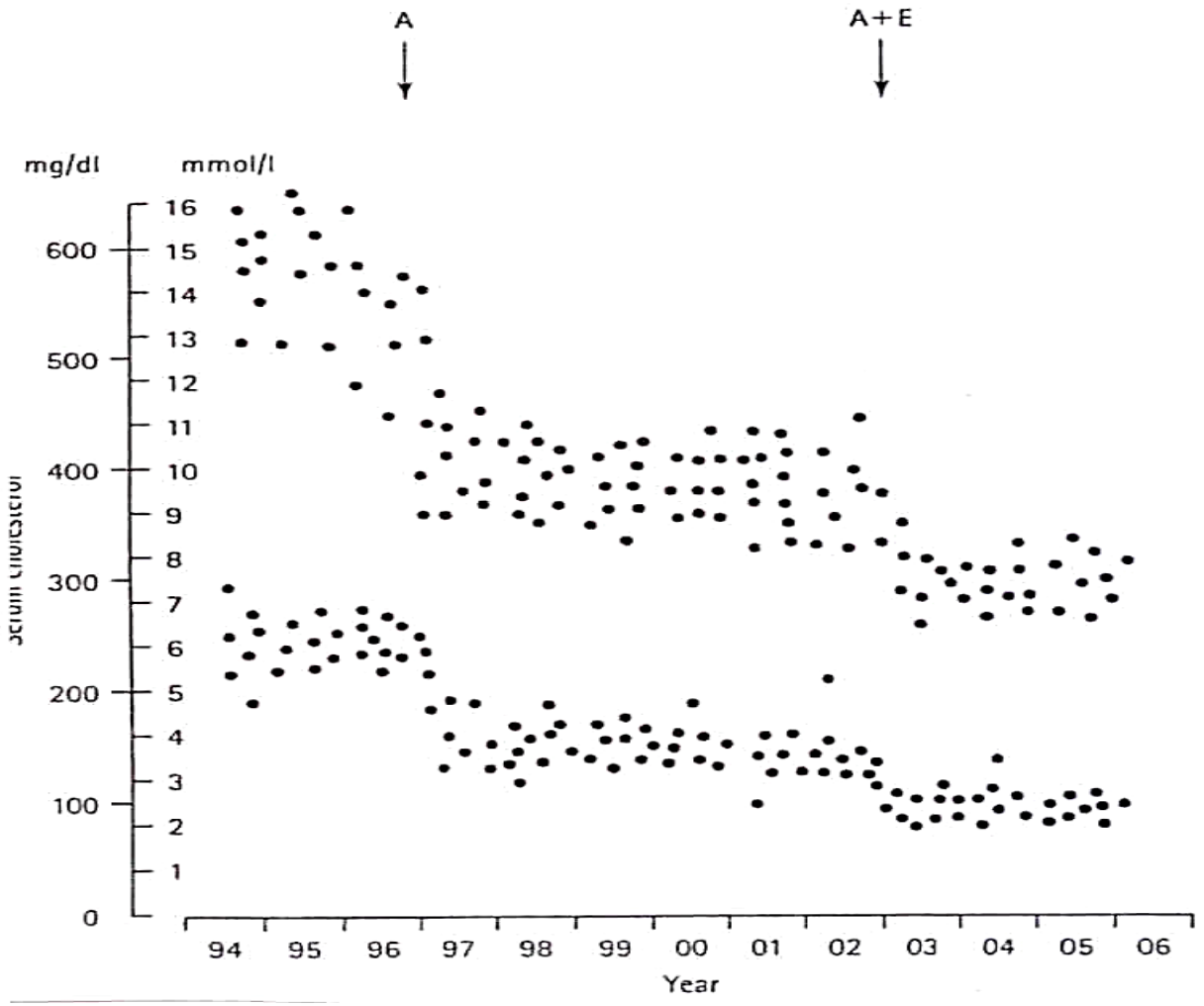
Remains >4mmol/L even with weekly apheresis



Adapted from Thompson et al. Lancet.1995;345(8953):811-816.

Treatment of homozygous FH (initial cholesterol 18-20mmol/l)

Patient received plasmapheresis every 2 weeks. At A she commenced atorvastatin 80mg daily and at A+E ezetimibe 10mg daily was added



Durrington Hyperlipidaemia, Diagnosis and Management Hodder Arnold 2007

Lipoprotein Apheresis – HoFH

Case presentations

- Patient 1
- HoFh c.2054C>T mutation
- Diagnosed age 4yrs
  - On treatment age 9 years
- On lipoprotein apheresis since age of 13
- Very compliant with apheresis

- Two successful pregnancies
  - Apheresis increased to weekly
  - C-section
    - Failure to progress
    - Placenta privia
- Age 39 in a good health
- **Most recent echo AS**
- **Coronary angiogram**
  - **No obstructive lesions**

- Patient 2
- HoFh c.2054C>T mutation
- Diagnosed age 5yrs
  - On treatment age 10 years
- On lipoprotein apheresis since age of 13
- Poor compliance with apheresis
  - CHD age 17…apheresis
  - CABG age 23

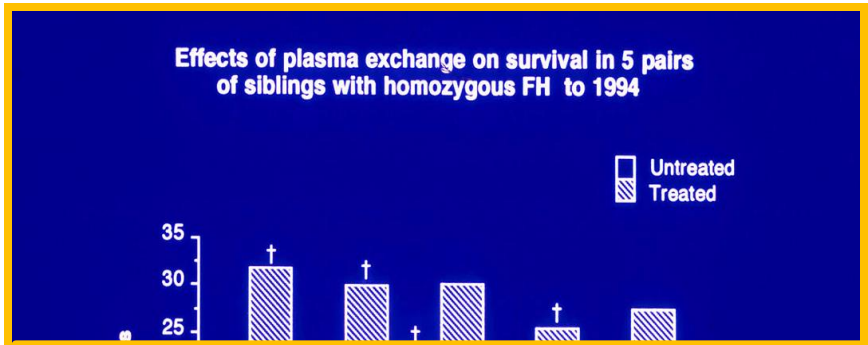
- Two successful pregnancies
  - Apheresis increased to weekly

- Stopped lipoprotein apheresis

- **Died age 27, was 4 months pregnant**

Unpublished data

Why to treat? Evidence? Lipoprotein Apheresis - HoFH



In a longer and larger observational study of German patients, followed up for **1–31 years**, mortality **was 43% among the seven** untreated homozygotes compared **with 21% in the 14 who were treated** with lipoprotein apheresis **for ≥1 year.**

All of the untreated siblings had died (**mean age of death 17.7** years), whereas **four of the five siblings** treated for 8.4 years with plasma exchange survived, with a mean **age of 23.2 years** at the time of the report (p = 0.03).

Thompson GR et al BMJ 1980; Keller C . Atheroscler. Suppl 2009;

Lipoprotein Apheresis
HoFH

Comparison of pre- and on-treatment serum total cholesterol (TC) in dead and alive HoFH.

Cardiovascular complications & surgical treatment.

Cardiovascular disease	Dead	Alive	P
A			
A			
C			
C			
H			
Carotid disease	1 (6%)	3 (10%)	>0.5

What about HeFH?

Thompson GR et al 2015

Reaching LDL-C target in patients with high baseline LDL-C concentrations

Average LDL-C decrease needed depending on baseline levels

Baseline LDL-C concentrations	4.9 mmo/l 190 mg/dl	5.7 mmo/l 220 mg/dl	6.5 mmo/l 250 mg/dl	7.2mmol/l 280 mg/dl	8 mmol/l 310 mg/dl
To reach LDL-C < 4.1 mmol/l (<160 mg/dl)	–16%	–27%	–36%	–43%	–48%
To reach LDL-C <2.6 mmol/l (<100 mg/dl)	–47%	–55%	–60%	–64%	–68%
To reach LDL-C <1.8 mmo/l (<70 mg/dl)*	–63%	–69%	–72%	–75%	–78%

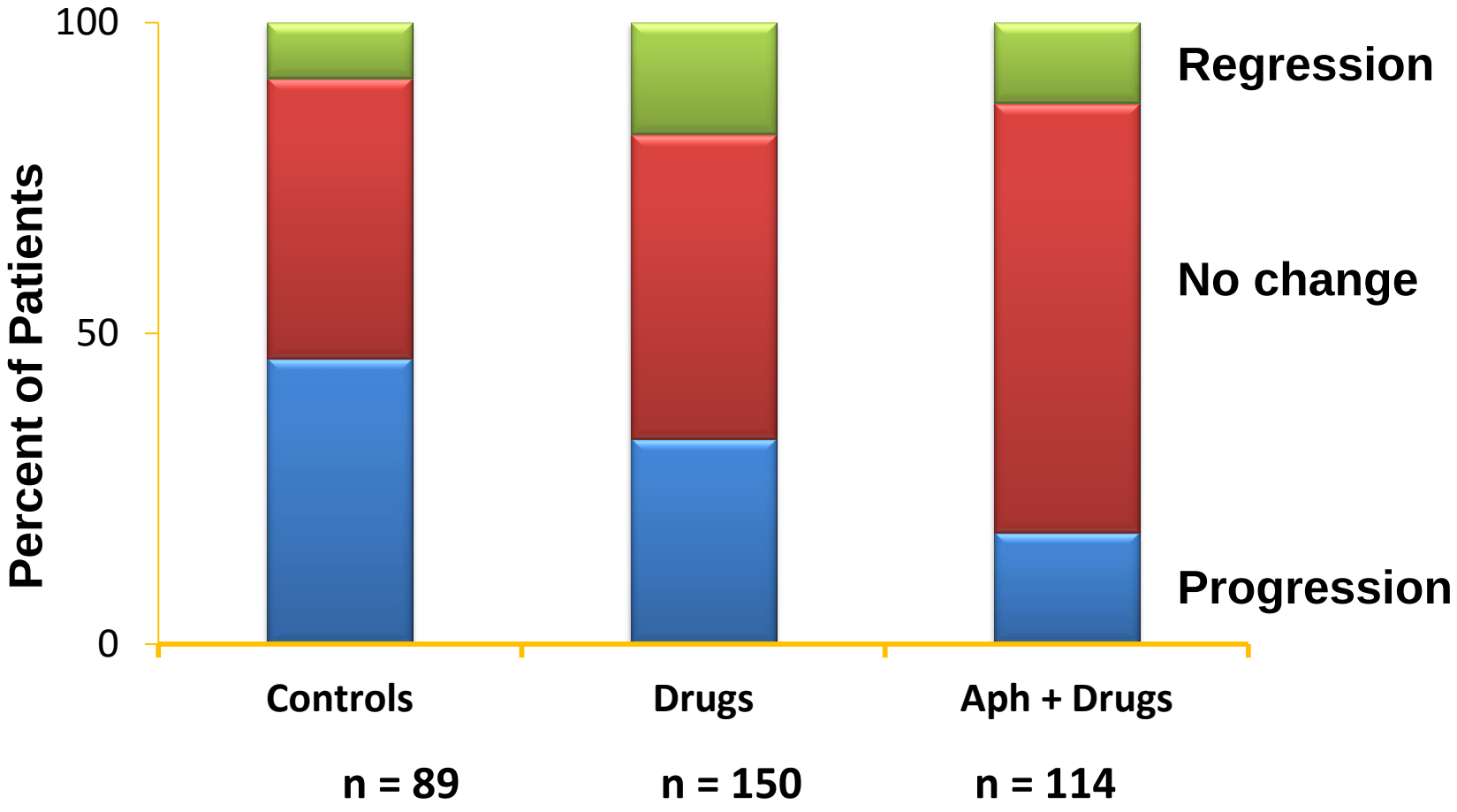
Patients with high LDL-C concentrations at baseline may be categorized as having "severe FH", regardless of the diagnosis based on DNA analysis (i.e. HoFH or HeFH)

*Percentage calculated

Civeira F *et al. Atherosclerosis* 2004;173:55

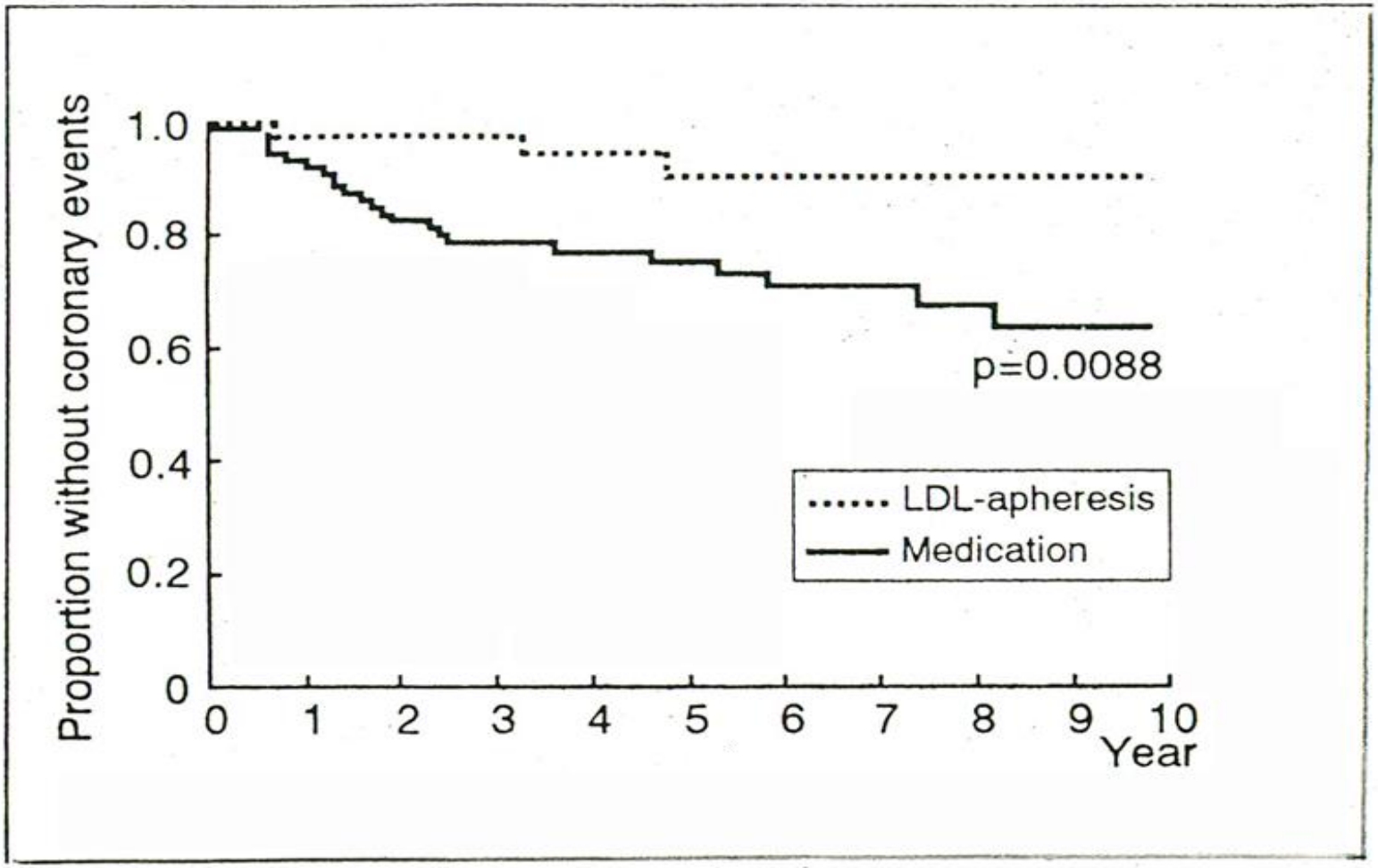
Lipoprotein Apheresis - HeFH

Frequency of coronary angiographic change (weighted means) in HoFH trials of 2 years duration



Thompson GR, et al 1995; Kroon AA, et al 1996; Nishimura S, et al 1996. Thompson GR et al, Atherosclerosis 2008

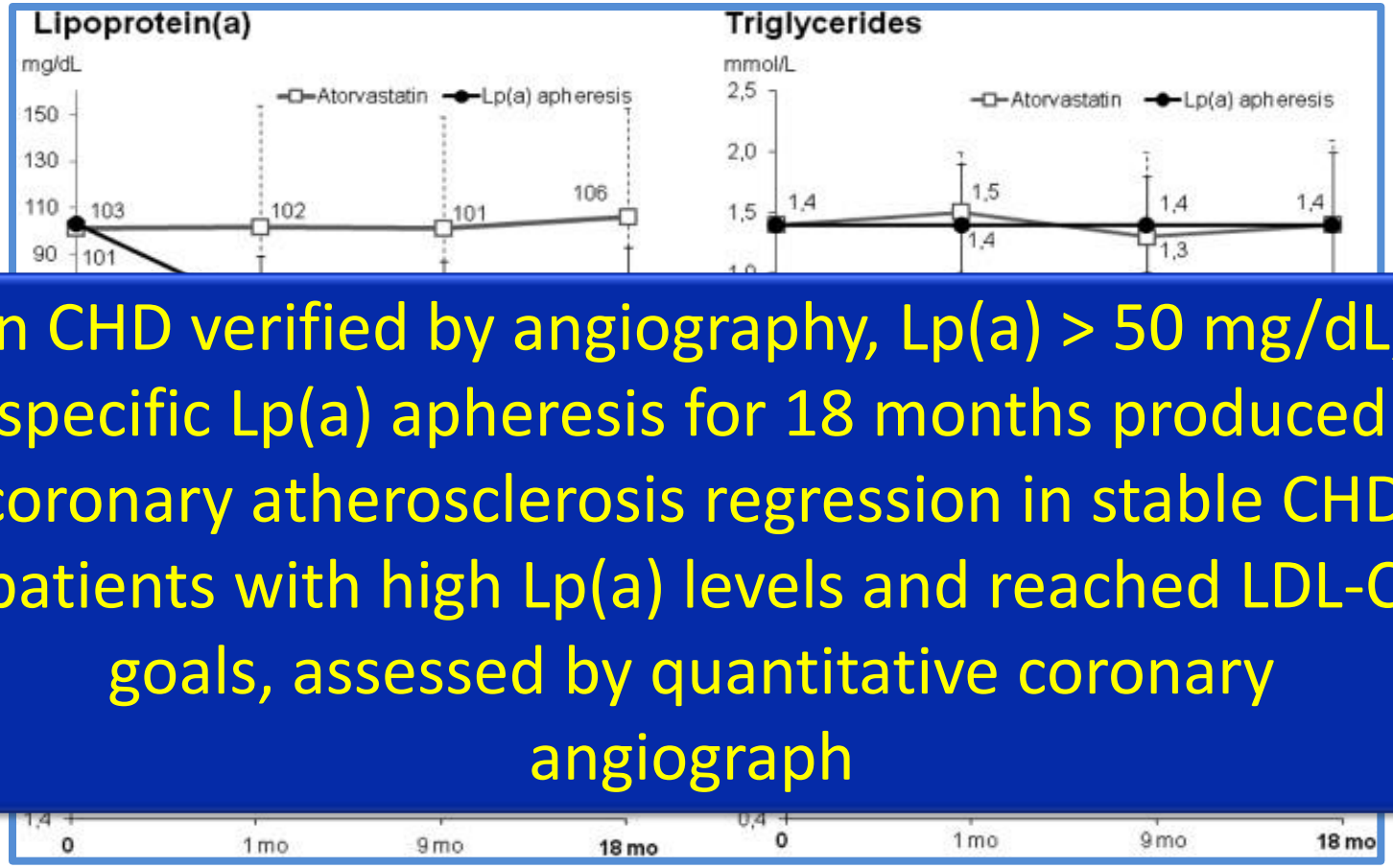
Kaplan-Meier curves of coronary events in HeFH



Mabuchi H et al Am J Cardiol 1998

Lipoprotein Apheresis – Lp(a)

Changes in serum lipoproteins in hyperLp(a) subjects on atorvastatin ± weekly Lp(a) apheresis (Safarova et al, 2013)



In CHD verified by angiography, Lp(a) > 50 mg/dL, specific Lp(a) apheresis for 18 months produced coronary atherosclerosis regression in stable CHD patients with high Lp(a) levels and reached LDL-C goals, assessed by quantitative coronary angiograph

Mean changes in lipid and lipoprotein levels over the 18-month study period, according to treatment group. The p values are given for the comparison between the two treatment groups at 18 months. The vertical bars indicate the standard deviation. HDL-C...

HEART UK indications for LDL apheresis (*Atherosclerosis* 2008;198:247-55)

- **Homozygous FH aged > 7 years if TC remains > 9 mmol/l or decreases < 50% on maximal drug therapy**
- **Heterozygous FH with progressive CAD if LDL-C remains > 5 mmol/l or decreases < 40% on maximal drug therapy**
- **Patients with Lp(a) > 60 mg/dl with progressive CAD** (if LDL-C is > 3.2 mmol/l) **despite maximal drug therapy**

Target levels (percentage decreases) of total cholesterol (TC), LDL cholesterol (LDL-C) and lipoprotein (a) [Lp(a)] for lipoprotein apheresis

Patient group	Lipid Profile	Baseline mmol/L (% decrease)*	Interval mean
HoFH	TC LDL-C	<9 (>50%) <8.5 (>55%)	<7 (%60) <6.5 (%65)
HeFH	LDL-C		<2.6 (>60)
High Lp(a)	Lp(a)		<500g/L (50mg/dl)

*Compared with baseline value of all lipid-lowering treatment

Thompson GR, Atherosclerosis 2013.

USA-FDA

***The Food and Drug Administration* (*FDA*) has approved the use of DSA and HELP apheresis in three categories of patient in the USA:**

- HoFH, with LDL-C > 13 mmol/l
- HeFH, with LDL-C > 7.8 mmol/l
- HeFH, with documented CHD and LDL-C > 5.2 mmol/l

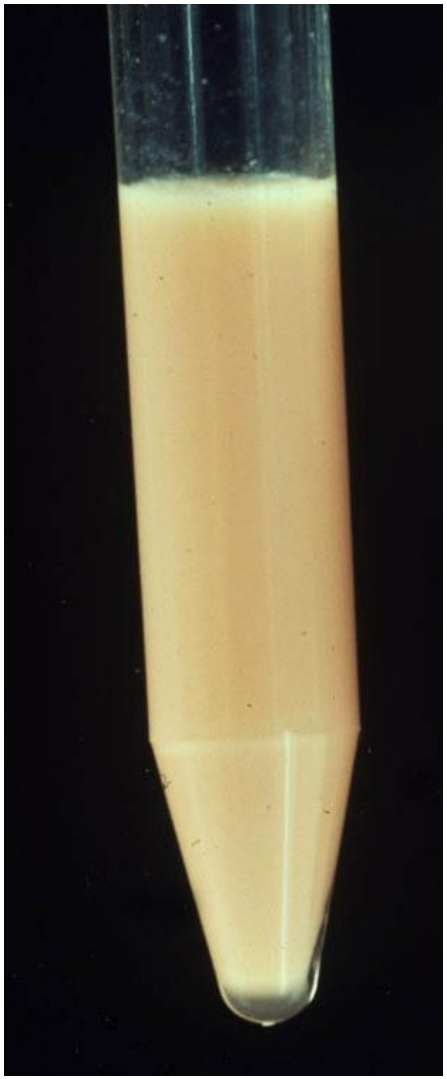
Germany

German Federal Committee of Physicians and Health Insurance Funds

The Federal Committee of Physicians and Health Insurance Funds has authorised the use of LDL apheresis in the following categories of patient:

- FH and LDL-C 4.2 mmol/L (160 mg/dL) after diet
- **Other indication?**
- Progressive CVD assessed by imaging and Lp(a) >60mg/dL

Hypertriglyceridaemic acute pancreatitis ?



If serum triglycerides > 10 mmol/l

AND

clinical evidence of acute pancreatitis

Challenges

Availability

A. Knowledge of apheresis in lipid clinics

   i. Access to treatment in UK & geographical variation

   ii. Germany 2 per 100 000

   iii. North America 0.13 per 100 000

   iv. UK 0.06 per 100 000

B. Establishing new patients on treatment

C. Justifying ongoing funding

Walji *et al* Clin Lip 2013

Challenges

Patients…

Vascular access

1. **Native vein**
2. **AV fistula and shunt**
3. **Central line**

Complications

Progress of atherosclerosis despite lipoprotein apheresis

MORE THERAPEUTIC OPTIONS NEEDED

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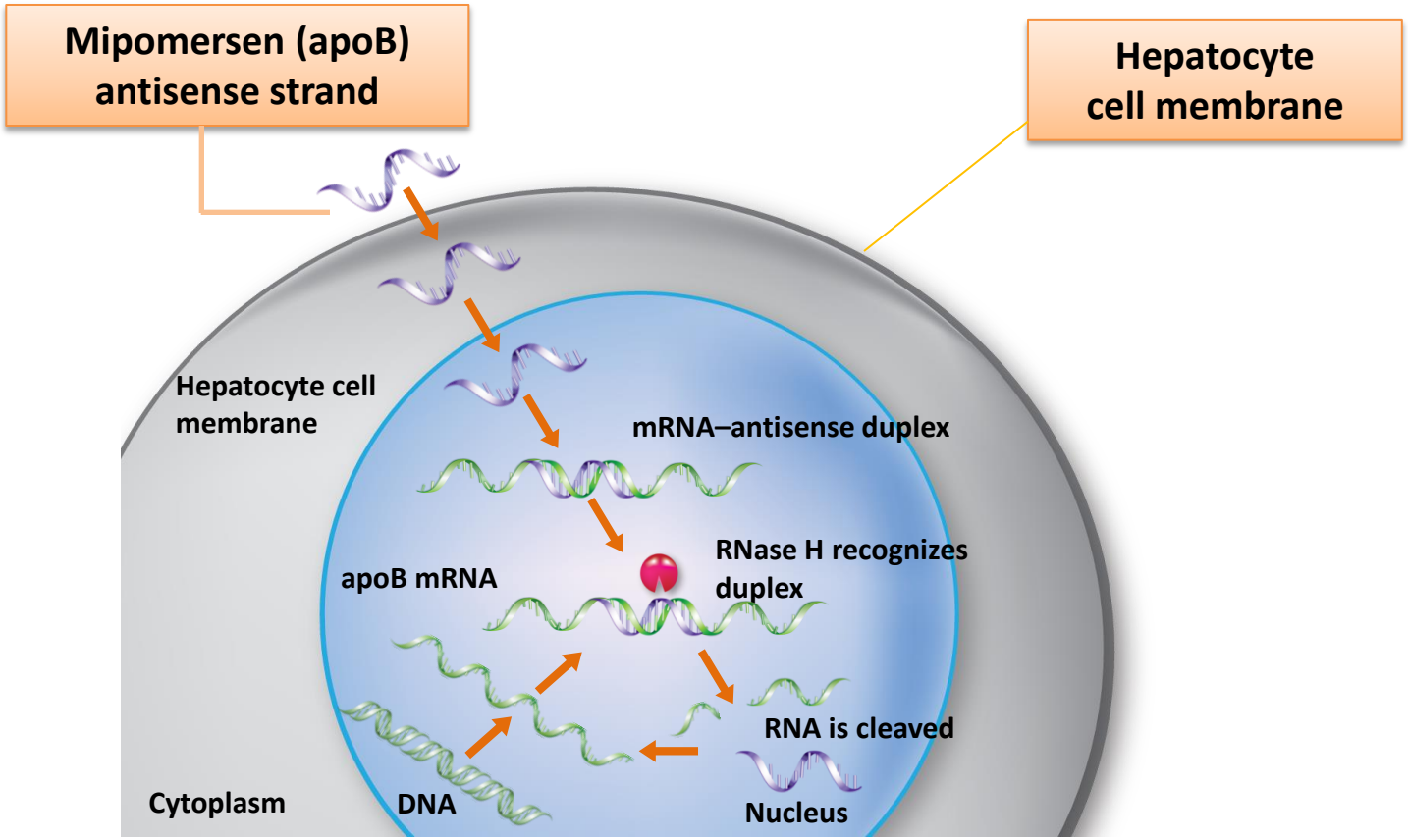
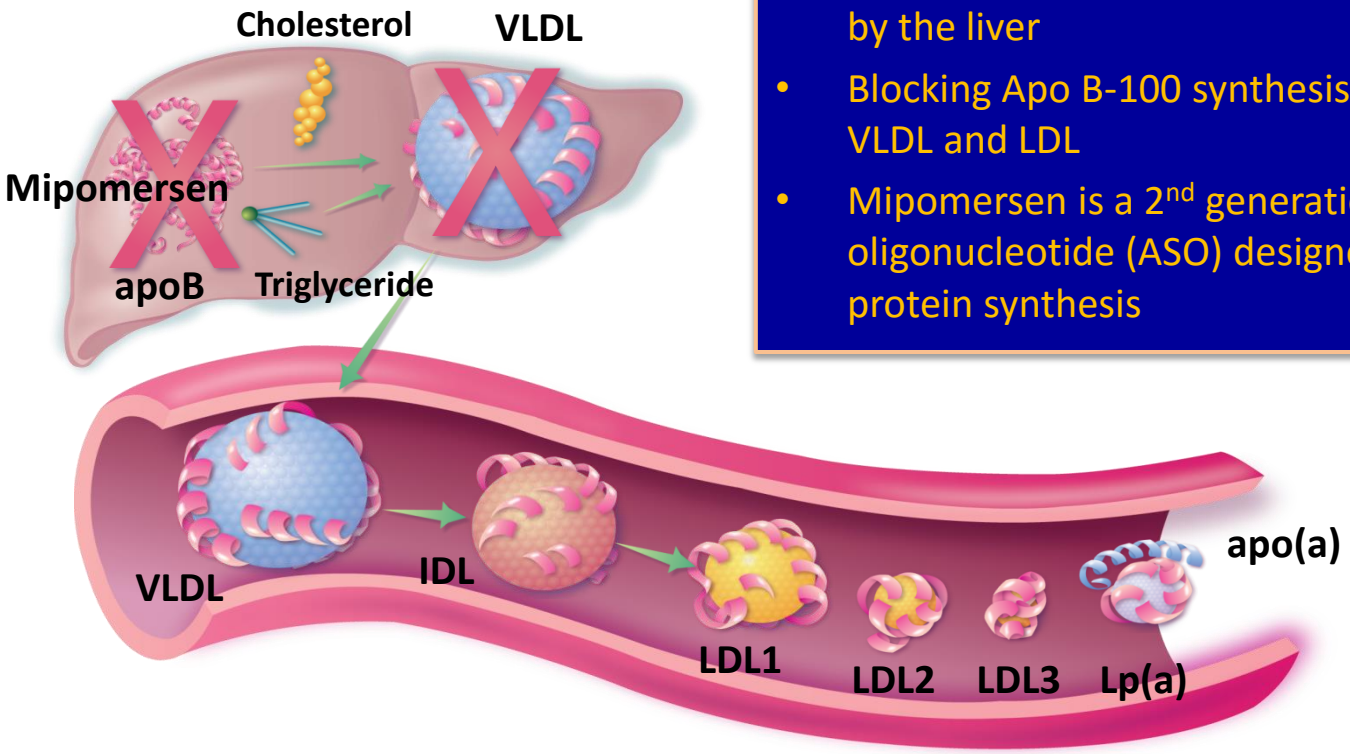
Mipomersen crosses the hepatocyte and nuclear membrane to target the mRNA for apoB



Adapted from Figure 1.10 in Crooke ST, ed. *Antisense Drug Technology: Principles, Strategies and Applications.* 2nd edn. 2008:601

Mipomersen: a second-generation ASO that targets apoB-100



- Apo B-100 is a key structural and functional component of all atherogenic lipoproteins produced by the liver
- Blocking Apo B-100 synthesis blocks production of VLDL and LDL
- Mipomersen is a 2nd generation antisense oligonucleotide (ASO) designed to inhibit Apo B protein synthesis

Davis RA. *Biochim Biophys Acta* 1999;1440:1
Crooke R, et al. In: Crooke ST, ed. Antisense drug technology: principles, strategies and applications. 2nd ed. Boca Raton, Florida: CRC Press, 2007:601

Phase III: efficacy on top of maximally-tolerated lipid-lowering therapies

Percentage change from baseline in LDL-C, apoB, Lp(a), TG and HDL-C in patients treated with mipomersen

		% change from baseline				
Patient population	Baseline LDL-C (mg/dl)	LDL-C Mean	ApoB Mean	Lp(a) Median	TG Median	HDL-C Mean
HoFH	439	–25%	–27%	–32%	–18%	19%
Severe HC	276	–36%	–36%	–39%	–15%	6%
HeFH with CAD	153	–28%	–26%	–21%	–14%	3%
HC at high risk for CAD	123	–37%	–38%	–26%	–26%	2%

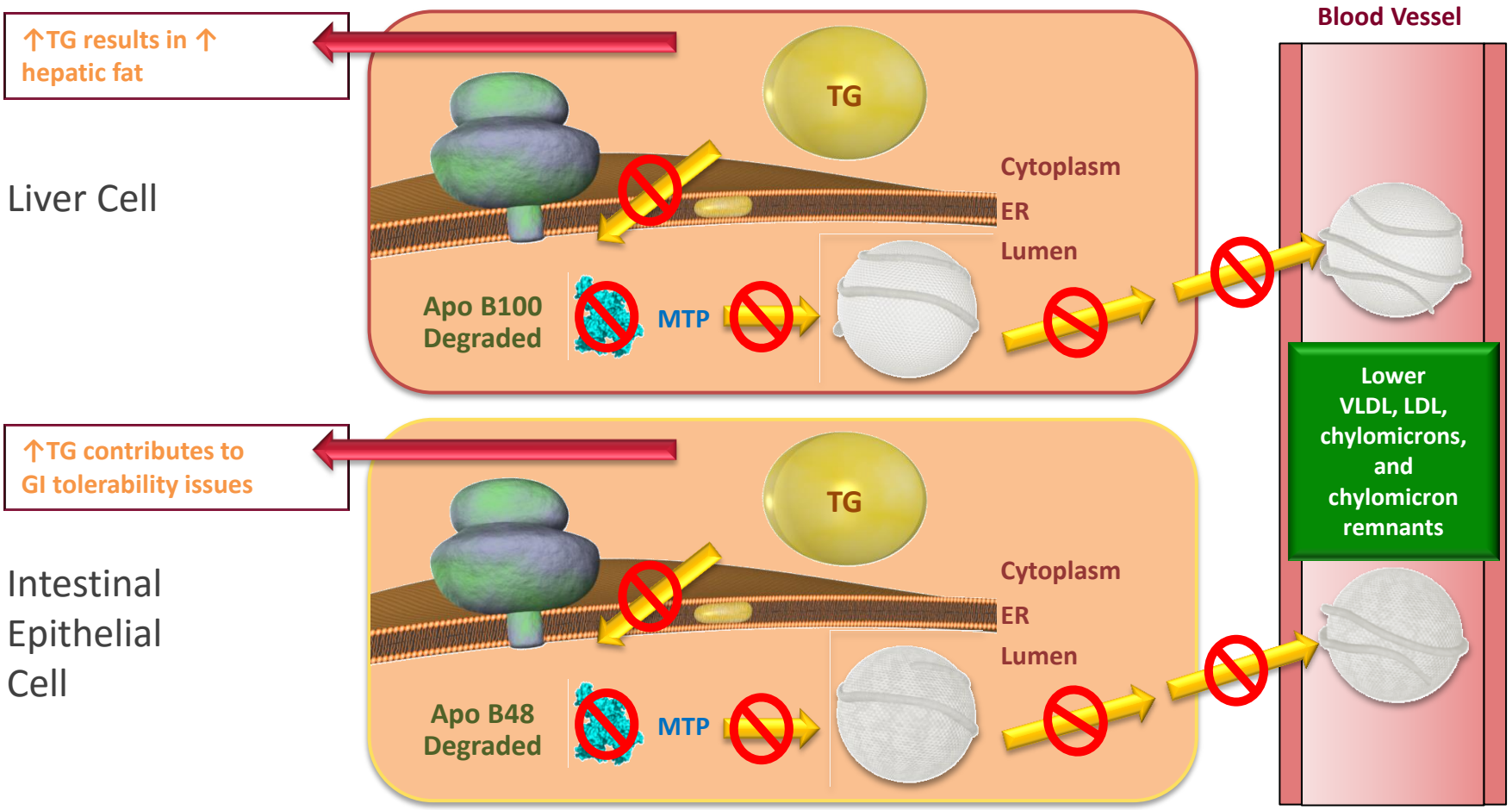
Raal FJ *et al. Lancet* 2010;375:998
Tardif JC *et al. J Am Coll Cardiol* 2011;57:Oral 920-3

Stein EA *et al. Circulation* 2012;126:2283
Cromwell W *et al. J Am Coll Cardiol* 2011;57:Poster 1011-304

Lomitapide

Assembly and Release of Apo B Containing Lipoproteins and MTP

(microsomal triglyceride transfer protein)

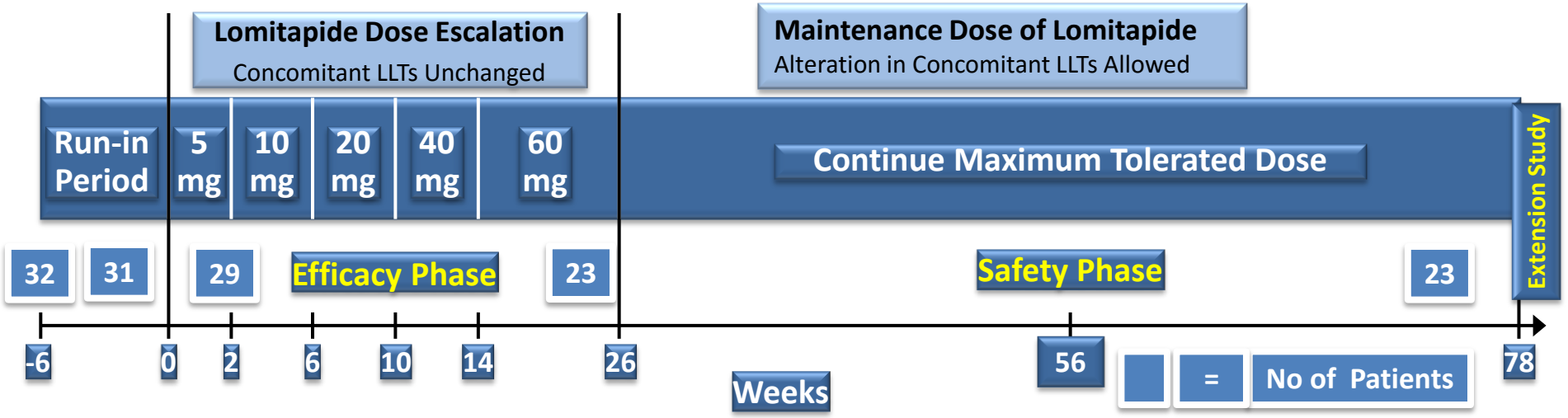


Hussain M, et al. J Lipid Res. 2003:44;22-32.

Phase 3 Study Design:
78 week study with 3 time periods: Safety Phase

Patients must have been diagnosed as having functional HoFH defined by at least one of the following criteria:

- Documented functional mutation(s) in both LDL receptor alleles or alleles of other genes known to affect LDL receptor functionality
- Skin fibroblast LDL receptor activity <20% normal
- Untreated TC >500 mg/dL (13mmol.l) and TG <300 (3.8 mmol/l) mg/dL and both parents have documented TC >250 mg/dL (6.5 mmol/l)

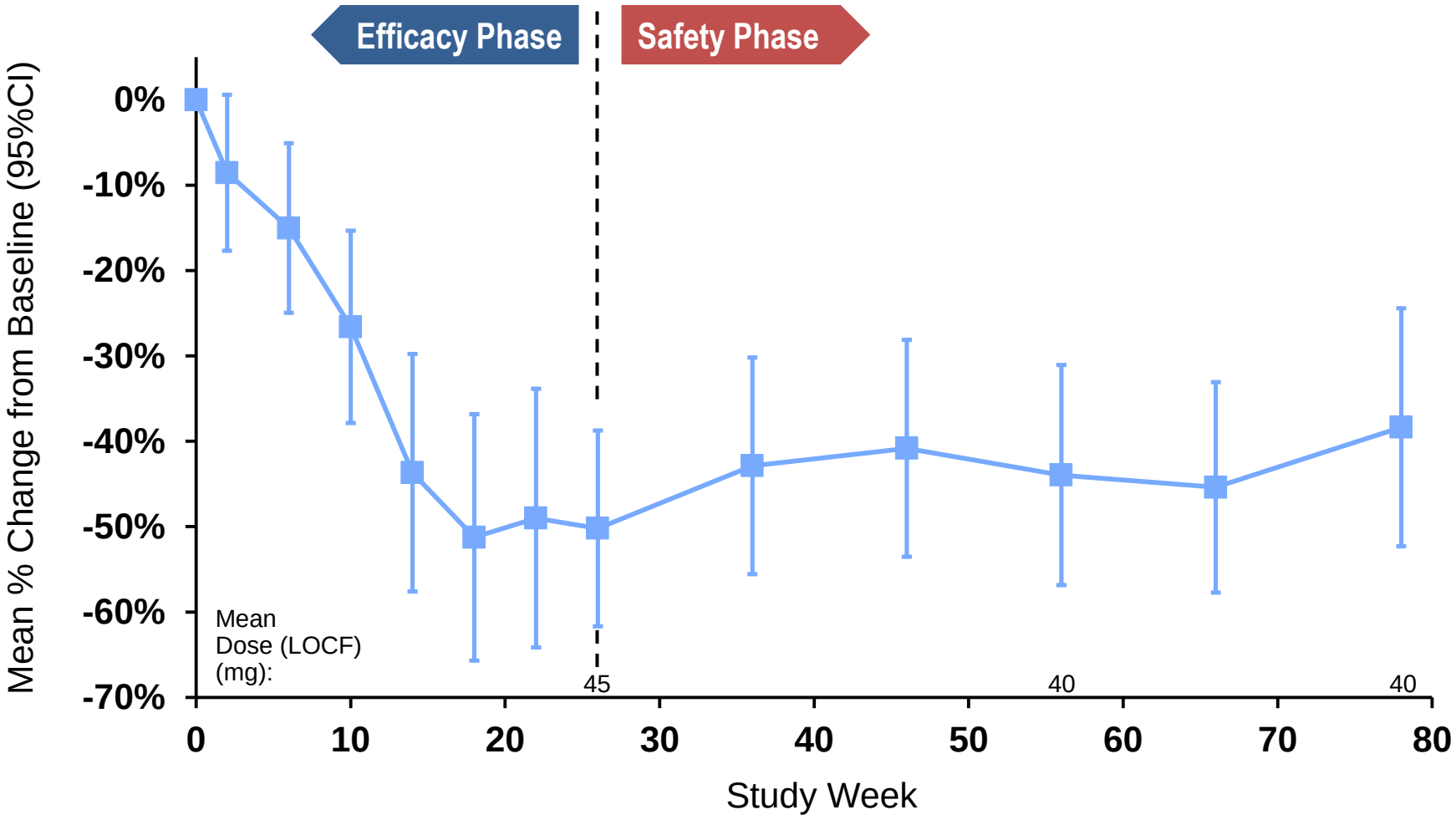


From Week 26 to Week 78 (Safety Phase):

- Patients continued on maximum tolerated dose of lomitapide established during the efficacy phase.
- Changes in concomitant LLTs were allowed unless dose alteration rules were met.
- An extension study was available for patients who successfully completed the phase 3 study

Cuchel, M. *et al*. Lancet 2013; 381: 40-46. (published online: 02 Nov 2012);
Juxtapid™ (lomitapide) capsules [US prescribing information]. Cambridge, MA: Aegerion Pharmaceuticals; 2012

Phase 3 Study Results: Change in LDL-C Through Week 78
(Completer Population, N=23)



Cuchel, M. et al. Lancet 2013; 381: 40-46. (published online: 02 November 2012)

Effect of lomitapide on apheresis
(Cuchel et al, 2012)

- 18 of 29 (62%) homozygotes were on apheresis at the start

- 3 of 18 (17%) were able to discontinue apheresis and
  3 others (17%) were able to reduce its frequency

Cost of new therapies?

TESLA: Patient Genotype and LDLR Activity

Patient	Mutation Allele 1 (Estimated LDLR Function)	Mutation Allele 2 (Estimated LDLR Function)	Overall LDLR Function
Patient 1	Asp266Glu (15%-30%)	Asp266Glu (15%-30%)	Receptor defective
Patient 2	1187-10 G>A† (Not determined)	Asp266Glu (15%-30%)	Receptor defective
Patient 3	Asp224Asn (<2%)	Cys296Tyr (Not determined)	Negative#
Patient 4	Deletion Exon 4-18 (Not determined)	Cys197Gly (Not determined)	Negative#
Patient 5	Asp221Gly (<2%)	Asp227Glu (5%-15%)	Receptor defective
Patient 6*	Asp227Glu (5%-15%)	Asp227Glu (5%-15%)	Receptor defective
Patient 7*	Asp227Glu (5%-15%)	Asp227Glu (5%-15%)	Receptor defective
Patient 8	Asp175Asn (Not determined)	Asp227Glu (5%-15%)	Receptor defective

#Confirmed by fibroblast culture
†Mutation at splice acceptor site 10 nucleotides upstream of the first nucleotide of exon 9, 1187
*True homozygous patient; patients share the same genotype

TESLA: LDL-C, Apo B, and Lp(a) Based on LDLR Status

Mutation Status	Percentage Change from Baseline, %, Mean (SD)					
	Week 12 Q4W Dosing			Week 12 Q2W Dosing		
	UC LDL-C	Apolipoprotein B	Lipoprotein (a)	UC LDL-C	Apolipoprotein B	Lipoprotein (a)
Defective LDLR (n=6)						-18.7 (14.1)
Negative LDLR (n=2)						-18.5 (5.3)
						Q2W Dosing
	U					Lipoprotein (a)
Defective LDLR (n=6)	(15.5) p=0.031†	- 18.0 (13.1)	-10.0 (11.5)	(20.4) p=0.031†	-22.1 (18.7)	-20.0 (12.1)
Negative LDLR (n=2)	4.4 (10.3)	1.4 (5.6)	-16.8 (8.0)	11.0 (23.6)	2.1 (7.9)	-22.7 (11.2)

LDL-C reduction in Rosuvastatin HoFH study:
Rosuvastatin 80: 19%
Atorvastatin 80: 18%

Marais *et al.* Atherosclerosis 2008.

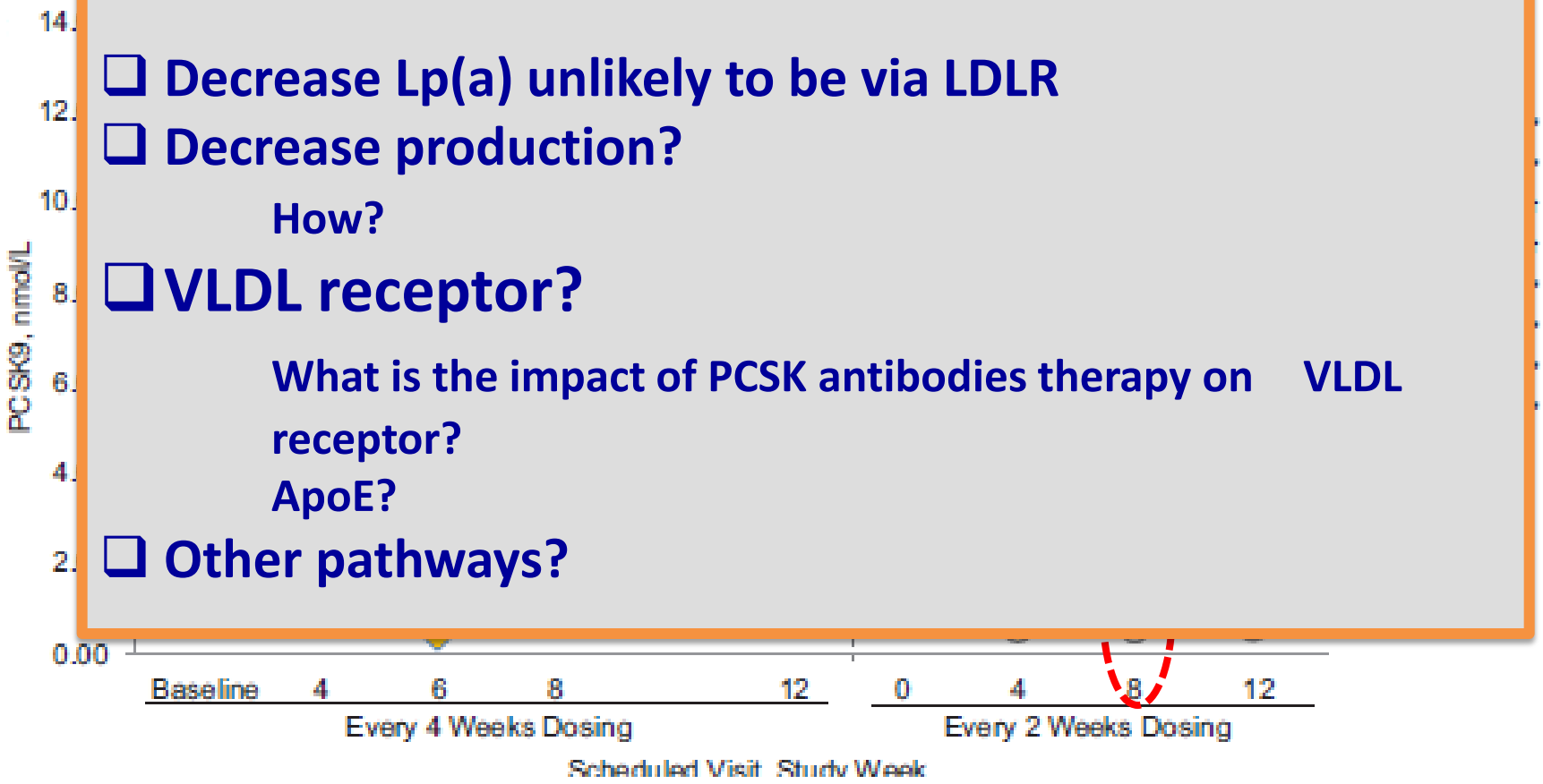
† Signed-rank test; * Lipoprotein (a) was only collected at week 12 for every-4-week dosing.
UC = ultracentrifugation; Q4W = every 4 weeks; Q2W = every 2 weeks; LDLR = low-density lipoprotein receptor

TESLA: LDL-C, Apo B, and Lp(a) Based on LDLR Status

Mutation Status	Percentage Change from Baseline, %, Mean (SD)					
	Week 12 Q4W Dosing			Week 12 Q2W Dosing		
	UC LDL-C	Apolipoprotein B	Lipoprotein (a)	UC LDL-C	Apolipoprotein B	Lipoprotein (a)
Defective LDLR (n=6)	-22.9 (17.5)	- 18.3 (14.9)	-10.0 (11.5)	-23.6 (7.6)	-17.9 (18.0)	-18.7 (14.1)
Negative LDLR (n=2)	2.6 (3.7)	-4.5 (3.5)	-16.8 (8.0)	15.3 (34.7)	3.4 (14.0)	-18.5 (5.3)
	Average of Week 4, 8, and 12 Q4W Dosing			Average of Week 4, 8, and 12 Q2W Dosing		
	UC LDL-C	Apolipoprotein B	Lipoprotein (a)*	UC LDL-C	Apolipoprotein B	Lipoprotein (a)
Defective LDLR (n=6)	-19.3 (15.5) p=0.031†	- 18.0 (13.1)	-10.0 (11.5)	-26.3 (20.4) p=0.031†	-22.1 (18.7)	-20.0 (12.1)
Negative LDLR (n=2)	4.4 (10.3)	1.4 (5.6)	-16.8 (8.0)	11.0 (23.6)	2.1 (7.9)	-22.7 (11.2)

† Signed-rank test; * Lipoprotein (a) was only collected at week 12 for every-4-week dosing.
UC = ultracentrifugation; Q4W = every 4 weeks; Q2W = every 2 weeks; LDLR = low-density lipoprotein receptor

TESLA: PCSK9 Levels By Patient
90% reduction



- ❑ Decrease Lp(a) unlikely to be via LDLR
- ❑ Decrease production?
  - How?
- ❑ VLDL receptor?
  - What is the impact of PCSK antibodies therapy on VLDL receptor?
  - ApoE?
- ❑ Other pathways?

An unconnected line indicates a missing value between two time points.
A dashed line indicates time between the two dosing periods of the study.
*Defective LDLR function; †Negative LDLR function
PCSK9 = proprotein convertase subtilisin/kexin 9; LDLR = low-density lipoprotein receptor

SUMMARY

- Lipoprotein apheresis involves the extracorporeal removal of LDL and Lp(a) from the circulation
- No outcome RCT studies but enough evidence to support lipoprotein apheresis
- Aortic stenosis and supravalvular disaese
- New therapies needed in HoFH and severe HeFH
- Evidence-based guidelines and treatment targets for lipoprotein apheresis have been published by HEART UK and other organisations

Questions