Management of Familial Hyperlipidaemias –

An Update

Dr RDG Neely
Department of Clinical Biochemistry and
the Lipid and Metabolic Clinic,
Royal Victoria Infirmary,
Newcastle upon Tyne
dermot.neely@nuth.nhs.uk

Prevalence of Primary Hyperlipidaemias

Hypercholesterolaemia	approx. frequency
Familial (heterozygous)	1 in 500
Familial (homozygous)	1 in 1,000,000
Polygenic	1 in 50
Hypertriglyceridaemia	
Familial lipoprotein lipase deficiency	1 in 1,000,000
Familial apolipoprotein CII deficiency	1 in 1,000,000
Familial Hypertriglyceridaemia	1 in 100
Combined Hyperlipidaemia	
Familial combined hyperlipidaemia	1 in 100
Familial Type III (Remnant) Hyperlipidaemia	1 in 5,000

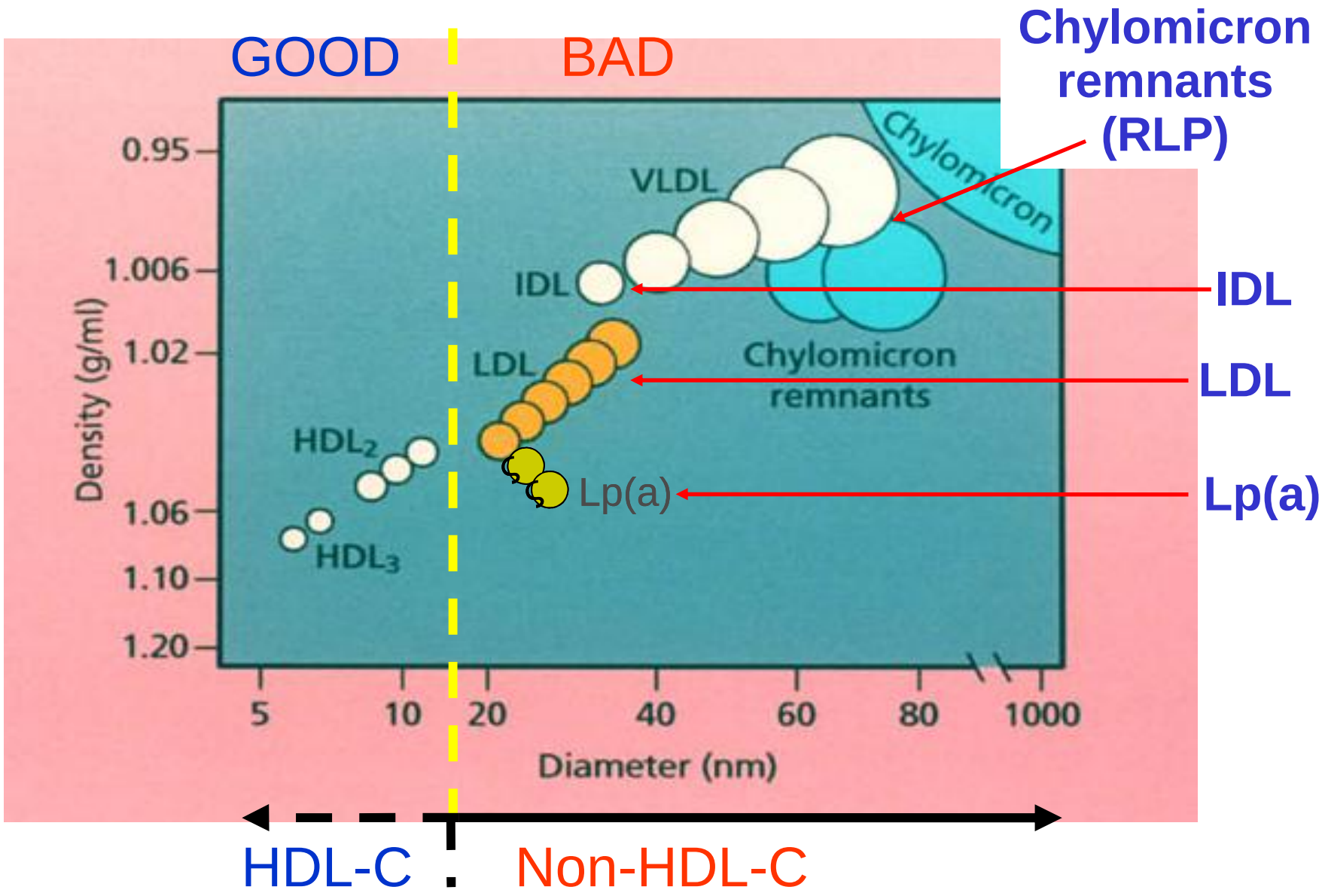
Familial lipoprotein disorders in patients with premature coronary artery disease

	% of total CHD
Elevated Lipoprotein(a)	19%
Hypertriglyceridaemia with low HDL	15%
Combined Hyperlipidaemia	14%
Hyperapobetalipoproteinemia	5%
Hypoalphalipoproteinaemia	4%
Hypercholesterolaemia	3%
Hypertriglyceridaemia	1%

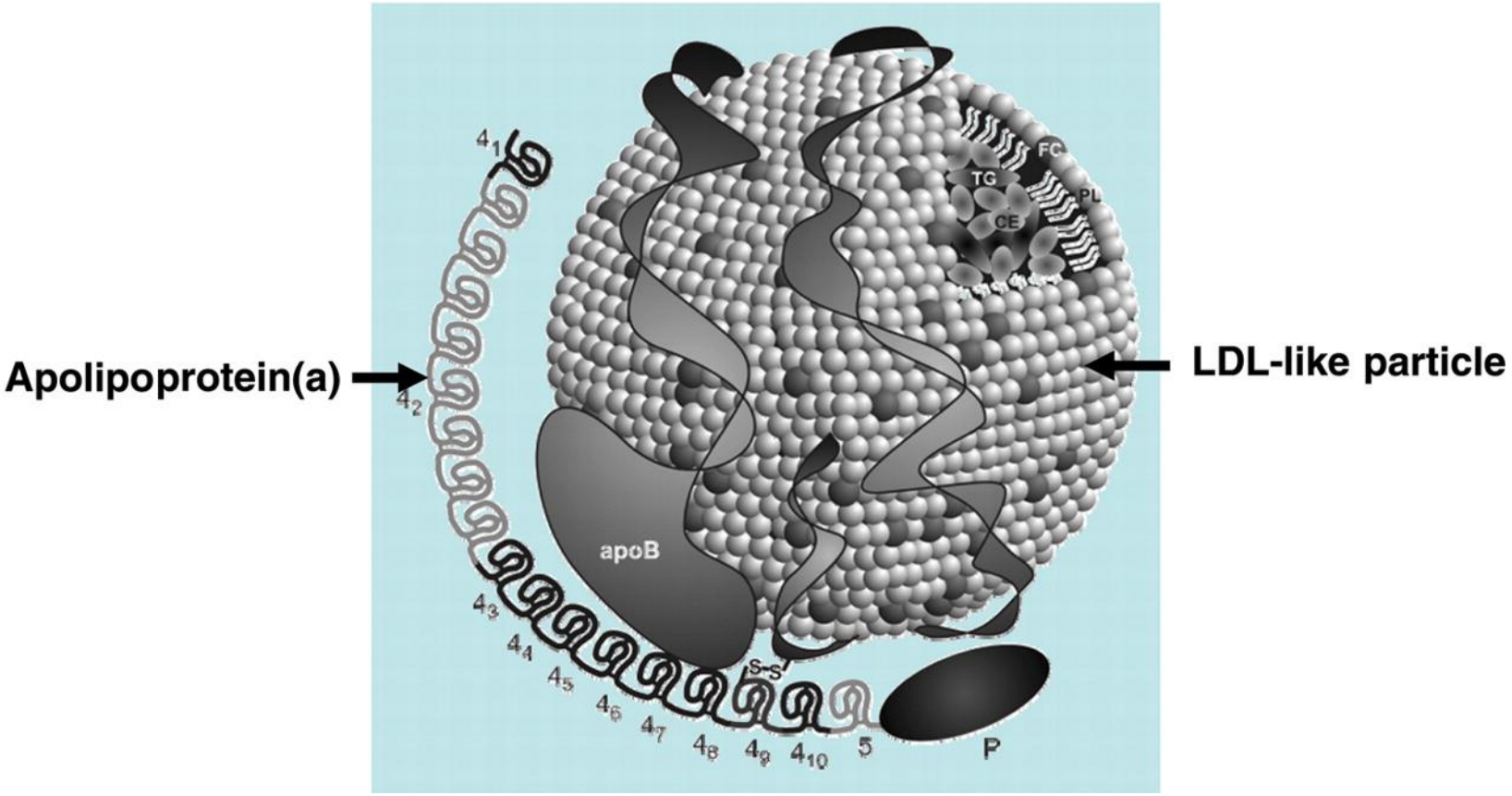
3 out of 4 patients with premature CHD have an abnormal lipid profile
More than 50% of patients with premature CHD have a Familial lipid disorder

Genest JJ et al., Circulation (1992) 85: 2025-33

Major Atherogenic Lipoproteins



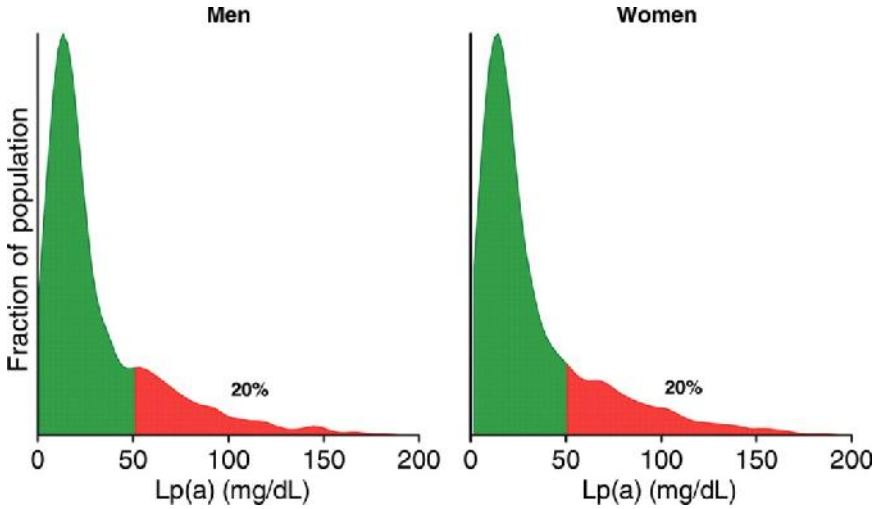
Lipoprotein(a) – unlike other atherogenic lipoproteins, not cleared by the LDL receptor



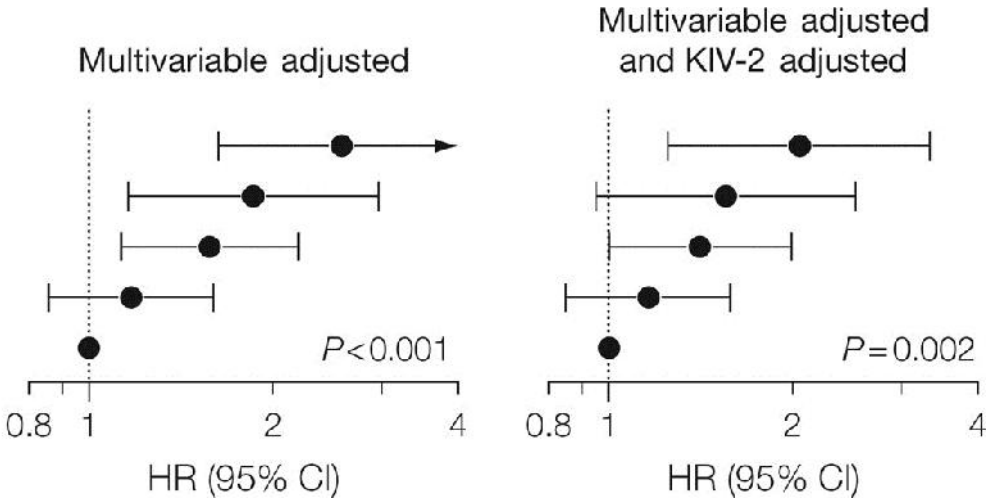
Nordestgaard B G et al. Eur Heart J 2010;31:2844-2853

European Heart Journal

Lipoprotein(a) and risk of myocardial infarction.



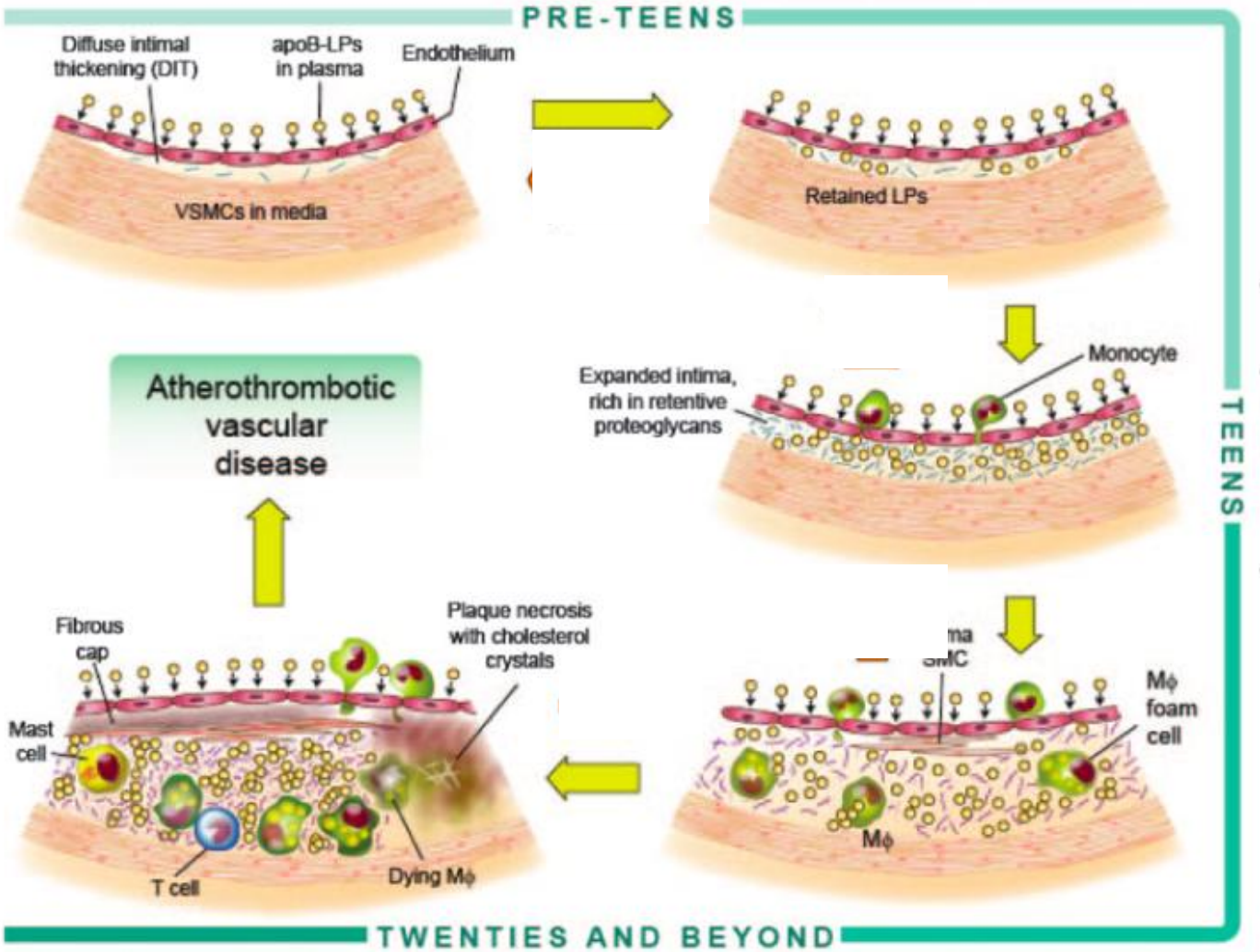
Lipoprotein(a) Percentile	mg/dL	Participants (no.)	Events (no.)
>95th	>117	376	46
90th–95th	77–117	450	46
67th–89th	30–76	1731	155
22nd–66th	5–29	3385	241
<22nd [reference]	<5	1582	104



Nordestgaard B G et al. Eur Heart J 2010;31:2844-2853

European Heart Journal

The Response-to-Retention model of atherogenesis

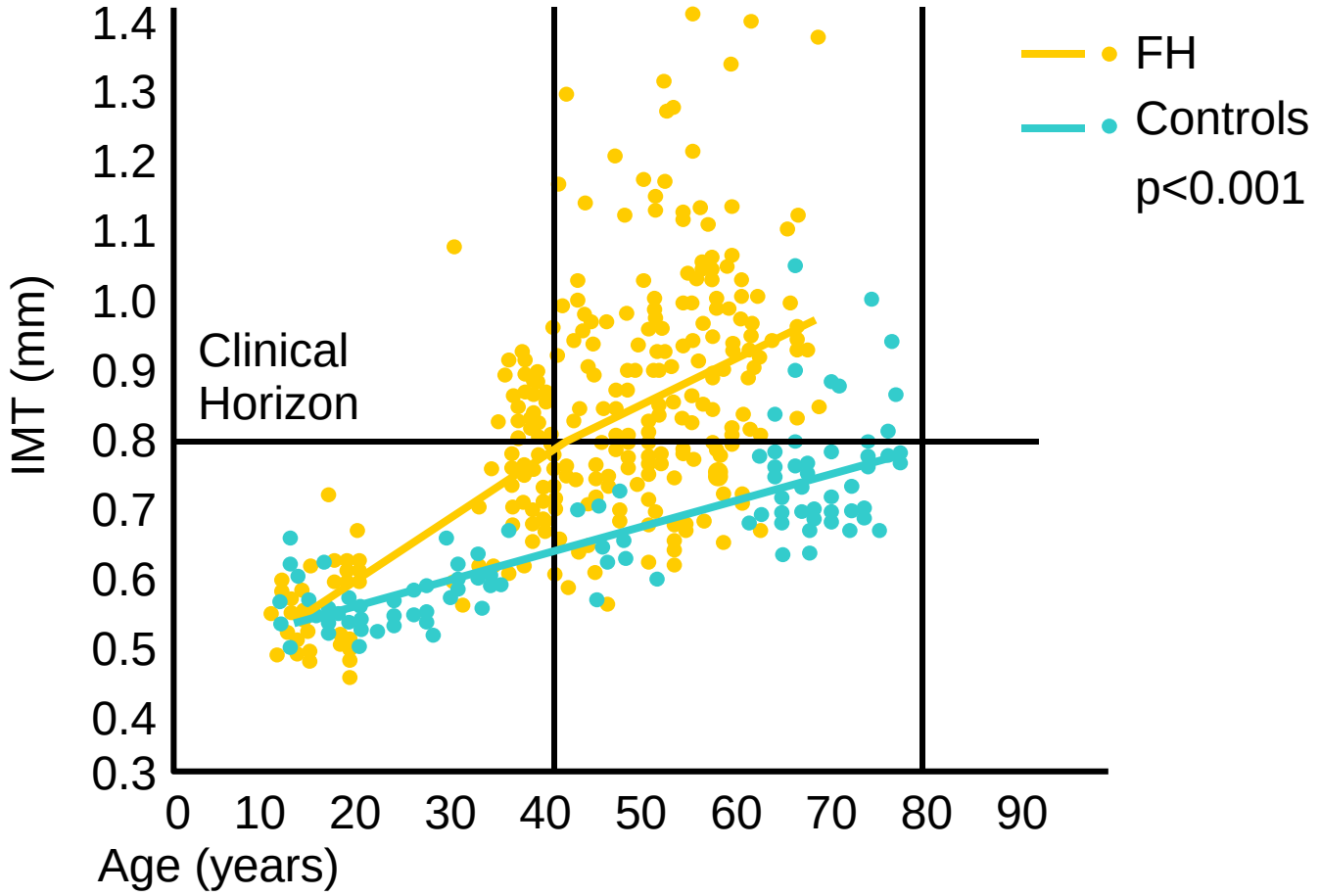


Circulation

Tabas, I. et al. Circulation 2007;116:1832-1844

Carotid atherosclerosis in HeFH

Carotid wall thickness (IMT) versus age in FH patients



Kastelein J. data presented at EAS 2002

Lipid Management – Key Principles

1 Baseline tests required before initiating treatment

Fasting lipids (including HDL), TFT, LFT, CK, Glucose

2 Low fat diet and exercise regime

Will reduce drug doses required. Monitoring weight is essential

3 Choice of drug therapy should be evidence based

Statins are of proven benefit - except when triglycerides >4.5

4 Dose titration to achieve appropriate targets

Treatment responses vary greatly

5 Monitoring of response and follow-up consultation essential

Adequacy of follow up is the most important factor in success

Current Lipid Lowering Drug Classes

1. **‘Statins’ – HMG Reductase inhibitors**
   Mode of Action: inhibit cholesterol synthesis, ↑ LDL Receptor

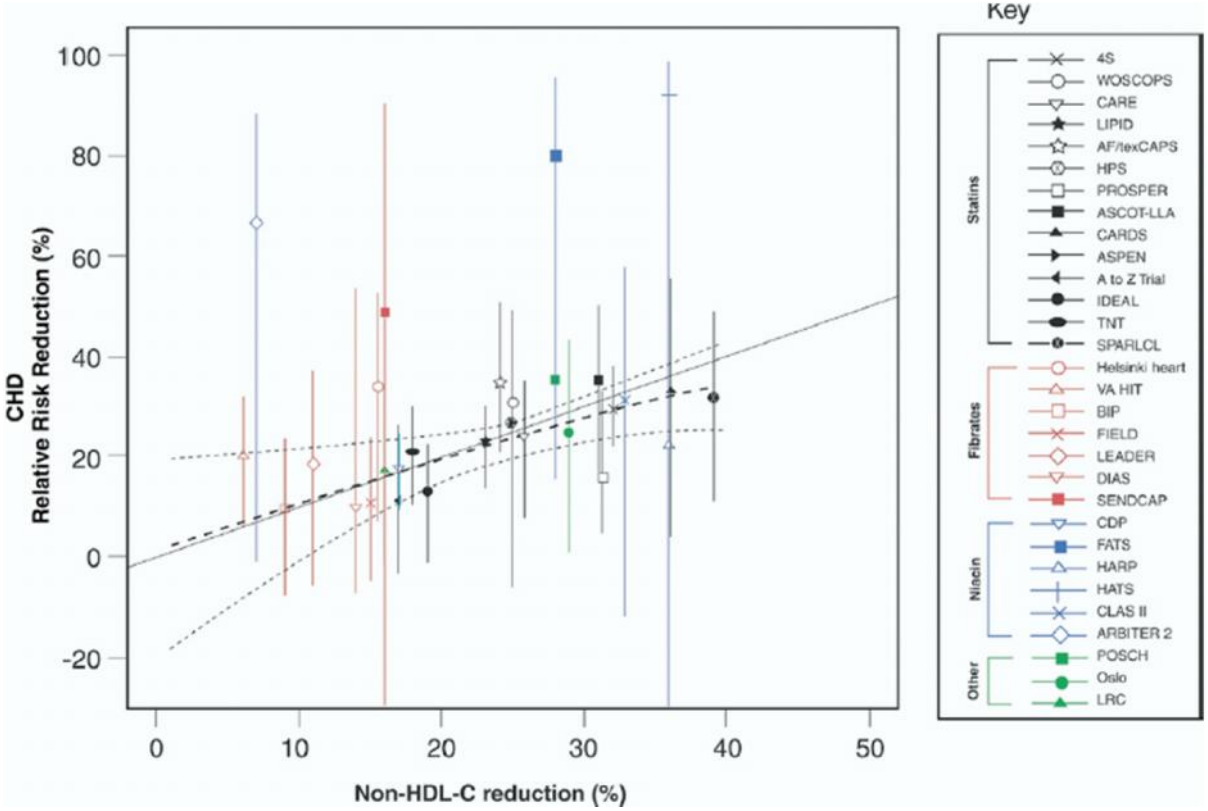
2. **Bile Acid Binding Resins- colestyramine, colesevelam**
   Mode of Action: divert cholesterol into bile acid synthesis ↑ LDL Receptor

3. **Cholesterol Absorption Inhibitors- ezetimibe**
   Mode of Action: reduce enterohepatic cholesterol cycling, ↑ LDL Receptor

4. **Fibrates- fenofibrate, bezafibrate**
   Mode of Action: induce lipoprotein lipase and other genes

5. **Nicotinic Acid (and niacin- laropiprant)**
   Mode of Action: inhibits lipolysis and fatty acid flux

Non–High-Density Lipoprotein Cholesterol Reduction and Coronary Heart Disease Risk – a Meta-Analysis



Each 1% decrease in non–HDL-C resulted in an estimated 4.5-year CHD RR of 0.99
On treatment non–HDL-C was twice as accurate as LDL-C in predicting outcomes

Robinson JG et al., J Am Coll Cardiol (2009) 53: 316

Regression of Coronary Atherosclerosis During Treatment of Familial Hypercholesterolemia With Combined Drug Regimens

John P. Kane, MD, PhD; Mary J. Malloy, MD; Thomas A. Ports, MD; Nancy R. Phillips, PhD; James C. Diehl; Richard J. Havel, MD

We conducted a randomized, controlled trial in 72 patients with heterozygous familial hypercholesterolemia to test whether reducing plasma low-density lipoprotein levels by diet and combined drug regimens can induce regression of coronary lesions. Four hundred fifty-seven lesions were measured before and after a 26-month interval by computer-based quantitative angiography. The primary outcome variable was within-patient mean change in percent area stenosis. Mean low-density lipoprotein cholesterol levels decreased from 7.32 ± 1.5 to 4.45 ± 1.6 mmol/L. The mean change in percent area stenosis among controls was +0.80, indicating progression, while the mean change for the treatment group was −1.53, indicating regression ($P = .039$ by two-tailed t test for the difference between groups). Regression among women, analyzed separately, was also significant. The change in percent area stenosis was correlated with low-density lipoprotein levels on trial. We conclude that reduction of low-density lipoprotein cholesterol levels can induce regression of atherosclerotic lesions of the coronary arteries in patients with familial hypercholesterolemia. The anticipation of benefit from treatment applies to women and men alike.

(*JAMA*. 1990;264:3007-3012)

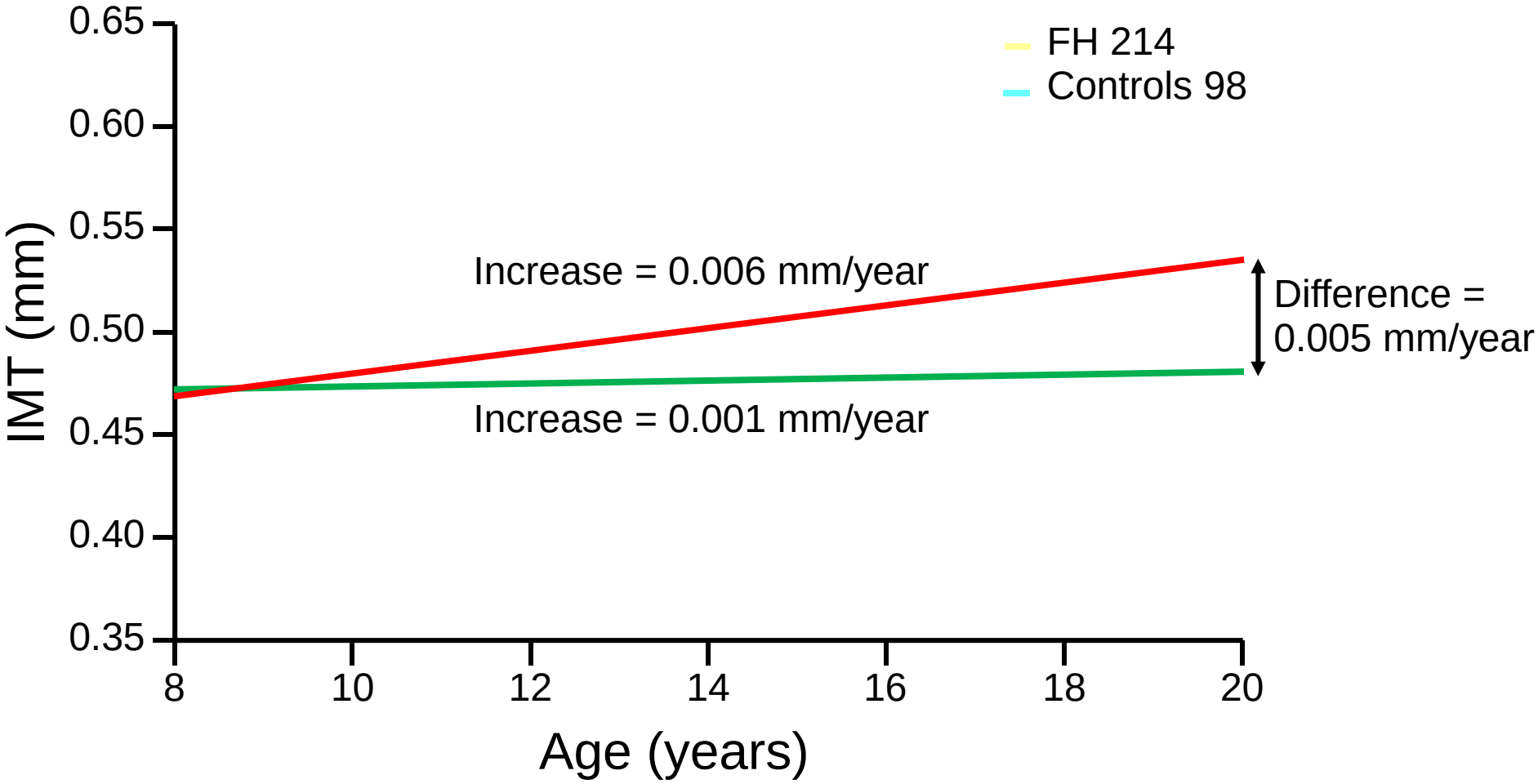
tion of LDL levels on atherosclerotic coronary lesions. We have adduced evidence for regression of coronary lesions in patients, most of whom were asymptomatic, who had coronary disease of moderate severity and few risk factors other than elevated LDL concentrations. This is the first report of regression of coronary atherosclerosis in women treated for hyperlipidemia.

PATIENTS AND METHODS

Study Design

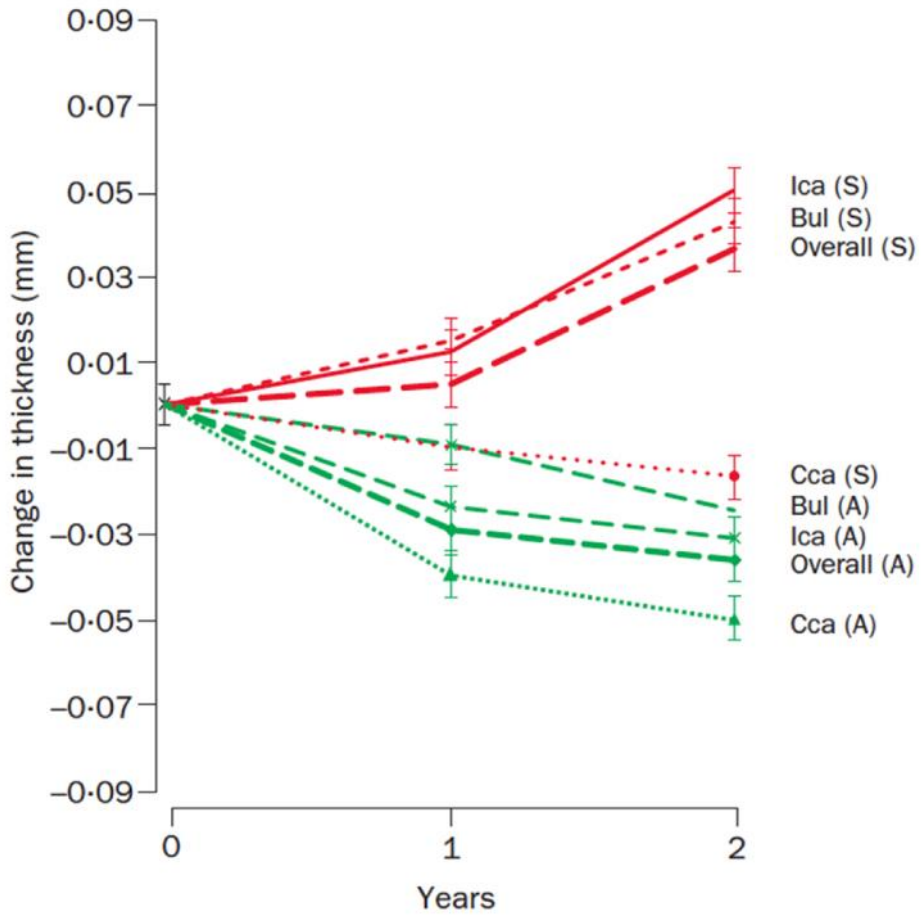
Our central hypothesis was that reduction of plasma levels of LDL inhibits progression of coronary atherosclerosis and may promote regression of existing lesions. Patients with heterozygous familial hypercholesterolemia with angiographically quantifiable lesions were

Progression of CIMT in FH



Kastelein J. data presented at EAS 2002

ASAP - aggressive versus conventional lipid lowering and atherosclerosis progression in FH



Aggressive LDL-cholesterol reduction by atorvastatin (green) was accompanied by regression of CIMT, conventional LDL lowering with simvastatin (red) was not.

Smilde TJ et al., Lancet (2001) 357: 577

BMJ

RESEARCH

Efficacy of statins in familial hypercholesterolaemia: a long term cohort study

Jorie Versmissen, researcher,[1] Daniëlla M Oosterveer, researcher,[1] Mojgan Yazdanpanah, epidemiologist,[1] Joep C Defesche, senior researcher,[2] Dick C G Basart, clinician,[3] Anho H Liem, clinician,[4] Jan Heeringa, statistician,[5] Jacqueline C Witteman, professor of epidemiology,[5] Peter J Lansberg, clinician,[2] John J P Kastelein, professor of vascular medicine,[2] Eric J G Sijbrands, associate professor[1]

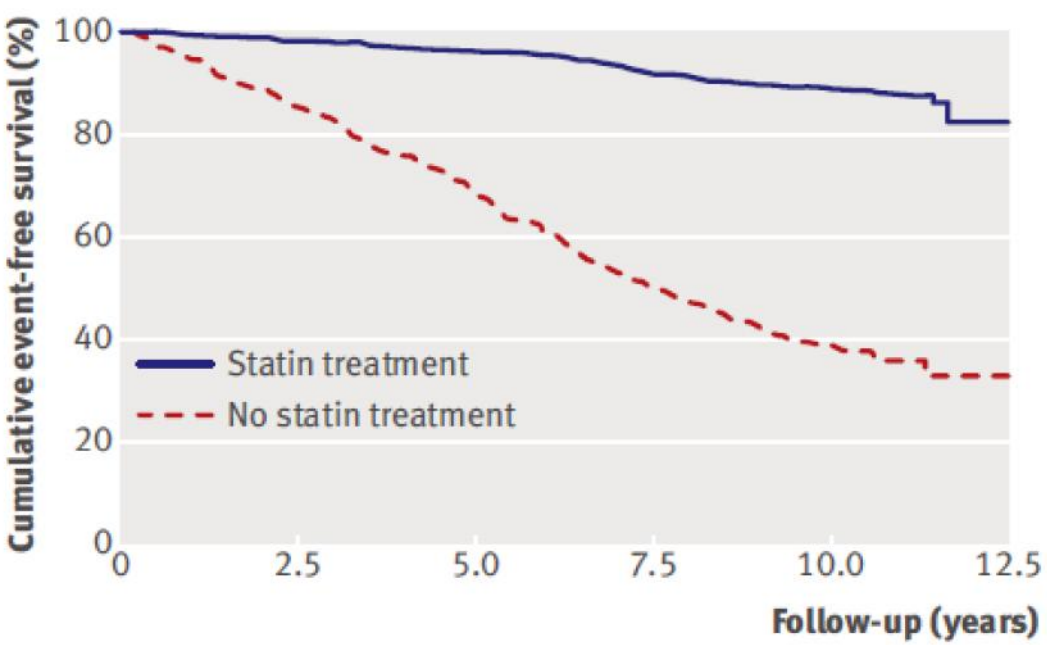


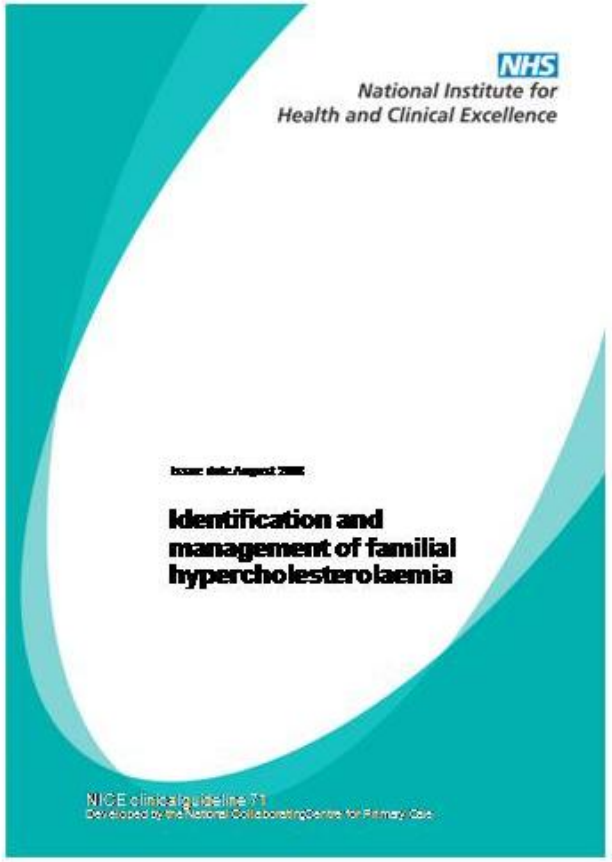
Fig 2 | Kaplan-Meier curve estimates of cumulative coronary heart disease-free survival among patients with familial hypercholesterolaemia according to statin treatment (P<0.001 for difference)

Vermissen J et al ; BMJ (2008) 337: 2423

“Rigorous detection and vigorous treatment of familial hypercholesterolaemia”

Durrington PN; Lancet (2001) 357: 574

NICE FH Guideline (CG71 August 2008)



Royal College General Practictioners Core Team
Kathy DeMott, Leo Nherera, Meeta Kathoria, Beth Shaw, Gill Richie, Vanessa Nunes, Nancy Turnball

Guideline Development Group (GDG)
GP Chair: Dr Rubin Minhas
Lead Advisor : Prof Steve Humphries
Lipidologists : Prof Andrew Neil, Dr Mary Seed, Dr Ian McDowell
Nurse Specialist/Genetic Counsellor : Ms Melanie Watson
Dietician : Ms Helen Stracey
Epidemiologist : Prof Margaret Thorogood
Paediatrician : Dr Philip Lee
GP : Dr Nadeem Qureshi
Patient Representatives : Dawn Davies, Phil Rowlands
Co-opted Experts : Tony Weirzbicki, Helen Williams, Aileen Parke, Richard Wray, Mahmoud Barbir, Anneke Lucassen

CG71 - Important points on management

Statins should be the initial treatment for all adults with FH. [1.3.1.1]

Adults - Prescription of a potent statin should usually be considered when trying to achieve a reduction of LDL-C concentrations of greater than 50% (from baseline). [1.3.1.2]

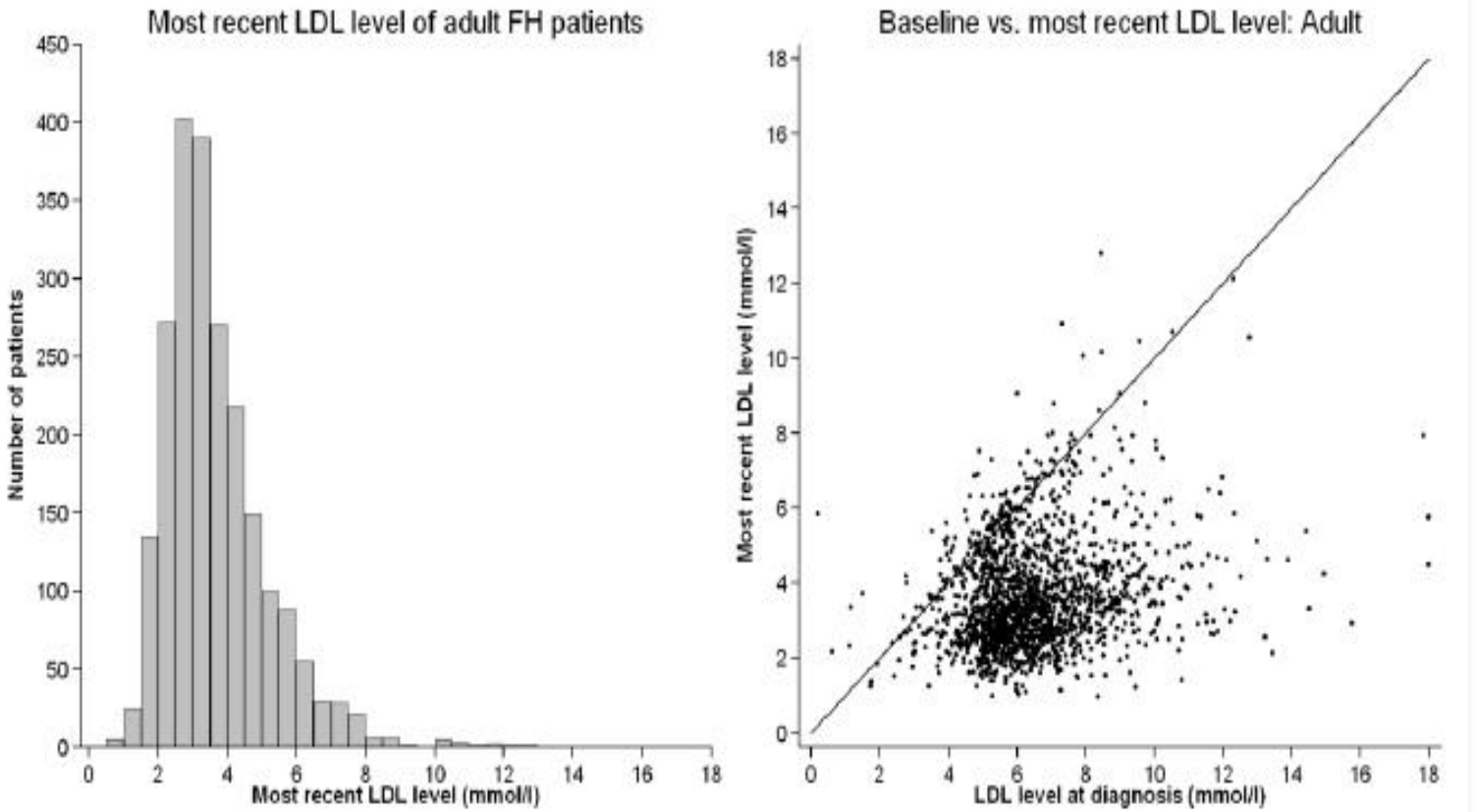
Individuals not achieving a reduction in LDL-C concentrations of greater than 50% from baseline should be referred to a specialist with expertise in FH. [1.3.1.10]

Individuals with intolerance or contraindications to statins or ezetimibe should be referred to a specialist with expertise in FH for consideration for treatment with either a bile acid sequestrant (resin), nicotinic acid, or a fibrate to reduce LDL-C concentrations. [1.3.1.12]

The 2010 RCP FH Audit

122 Lipid Clinics,
2324 adult and
147 child patients, and data were duplicated for 268 to assess data reliability

Achievement of LDL-C goals in RCP FH Audit

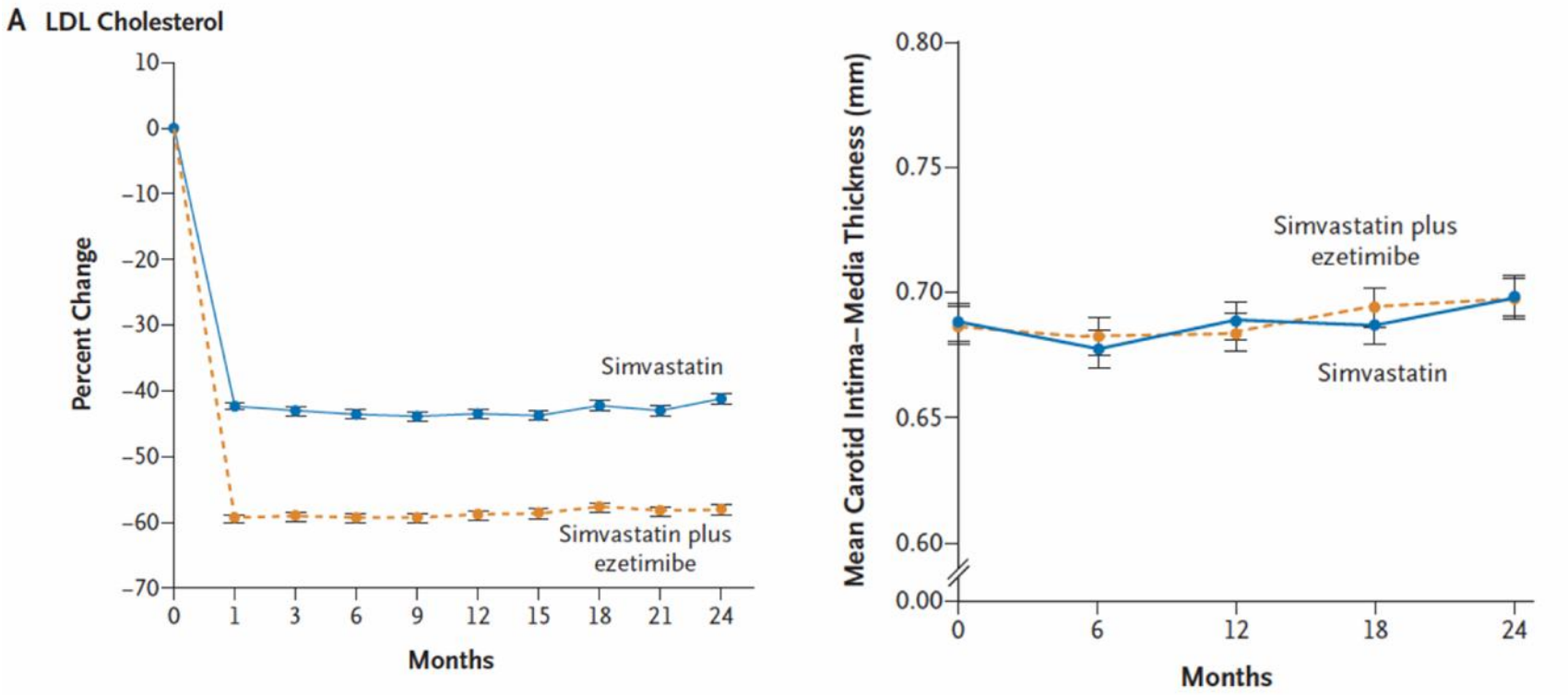


“Only 44% of the adult patients achieved the recommended target of 50% reduction in LDL-C from the untreated level.
Overall, treated LDL-C was reduced from a median of 6.1mmol/l to 3.5mmol/l (mean reduction 37%, median 33%, IQR 23% - 47%).“

Why Do Patients Fail to Reach Treatment Targets?

1. **Poor concordance with drug therapy**
2. **Intolerance of Drug therapy**
3. **Poor adherence to diet resulting in weight gain**
4. **Inadequacy of follow-up and monitoring**
5. **Development of a secondary hyperlipidaemia**
6. **Poor Response to Drug Therapy**

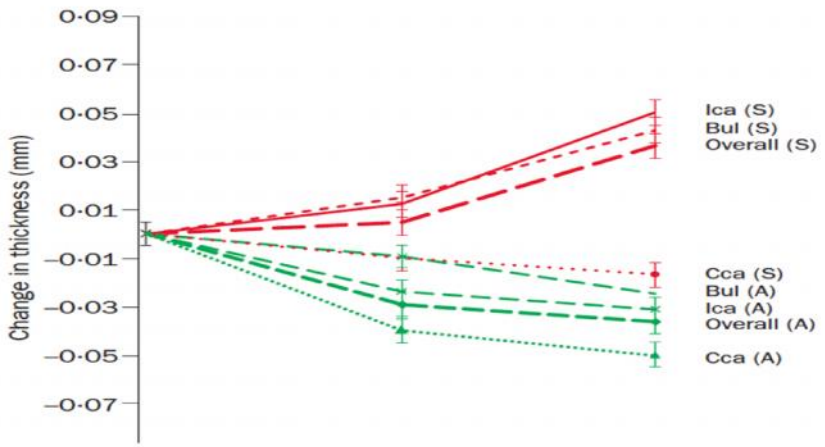
Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) (or does it?) trial



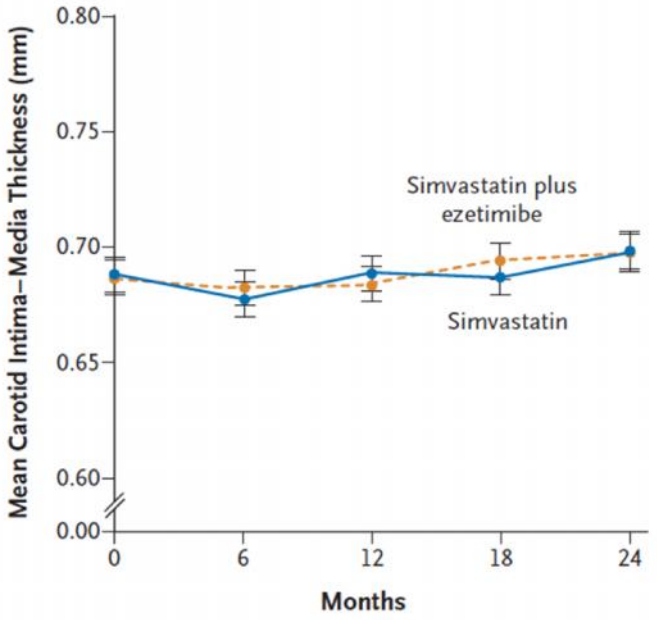
Despite greater reduction of LDL-cholesterol (4.60 vs 3.34 mmol/L) with simvastatin plus ezetimibe, after 24 months there was no difference in cIMT in the two groups

Kastelein JJP et al ; N Engl J Med (2008) 358:1431

ASAP –
baseline cIMT 0.093



ENHANCE –
baseline cIMT 0.069



IMPROVE-IT: Examining Outcomes in Subjects With Acute Coronary Syndromes (simvastatin vs simvastatin plus ezetimibe) is expected to be completed in late 2014

The last resort? LDL- apheresis

NICE FH Guideline CG 71 - Indications for LDL Apheresis

1.3.3.1 Adults and children with clinical homozygous FH should be considered for apheresis. The timing of initiation of apheresis will depend on other factors, such as response to lipid modifying medication and presence of coronary heart disease.

1.3.3.2 In exceptional cases, individuals with heterozygous FH with progressive, symptomatic CHD, despite maximal tolerated lipid modifying medication and optimal medical therapy, should be considered for apheresis. This should be undertaken in a specialist centre on a case by case basis and data collected into an appropriate registry.

New Lipid Lowering Drug Classes

1. **Antisense oligonucleotide inhibition of ApoB synthesis - mipomersen**
   Mode of Action: reduce apolipoprotein B translation, ↓ ApoB lipoproteins

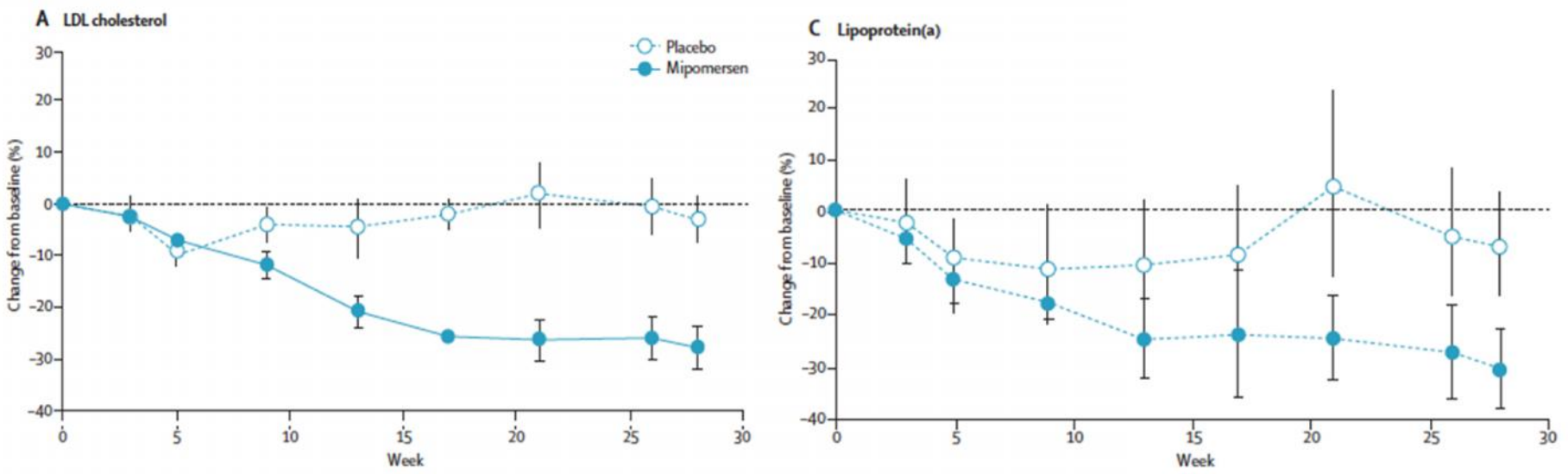
2. **MTP inhibitors - lomitapide**
   Mode of Action: reduce lipidation of apolipoprotein B ↓ ApoB lipoproteins

3. **Cholesterol Ester Transfer Protein (CETP) inhibitors - anacetrapib**
   Mode of Action: inhibit cholesterol ester exchange, ↑ HDL cholesterol

4. **PCSK9 inhibitors**
   Mode of Action: increase LDL receptor recycling ↑ LDL Receptor activity

5. **Thyroid Hormone receptor beta agonists – epitirome- DEVELOPMENT STOPPED**
   Mode of Action: hepatic specific thyromimetic effect ↓ ApoB lipoproteins

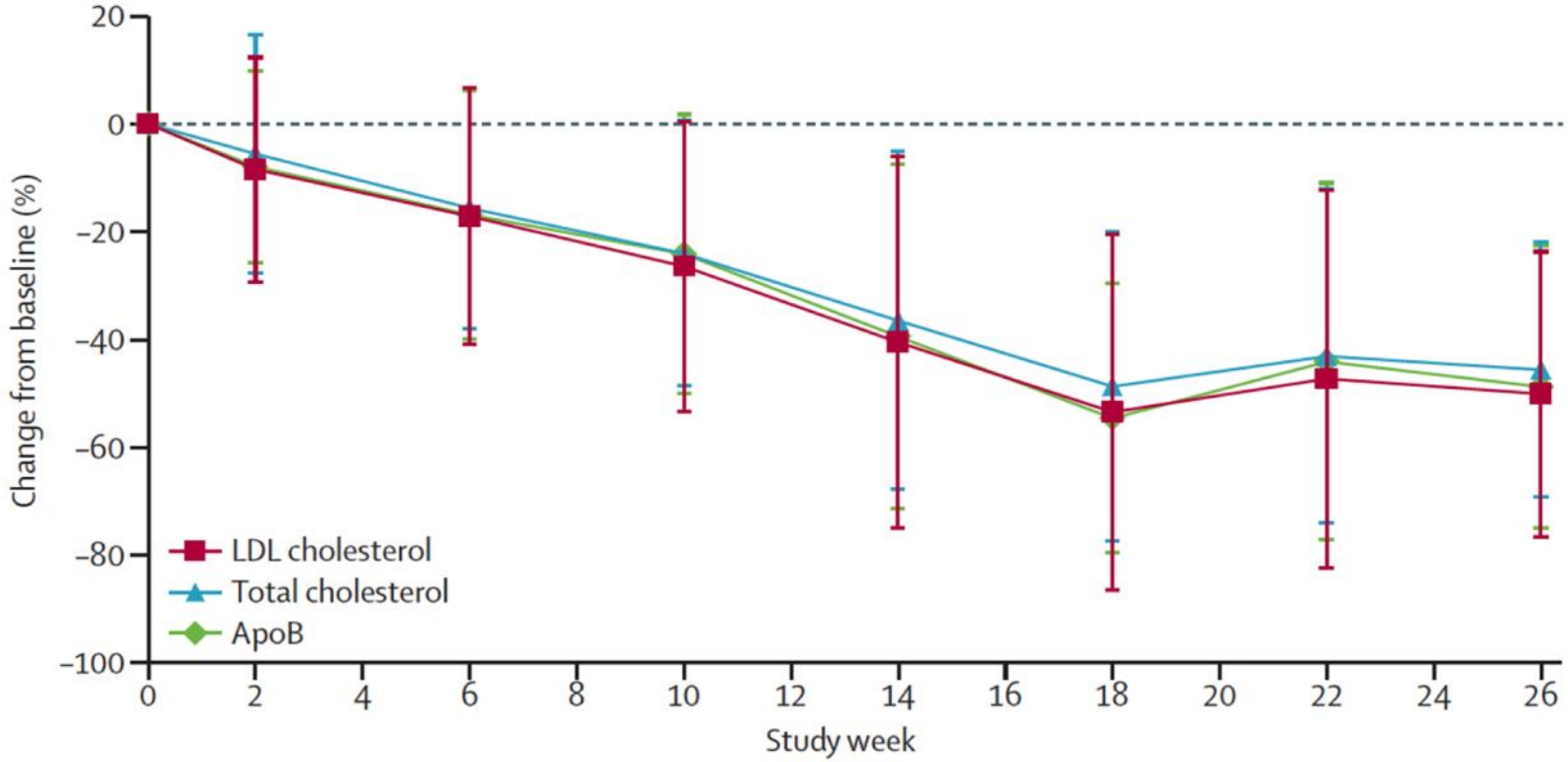
Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial



Mipomersen reduced LDL-cholesterol by 25% at week 26 and also Lp(a) by 23%, the main adverse effects being injection site reactions and transaminase increases

Raal FJ et al ; Lancet (2010) 375:998

Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study



Lomitapide reduced LDL-cholesterol by 50% at week 26 (comparable to apheresis), but at the expense of an increase mean hepatic fat which rose from from 1.0% to 8.6% at week 26, but did not increase further for the remainder of the 78 week study

Cuchel M et al., Lancet (2012) Published Online Nov 2

FDA Panel Recommends Approval Of Mipomersen For Familial Hypercholesterolemia

The FDA's Endocrinologic and Metabolic Drugs Advisory Committee gave a weak endorsement to mipomersen, an antisense oligonucleotide inhibitor manufactured by Genzyme, for use in homozygous familial hypercholesterolemia (FH). With its relatively close 9-6 vote, and with its comments, the committee expressed concerns about both the efficacy and safety of the drug, but ultimately the severity of homozygous FH led the panel to recommend approval.

"We need a toolkit, we need as many options as possible for these patients," said one panel member.

genzyme
A SANOFI COMPANY

On Wednesday the same committee voted 13-2 in favor of a similar indication for lomitapide capsules, manufactured by Aegerion. On both days, panel members strongly urged the FDA to restrict use of lomitapide and mipomersen to patients with homozygous FH and "avoid the slippery slope" of using the drugs in heterozygous FH or in patients with resistant hypercholesterolemia.

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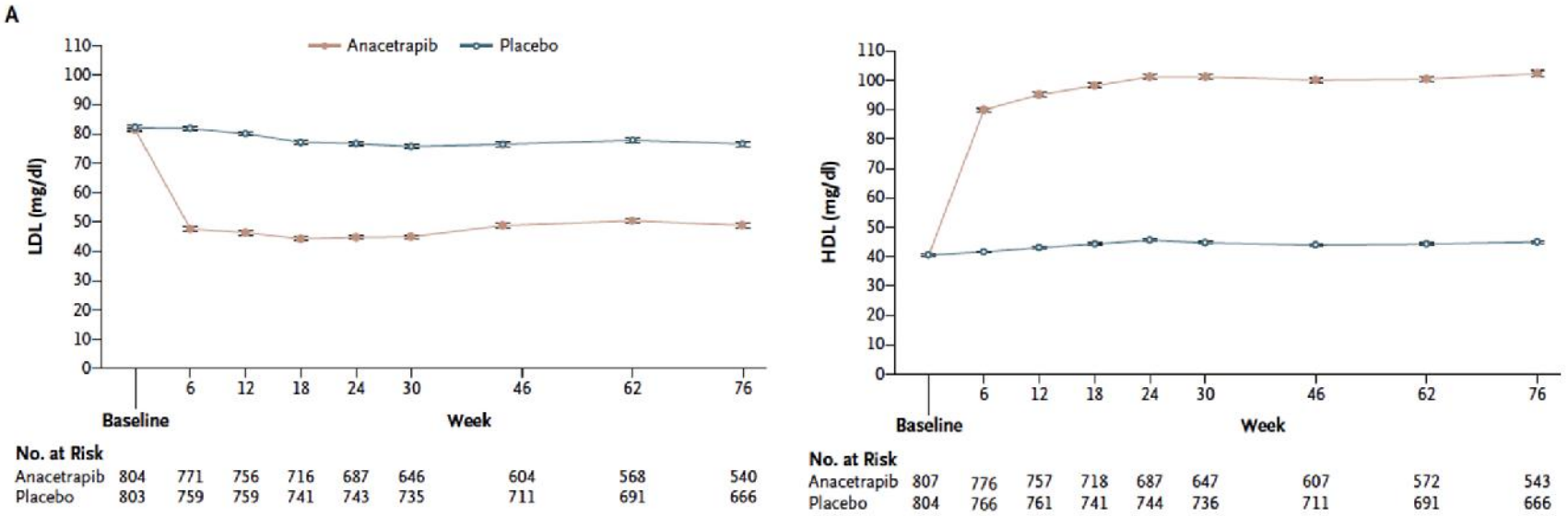
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety of Anacetrapib in Patients with or at High Risk for Coronary Heart Disease

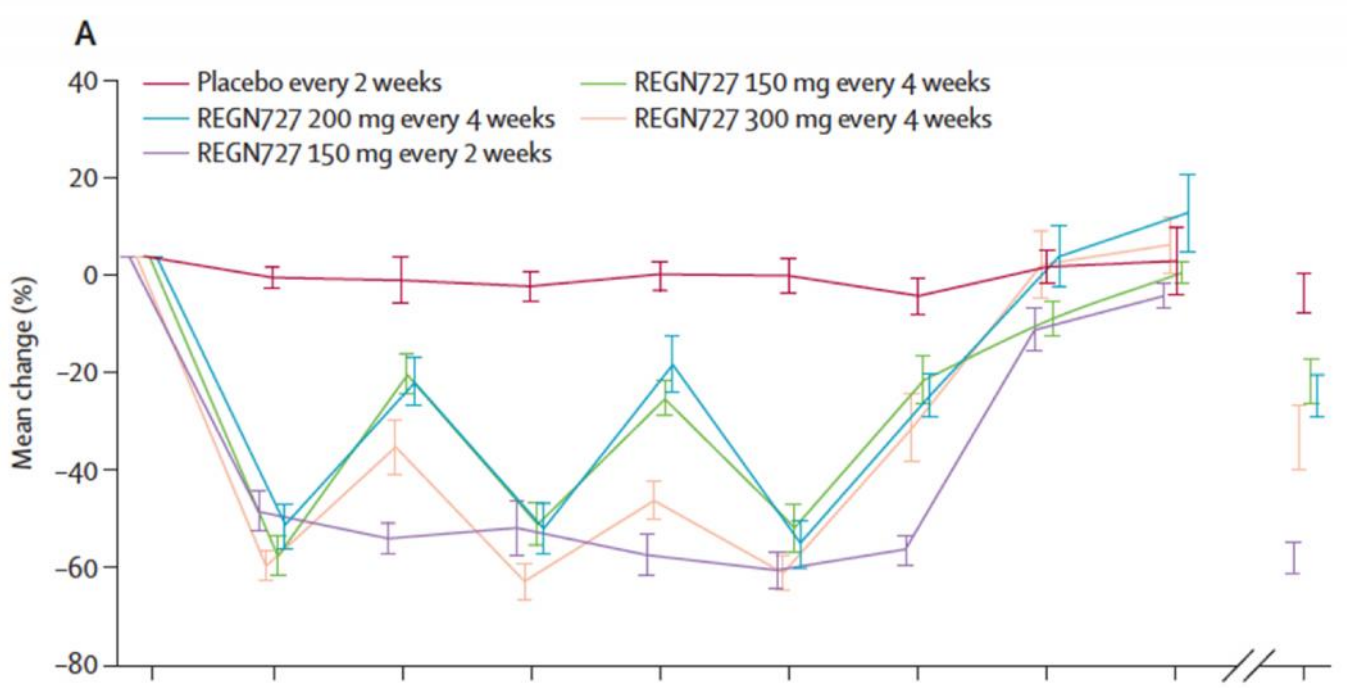


In addition to robust effects on LDL and HDL cholesterol anacetrapib lowered Lipoprotein(a) by 17% and unlike torcetrapib had no adverse effects on blood pressure.

Phase 3 trials with anacetrapib now ongoing in CHD (REVEAL) and FH (REALISE)

Cannon CP et al ; N Engl J Med (2010) 363: 2406

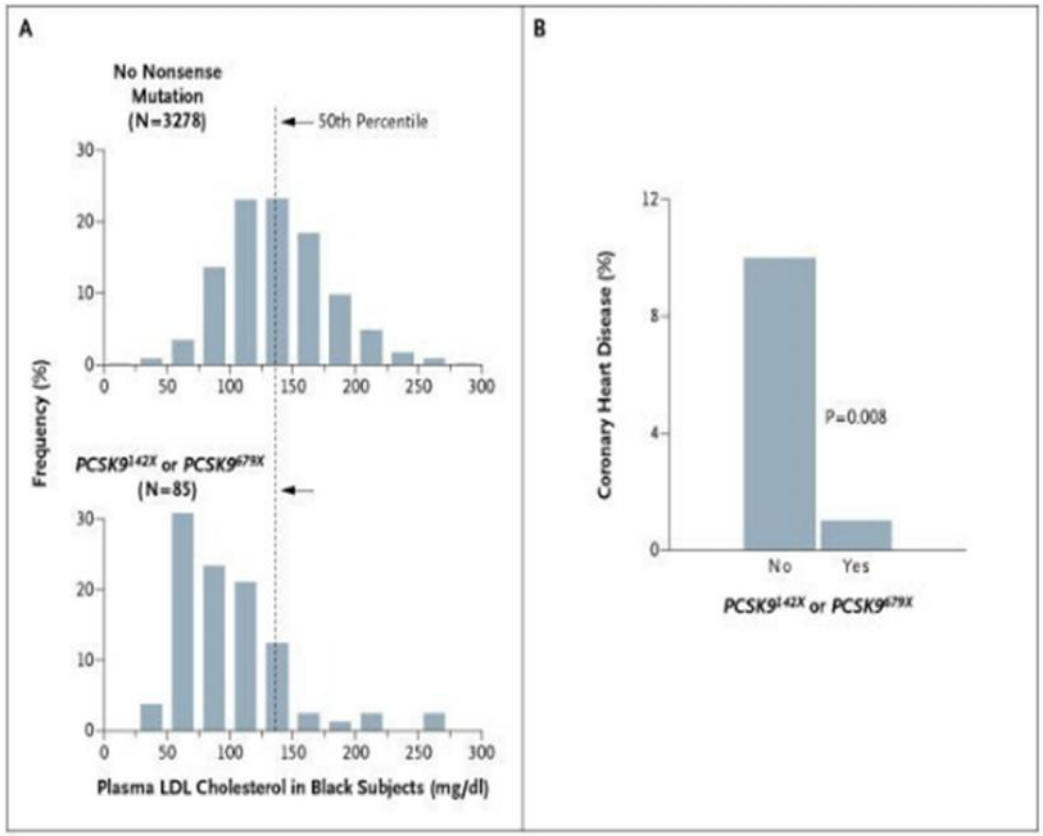
Effect of a monoclonal antibody to PCSK9, REGN727/ SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial



Over 12 weeks treatment in addition to statin with or without ezetimibe anti-PCSK9 MAb 150mg every 2 weeks reduced LDL by 68%, 81% of patients having achieved LDL-C <1·8 mmol/L at week 12 (%). Lipoprotein(a) was also reduced by 23%

Stein EA et al., Lancet (2012) 380: 29

Mendelian Randomisation shows that Lifelong lowering of LDL cholesterol 1 mmol/L is associated with reduction in CHD events of greater than 80%



Distribution of Plasma LDL Cholesterol Levels (Panel A) and Incidence of Coronary Heart Disease (Panel B) among Black Subjects, According to the Presence or Absence of a *PCSK9142X* or *PCSK9679X* Allele.

Cohen JC et al ; N Engl J Med (2006) 354: 1264

Summary

Familial hyperlipidaemias contribute significantly to premature CVD

The evidence supports treatment to targets, fire but don’t forget!

Current therapies are largely ineffective in reducing lipoprotein(a)

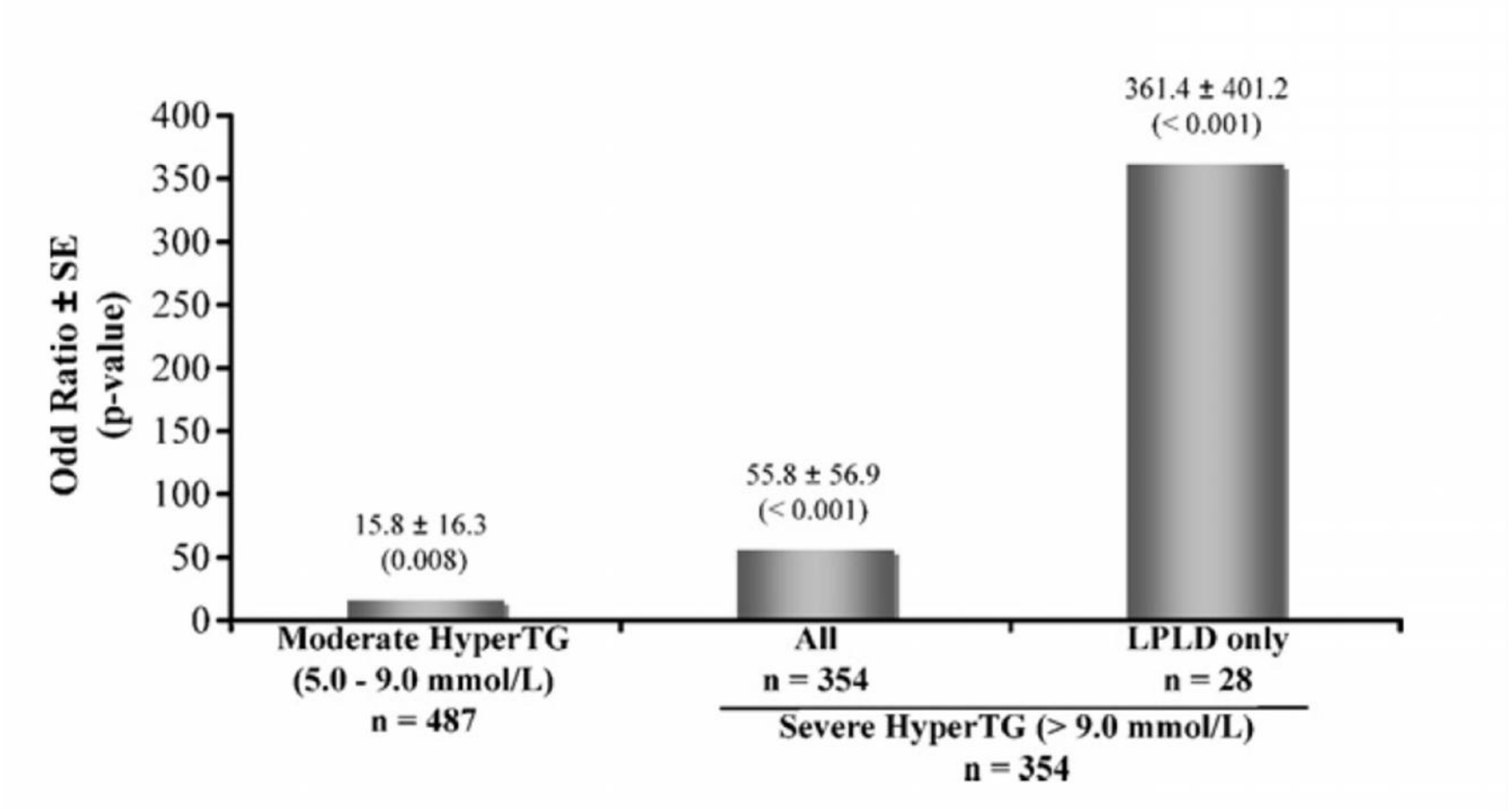
Non-HDL-Cholesterol should replace LDL-C for monitoring treatment

Mipomersen and lomitapide may improve the prognosis of HoFH

Novel therapies directed against PCSK9 look promising in HeFH

Earlier intervention may be the key to improving CVD outcomes

Risk of Acute Pancreatitis in Severe Hypertriglyceridaemia due to Lipoprotein Lipase Deficiency (LPLD)



Gaudet D et al ; Atherosclerosis Supplements 11 (2010) 55

Alipogene tuparvovec gene therapy – a novel treatment for LPLD

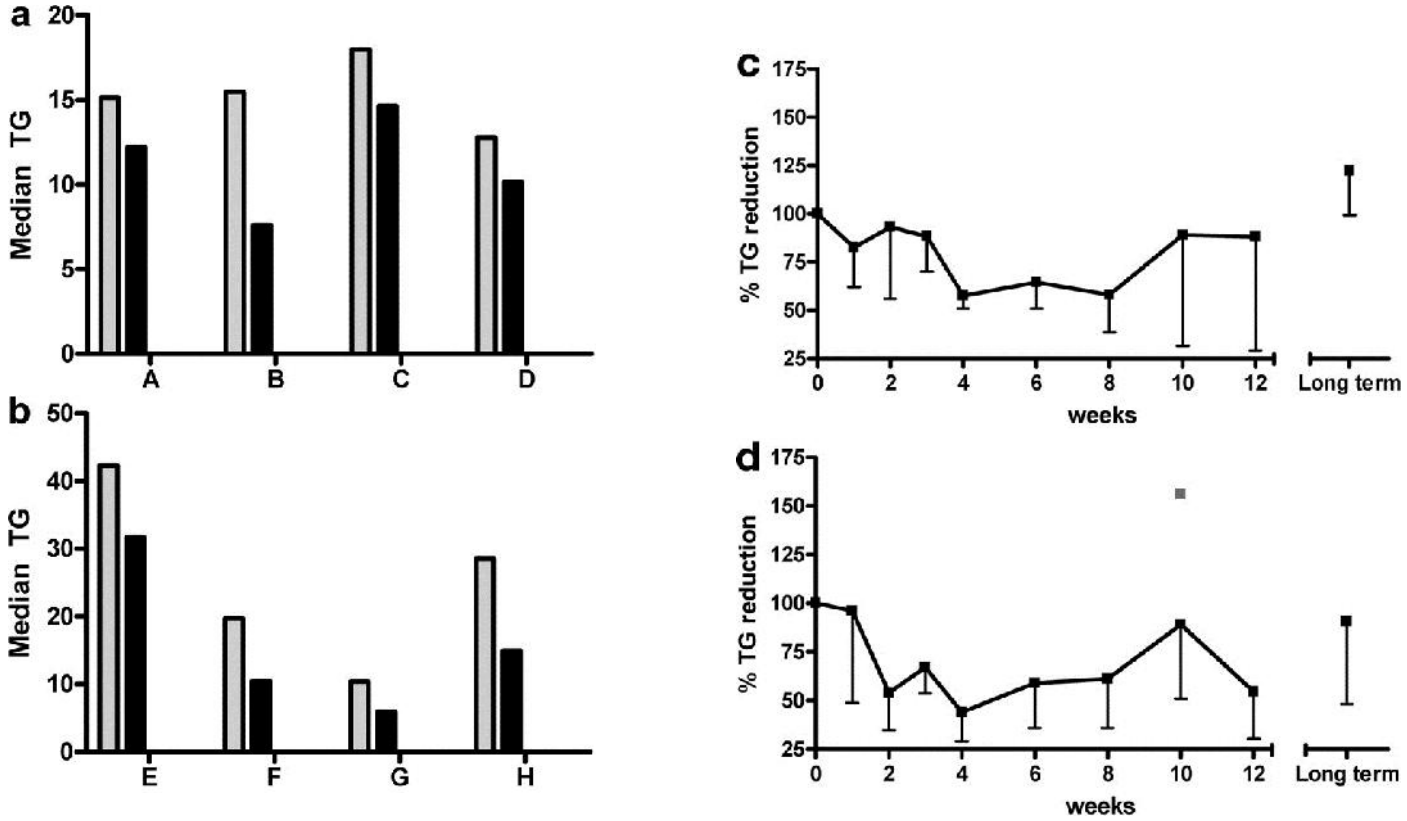


Figure a+b: Plasma TG levels after intramuscular administration of AAV1-LPLS447X.a. 1 × 1011 gc/kg; b. 3 × 1011 gc/kg; Gray bars: median fasting TG at baseline; Black bars: median fasting TG after vector administration.c+d: Mean % fasting TG reduction compa...

Stroes E S et al. Arterioscler Thromb Vasc Biol 2008;28:2303-2304

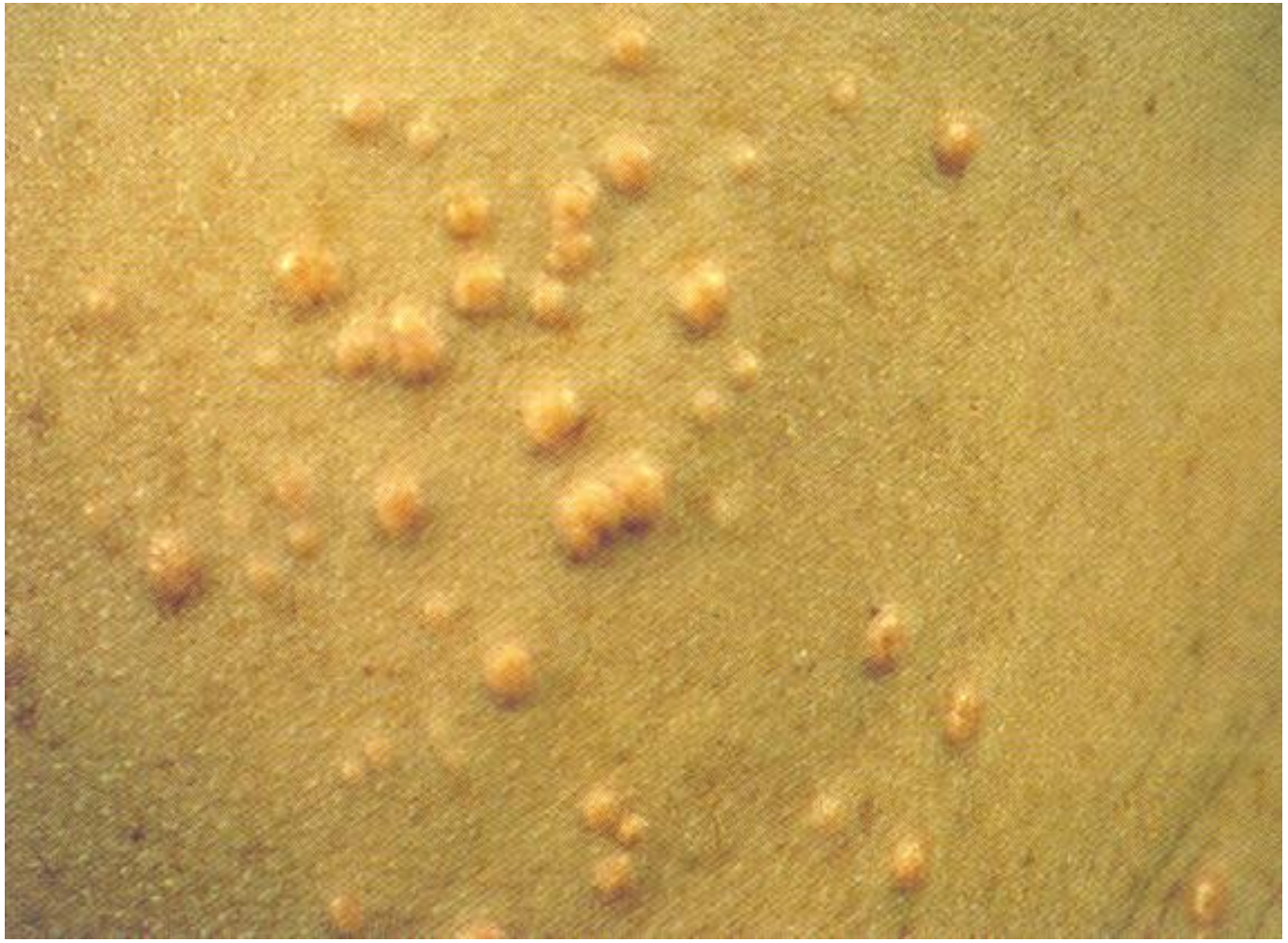
American Heart Association
Learn and Live

Familial Hypertriglyceridaemia

Mechanism:	not established for milder forms, homozygous lipoprotein lipase or apoCII deficiency in more severe forms
Prevalence:	Mild forms 1 in 300, severe forms rarer
Lipid Profile:	Elevated triglyceride, TG 2.3 – 6.0 in mild, in severe TG >11mmol/L, can be >100 Normal apolipoprotein B (<1.2g/L) Small, dense LDL (“pattern B” on gradient gel) Low HDL-cholesterol frequent (NB alcohol)
Inheritance:	Mild overlaps with FCH, severe autosomal recessive
Physical Signs:	Eruptive xanthomas, lipaemia retinalis in severe
CHD risk:	variable, severe forms prone to pancreatitis, metabolic syndrome, diabetes mellitus

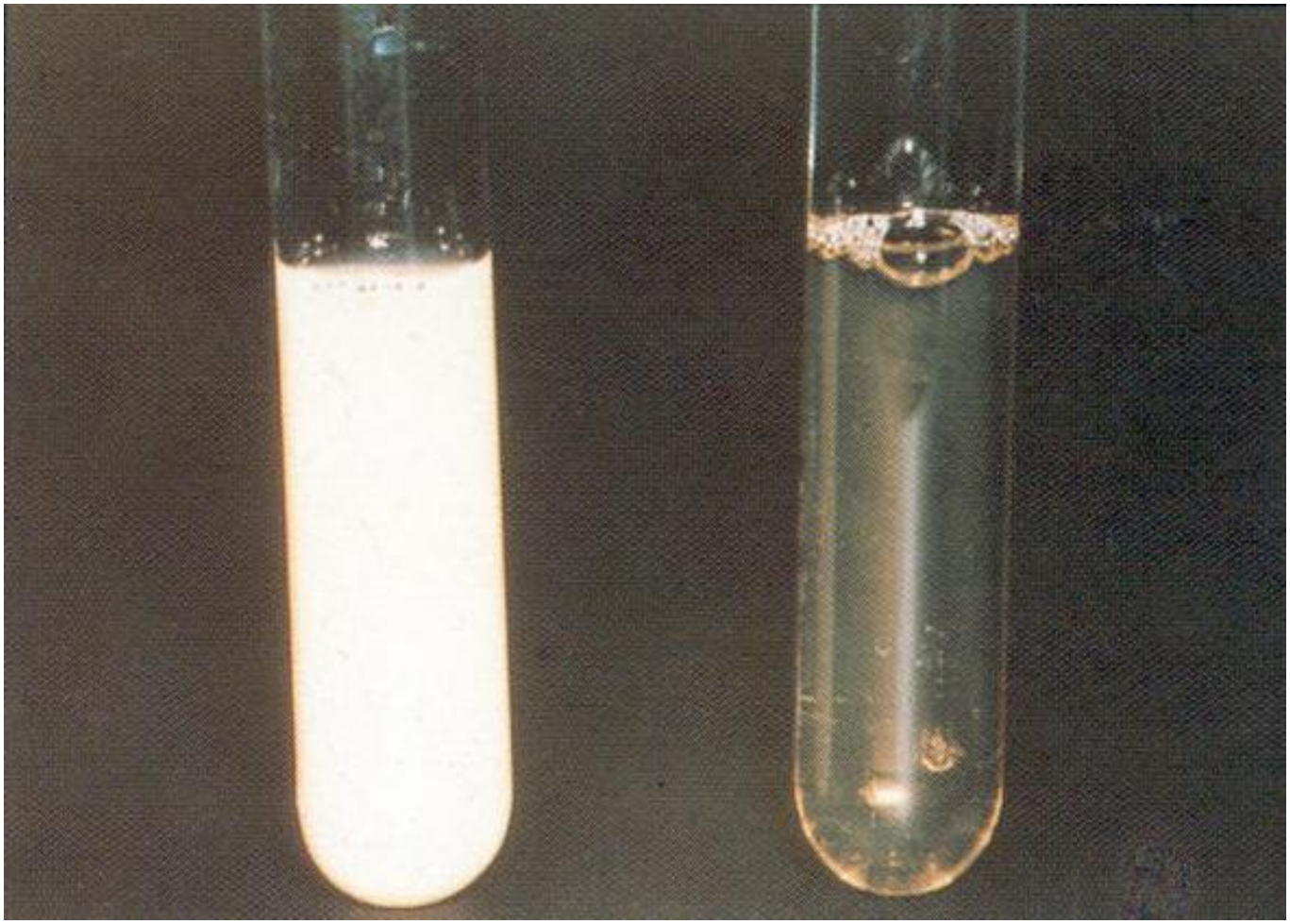
*Determined by ultracentrifuge

Eruptive Xanthomata in Chylomicronaemia



Typically found over buttocks, calves

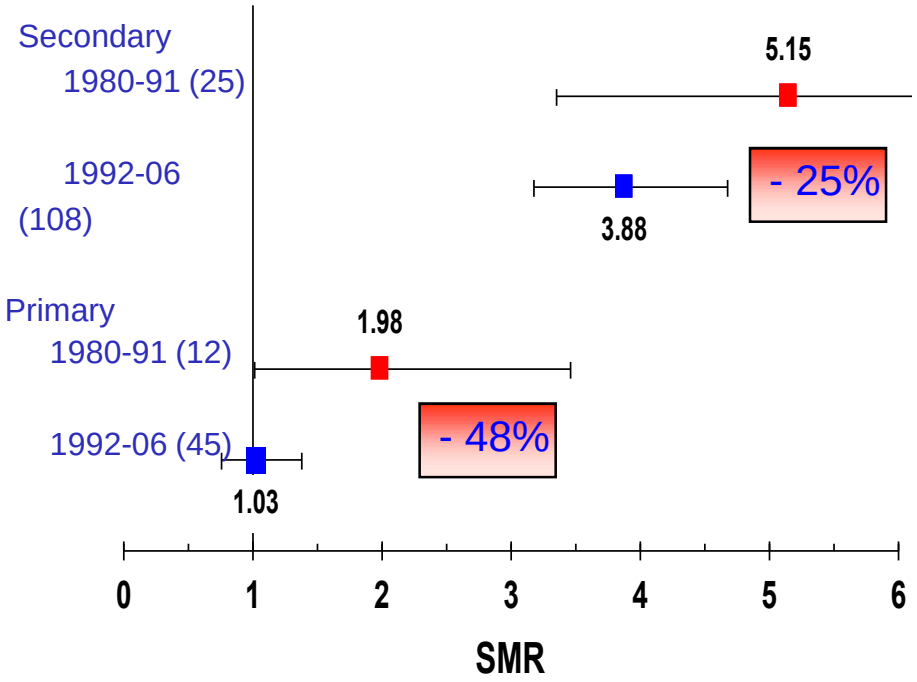
Appearance of Serum in Chylomicronaemia



Serum is milky, whole blood looks like strawberry milkshake

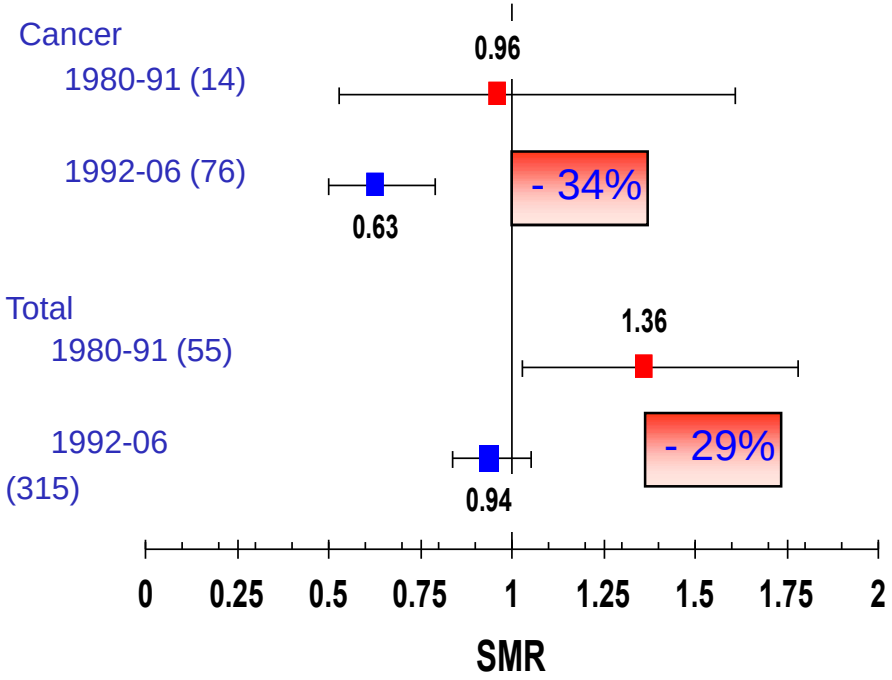
Current Life Expectancy in treated FH patients

CHD Mortality in those with/without CHD



Finding FH *BEFORE* CHD → Life expectancy not lower

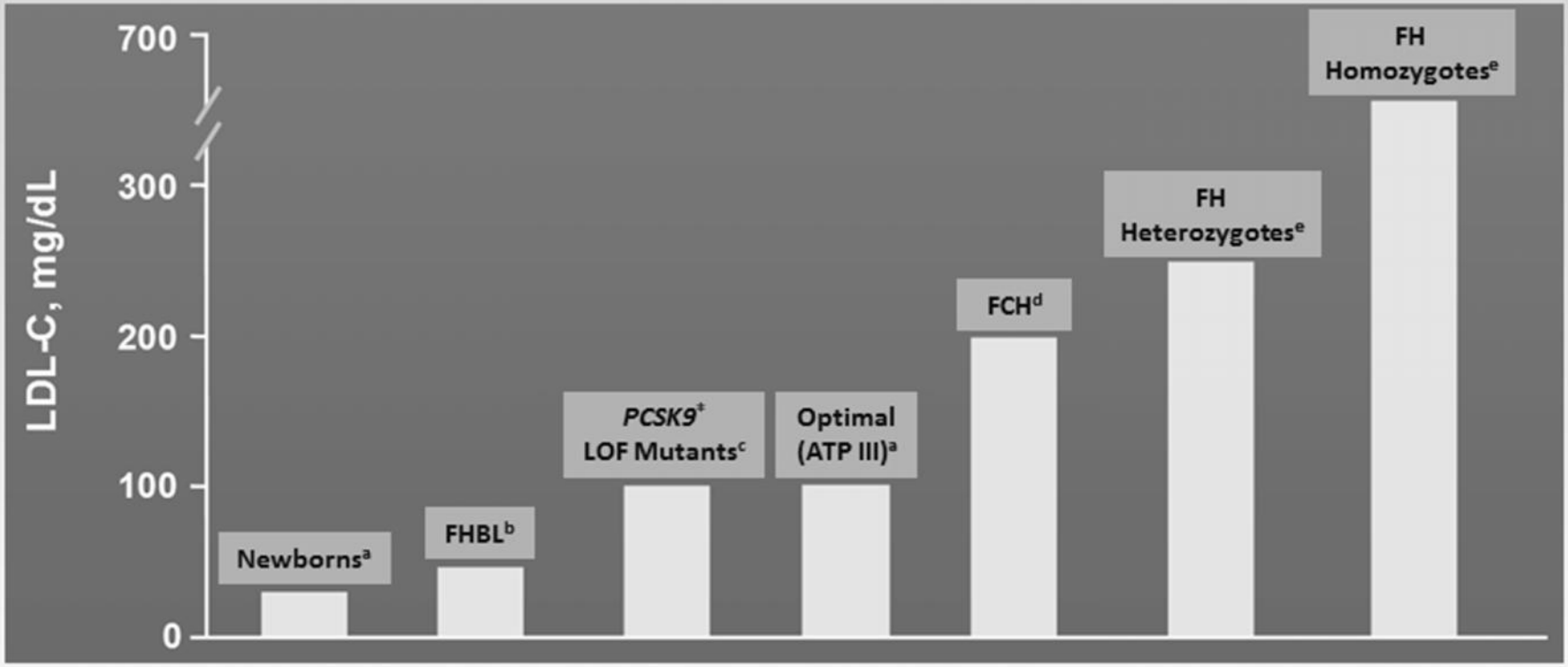
Cancer and Total Mortality



Because of low smoking rate, good diet, annual checks

Based on 2766 (1456 M/1310 F) DFH + PFH patients. 190 CHD and 90 cancer deaths (37727 person years follow-up)

LDL-C Levels Vary With Genetic Variants in Cholesterol Metabolism



*Loss-of-function *PCSK9*^{142X} or *PCSK9*^{679X} mutants

a. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Circulation*. 2002;106:3143-3421; b. Glueck CJ, et al. *J Lab Clin Med*. 1976;88:941-957; c. Cohen JC, et al. *N Engl J Med*. 2006;354:1264-1272; d. Pauciullo P, et al. *Atherosclerosis*. 2009;203:320-324; e. Brown MS, et al. *Science*. 1986;232:34-47.