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PCCS Lipid QI Programme

Familial Hypercholesterolemia & Genetic lipid disorders

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Declaration of conflict of interests

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Declarations

Honoraria and/or expenses received from the following pharmaceutical companies for attending conferences and advisory boards, and delivering educational lectures: Amarin, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Edwards Scientific, Eli Lilly, Genomics PLC, Medtronic, Novartis, Pfizer, Roche, Roche Diagnostics, Sanofi, Servier, Vifor.

The ‘ABC’ of cardiovascular disease

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The ‘ABC’ approach is outlined in the NHS Long Term Plan as one of the key vehicles for the prevention of cardiovascular disease:[1]

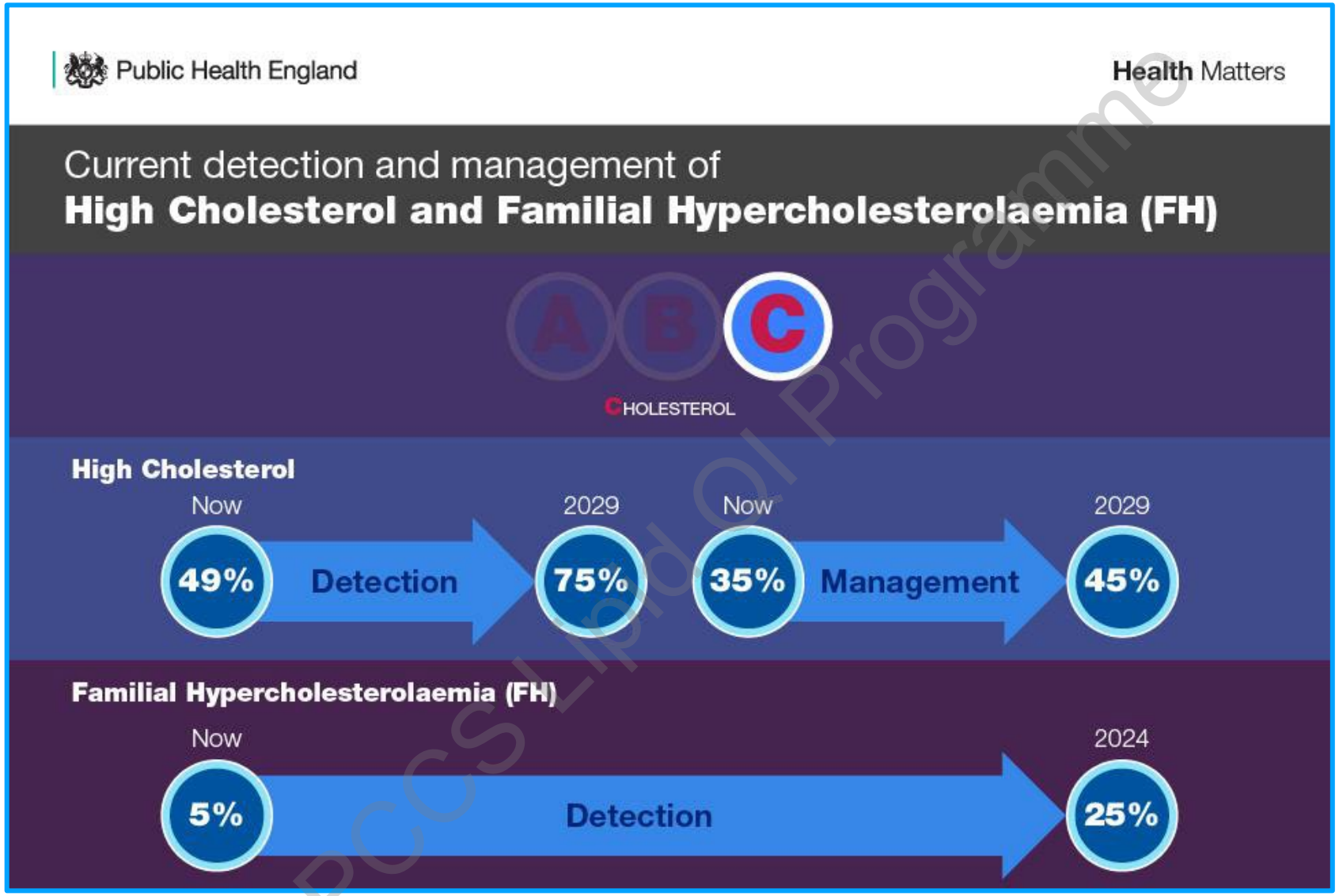
- **A** **A**trial fibrillation
- **B** High **B**lood pressure
- **C** Raised **C**holesterol

Improving detection of at-risk people and optimising medical management

Reduce cardiovascular morbidity and mortality and help address the national cardiovascular disease burden[1]

NHS, National Health Service.

1. NHS. The NHS Long Term Plan. January 2019. Available at: https://www.longtermplan.nhs.uk/wp-content/uploads/2019/08/nhs-long-term-plan-version-1.2.pdf. Accessed November 2023.



GOV.UK. Blog UK Heath Security Agency: The 10-year CVD ambitions for England – one year on. February 2020. Available at: https://ukhsa.blog.gov.uk/2020/02/06/the-10-year-cvd-ambitions-for-england-one-year-on/. Accessed November 2023.

Familial hypercholesterolaemia[1,2]

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- FH is an autosomal dominant genetic condition that leads to doubling of LDL-C levels from soon after birth
  - Average LDL-C is 5.7 mmol/L in HeFH and > 13 mmol/L in HoFH
- Lifetime burden of high LDL-C leads to dramatically increased risk of premature cardiovascular disease
  - >20-fold increased risk of premature myocardial infarction (MI before 60 years)
- FH is among the most common inherited conditions:
  - Prevalence of HeFH is 1:200–1:300
  - HoFH is rare at 1:250,000 but has terrible consequences (MI in childhood)
  - FH affects all race/ethnic groups

FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

1. Bouhairie VE, et al. Cardiol Clin 2015; 33(2):169–179; 2. NICE. Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (TA385). February 2016. Available at: www.nice.org.uk/guidance/ta385. Accessed November 2023.

FH – natural history

Age (years)	♂ % CHD	♀ % CHD
<30	5	0
30-39	22	2
40-49	48	7
50-59	80	51
60-69	100	75

CHD, coronary heart disease; FH, familial hypercholesterolaemia.

FH - diagnosis

- Lipid levels
- Family history
- Physical findings
- Genetic testing

FH, familial hypercholesterolaemia.

Diagnosis and management of familial hypercholesterolaemia[1,2]

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- Systematically search records for people
  - <30 years old with a total cholesterol >7.5 mmol/L, *and*
  - ≥30 years old with a total cholesterol >9.0 mmol/L

Simon Broome criteria*	
Possible	Definite
TC >7.5 mmol/L *or* LDL >4.9 mmol/L, *and* • Family history of MI†, *or* • Family history of raised cholesterol	TC >7.5 mmol/L *or* LDL >4.9 mmol/L, *and* • Personal/family history of tendon xanthomata • DNA-based evidence of an LDL receptor mutation, familial defective apo B-100, or a PCSK9 mutation

- People with a clinical diagnosis of familial hypercholesterolaemia (FH) are referred for specialist assessment to include DNA testing
- Once an accurate diagnosis has been made, people with FH can receive appropriate treatment, and cascade testing can be started to affected family members

Offer high-intensity statin and aim for >50% reduction in LDL-C

*In adults; values are different for children aged <16 years. †Before 60 years in 1° relative and before 50 years in 2° relative.
Apo B-100, apolipoprotein B-100; DNA, deoxyribonucleic acid; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9; TC, total cholesterol.

1. NICE. Familial hypercholesterolaemia: identification and management (CG71). August 2008. Available at: www.nice.org.uk/guidance/cg71. Accessed November 2023; 2. NICE CKS. Hypercholesterolaemia – familial. April 2023. Available at: https://cks.nice.org.uk/topics/hypercholesterolaemia-familial/. Accessed November 2023.

Genotype Scoring Criteria for Patients with a clinical diagnosis of Familial Hypercholesterolemia Please note these criteria only apply for index case, not family members of a known genotype positive patients		Points
Family History	1st or 2nd Degree relatives	
	Known with premature (<60yrs) CHD	1
	Known with premature (<45yrs) CHD	2
	Known with LDL-C >4.9mmol/l (or total cholesterol >7.5mmol/l)	2
	Known with LDL-C >4.0mmol/l (or total cholesterol >6.7mmol/l)	1
	Please specify relation to index case	
Physical Examination	Tendon xanthomata (in 1st/2nd degree relatives)	6
	Premature corneal arcus (no score arcus senilis)	4
Clinical History	Patient has premature CHD (<45 yrs)	4
	Patient has premature CHD (<50 yrs)	3
	Patient has premature CHD (<60 yrs)	2
	Patient has premature Stroke/TIA or PVD (<60 yrs)	1
Untreated or Corrected LDL-cholesterol	LDL-Cholesterol ≥ 8.5	8
	LDL-Cholesterol 6.5-8.4	5
	LDL-Cholesterol 5.0-6.4	3
	LDL-Cholesterol 4.0-4.9	1
Fasting Triglycerides	Triglyceride 2.5-3.4	Minus 2
	Triglyceride 3.5-4.9	Minus 3
	Triglyceride ≥ 5.0	Minus 4
	Please record in referral any secondary issue that may predispose to raised TG's such as diabetes	
TOTAL SCORE		
Eligibility for FH genotyping	6 or above eligible for genotyping	
	5 or less usually not eligible except in exceptional circumstances	

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Dutch Lipid Network Score

When assessment completed, if the patient is eligible, please refer to:

Professor Ahmet Fuat
Darlington Community Lipid Clinic
Carmel Medical Practice
Or County Durham and Darlington Foundation Trust Lipid service

CHD, coronary heart disease; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; PVD, peripheral vascular disease; TG, triglycerides; TIA, transient ischaemic attack.

Affinity Care PCN December 2021.

Genetic disorders of lipoprotein metabolism (1)

EAS ESC European Society of Cardiology

Disorder	Prevalence	Gene(s)	Effect on lipoproteins
HeFH	1 in 200-250	LDLR APO B PCSK9	↑ LDL-C
HoFH	1 in 160 000-320 000	LDLR APO B PCSK9	↑↑ LDL-C
FCH	1 in 100/200	USF1 + modifying genes	↑LDL-C ↑VLDL-C ↑ ApoB
Familial dysbetalipoproteinaemia	1 in 5000	APO E	↑↑IDL and chylomicron remnants (βVLDL)

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

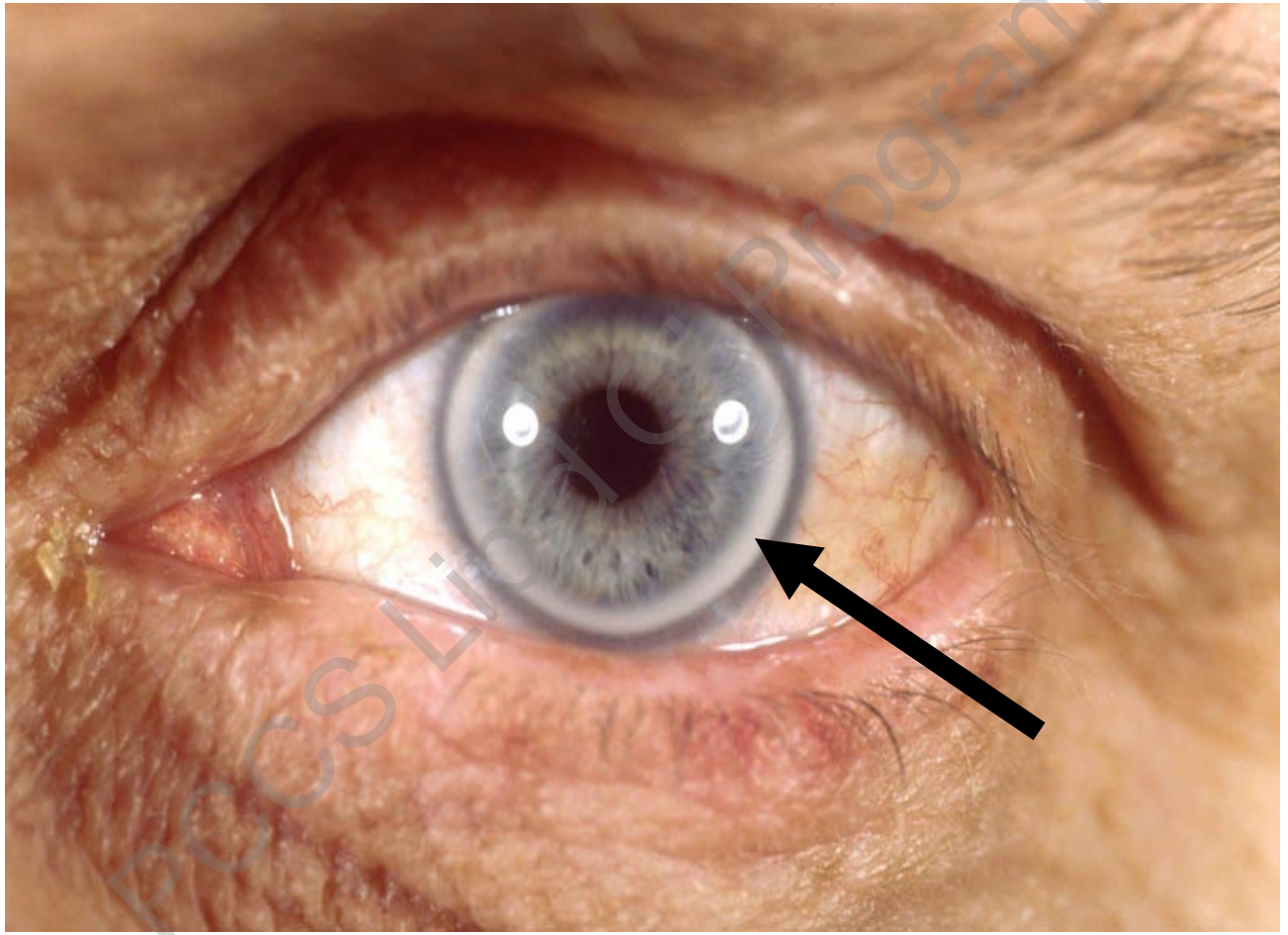
Genetic disorders of lipoprotein metabolism (2)

EAS ESC European Society of Cardiology

Disorder	Prevalence	Gene(s)	Effect on lipoproteins
Familial lipoprotein lipase deficiency (familial chylomicron syndrome)	2 in 10^6	LPL APO C2 ApoAV, GPIHBP1 LMF1	↑↑chylomicrons and VLDL-C
Tangier disease (analphalipoproteinaemia)	1 in 10^6	ABCA 1	↓↓HDL-C
Familial LCAT deficiency	1 in 10^6	LCAT	↓HDL-C

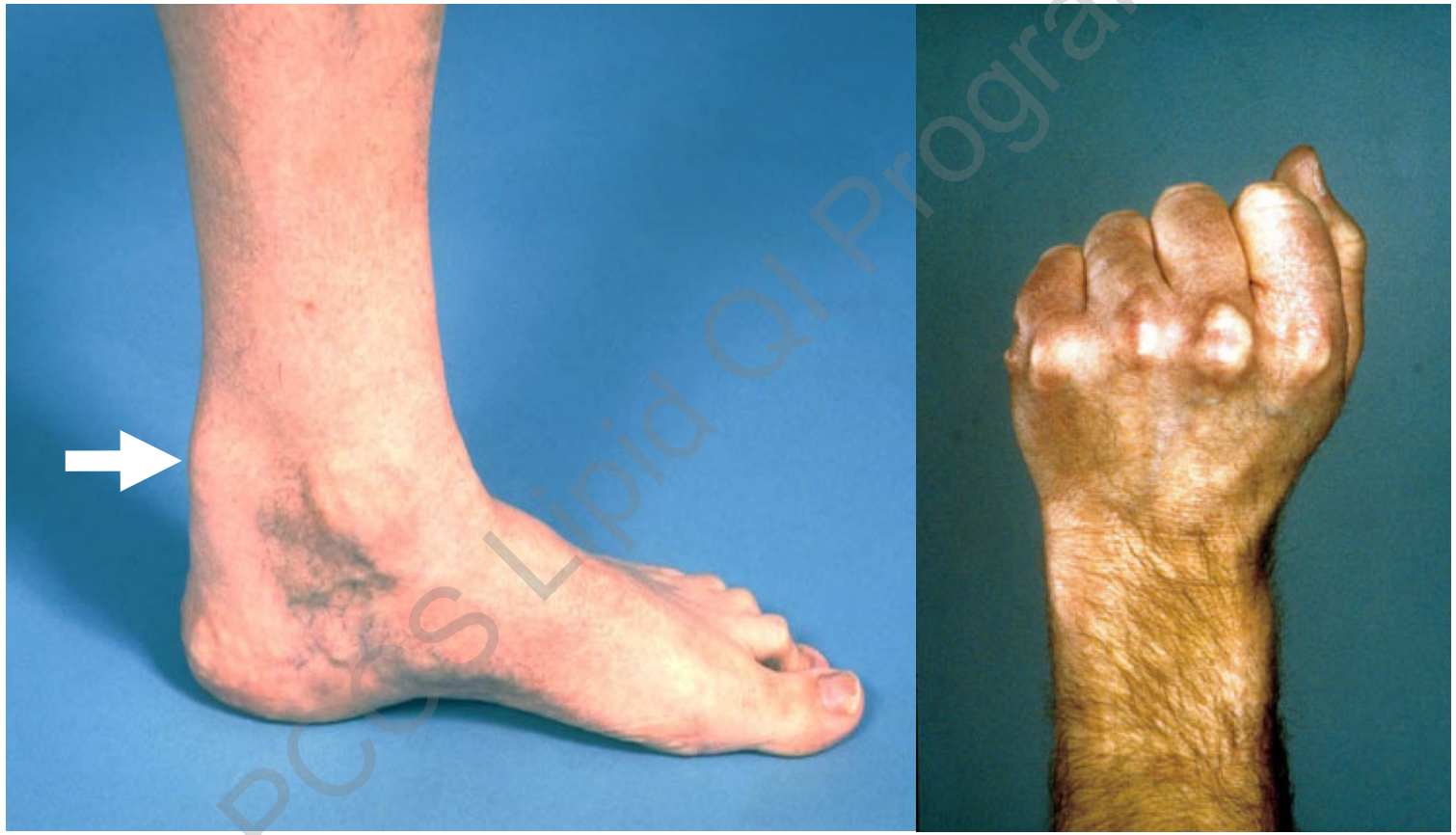
2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Corneal arcus lipidus



The British Journal of Cardiology. An educational resource from the BJC. Available at: https://bjcardio.co.uk/learning/. Accessed November 2023.

Tendon xanthoma



Diagnostic criteria for heterozygous FH

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Simon Broome Register Criteria (UK) for HeFH in probands

1.	Total cholesterol above 7.5mmol/l or LDL cholesterol above 4.9mmol/l in an adult (levels either pre-treatment or highest on treatment) Total cholesterol above 6.7mmol/l or LDL cholesterol above 4.0mmol/l in a child aged under 16 years
2.	Tendon xanthomas in patient, 1st degree relative (parent, sibling, child), or 2nd degree relative (grandparent, uncle, aunt)
3.	DNA-based evidence of an LDL receptor mutation, familial defective apo B-100, or a PCSK9 mutation
4.	Family history of premature myocardial infarction: below age of 50 years in 2nd degree relative or below age 60 years in 1st degree relative
5.	Family history of raised total cholesterol: above 7.5mmol/l in adult 1st or 2nd degree relative or above 6.7mmol/l in child or sibling aged under 16 years.

FH "definite" if 1 + (2 or 3) are present, "possible" if 1 + (4 or 5)

Apo B-100, apolipoprotein B-100; DNA, deoxyribonucleic acid; HeFH, heterozygous familial hypercholesterolaemia; FH, familial hypercholesterolaemia; LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9; UK, United Kingdom.

Heart UK. What are the diagnostic criteria for FH? Available at: https://www.heartuk.org.uk/fh/fh-diagnosis-criteria. Accessed November 2023.

Recommendations for the detection and treatment of patients with heterozygous familial hypercholesterolaemia (1)

EAS ESC European Society of Cardiology

Recommendations	Class	Level
It is recommended to consider the diagnosis of FH in patients with CHD aged <55 years for men and <60 years for women, in people with relatives with premature fatal or non-fatal CVD, in people with relatives who have tendon xanthomas, in people with severely elevated LDL-C (in adults >5 mmol/L [>190 mg/dL], in children >4 mmol/L [>150 mg/dL]), and in first-degree relatives of FH patients.	I	C
It is recommended that FH should be diagnosed using clinical criteria and confirm, when available, with DNA analysis.	I	C

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Recommendations for the detection and treatment of patients with heterozygous familial hypercholesterolaemia (2)

EAS ESC European Society of Cardiology

Recommendations	Class	Level
Once the index case is diagnosed, family cascade screening is recommended.	I	C
It is recommended to treat FH patients with ASCVD or who have another major risk factor as very-high-risk, and those with no prior ASCVD or other risk factors as high-risk.	I	C
For FH patients with ASCVD who are at very-high risk, treatment to achieve at least a 50% reduction from baseline and an LDL-C <1.4 mmol/L (<55 mg/dL) is recommended. If goals cannot be achieved, a drug combination is recommended.	I	C

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Recommendations for the detection & treatment of patients with heterozygous familial hypercholesterolaemia (3)

EAS ESC European Society of Cardiology

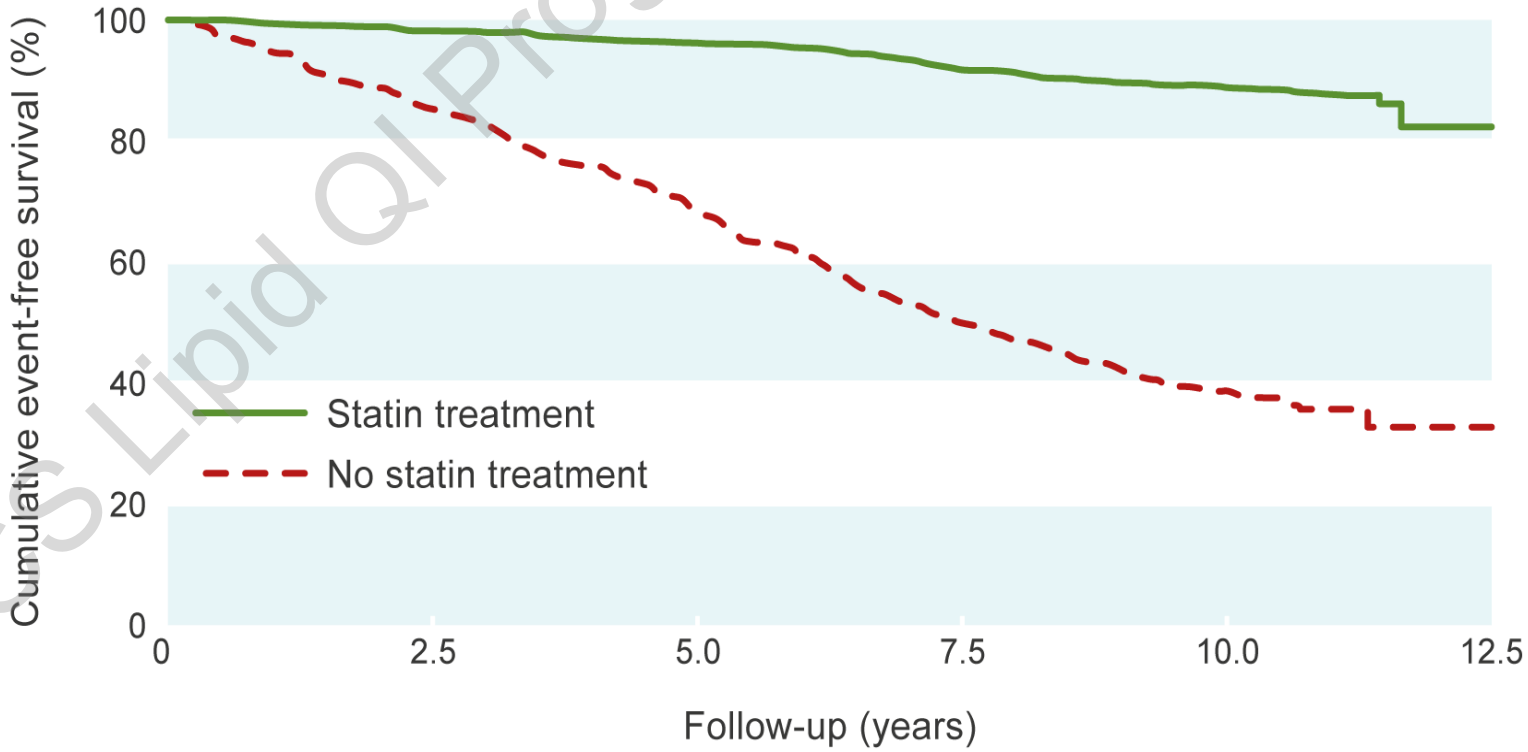
Recommendations	Class	Level
In primary prevention, for individuals with FH at very-high risk, an LDL-C reduction of at least 50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.	IIa	C
Treatment with a PCSK9 inhibitor is recommended in very-high-risk FH patients if the treatment goal is not achieved on maximal tolerated statin plus ezetimibe.	I	C
In children, testing for FH is recommended from the age of 5 years, or earlier if homozygous FH is suspected.	I	C
Children with FH should be educated to adopt a proper diet and treated with a statin from 8–10 years of age. Goals for treatment should be LDL-C <3.5 mmol/L (<135 mg/dL) at >10 years of age.	IIa	C

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Efficacy of statins in FH: a long-term cohort study[1]

- Statin treated patients with FH had a significantly better event-free survival compared with untreated patients with FH (P<0.001)

KAPLAN-MEIER CURVE ESTIMATES OF CUMULATIVE CHD-FREE SURVIVAL AMONG PATIENTS WITH FH ACCORDING TO STATIN TREATMENT (P<0.001 FOR DIFFERENCE)



CHD, coronary heart disease; FH, familial hypercholesterolaemia.

1. Versmissen J, et al. BMJ 2008; 337:a2423.

Polygenic hypercholesterolaemia

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- Polygenic hypercholesterolaemia is high cholesterol which is caused by problems with a number of different genes
- Polygenic hypercholesterolaemia is different to FH which is caused by a problem with one gene, rather than many
- It's possible to have polygenic hypercholesterolaemia and FH at the same time. Around one in 250 people in the UK have FH, and some of these will also have one or more other genes which all raise their cholesterol a little higher

FH, familial hypercholesterolaemia; UK, United Kingdom.

Heart UK. Polygenic hypercholesterolaemia. Available at: https://www.heartuk.org.uk/genetic-conditions/polygenic-hypercholesterolaemia. Accessed November 2023.

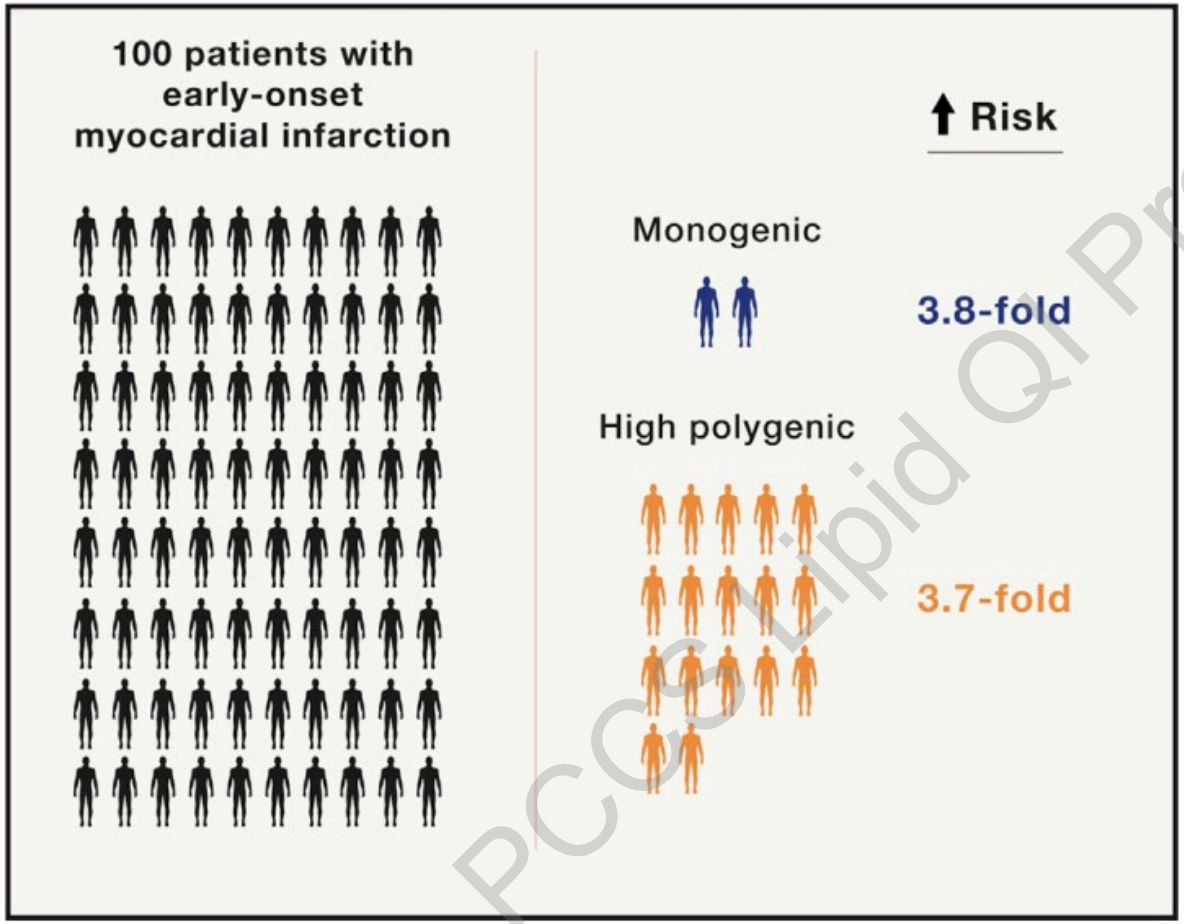
Polygenic hypercholesterolaemia

Polygenic Hypercholesterolaemia	Familial Hypercholesterolaemia
Polygenic hypercholesterolaemia is caused by several altered or faulty genes.	FH is caused by one faulty gene.
Each faulty gene raises LDL cholesterol a little.	The faulty gene raises LDL cholesterol to a very high level.
The faulty genes can be inherited from both parents.	There is usually one faulty gene which is inherited from one parent.
Your parents might have healthy LDL cholesterol levels – as each parent might not have enough of the faulty genes to raise their cholesterol.	The parent with the faulty gene is very likely to have high LDL cholesterol.
The risk of heart disease is thought to be lower than with FH.	The risk of heart disease is thought to be higher than with PH.

FH, familial hypercholesterolaemia; LDL, low-density lipoprotein; PH, polygenic hypercholesterolaemia.

Heart UK. Polygenic hypercholesterolaemia. Available at: https://www.heartuk.org.uk/genetic-conditions/polygenic-hypercholesterolaemia. Accessed November 2023.

Relative contributions of monogenic risk and polygenic risk for early-onset MI



For every 100 patients with early-onset myocardial infarction, roughly two harbour a rare coding mutation in a monogenic familial hypercholesteremia gene, whereas about 17 have a high genome-wide polygenic score (Khera et al., 2018a; Khera et al., 2018b). The increases in risk for early-onset myocardial infarction conferred by rare coding mutations versus a high polygenic score are equivalent.

MI, myocardial infarction.

Musunuru K and Kathiresan S. Cell 2019; 177:132-145.

Lipoprotein(a) is an independent risk factor for CVD and currently not treatable

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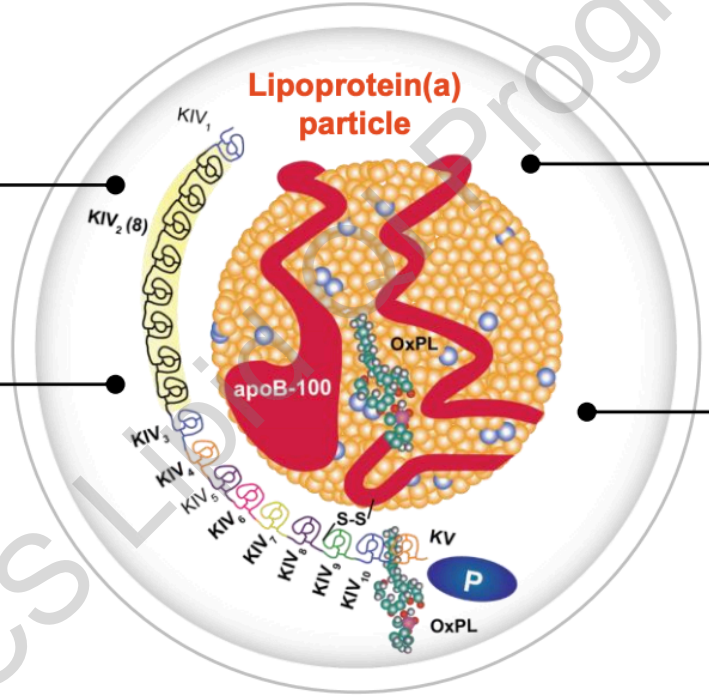
Lp(a) is an independent, genetic and causal risk factor for CVD, with elevated Lp(a) mediating MI, stroke, and PAD

Lp(a) consists of an LDL-like particle which is covalently bound to apo(a)



Lp(a) levels are primarily genetically determined and not influenced by diet or exercise

There are currently no approved therapies to treat elevated Lp(a)

Apo(a), apolipoprotein(a); ApoB-100, apolipoprotein B-100; CVD, cardiovascular disease; KIV, kringle IV; KV, kringle V; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); MI, myocardial infarction; OxPL, oxidised phospholipids; P, inactive protease-like domain; PAD, peripheral arterial disease.

Adapted from: Tsimikas S. J Am Coll Cardiol 2017;69:692-711.

Around one in five people worldwide are at increased risk of developing CVD due to Lp(a)[1]

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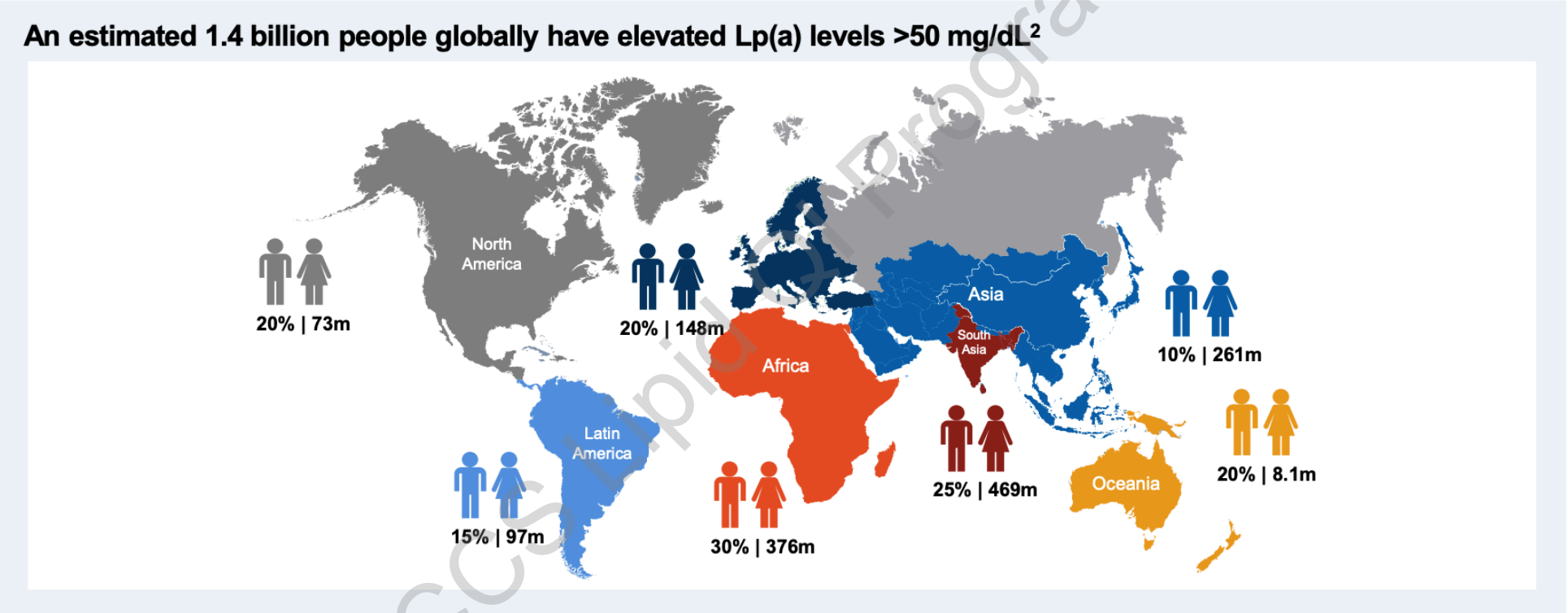
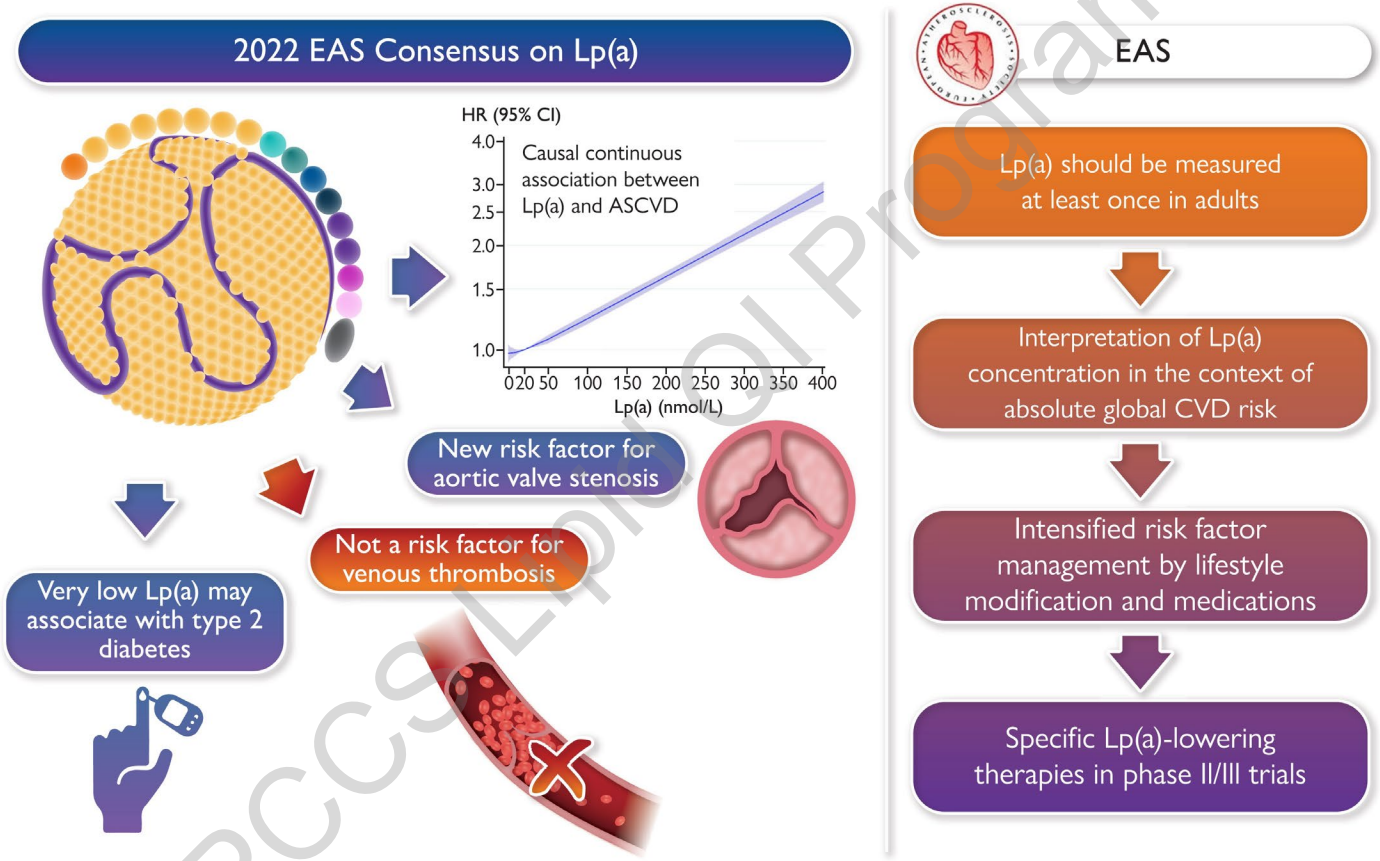


Figure taken from Tsimikas S, et al. J Am Coll Cardiol 2018;71:177-192.

CVD, cardiovascular disease; Lp(a), lipoprotein(a).

1. Tsimikas S, et al. J Am Coll Cardiol 2018;71:177-192; 2. Nordestgaard BG, et al. Eur Heart J 2010;31:2844-2853.

Graphical abstract: key points from the 2022 Lp(a) consensus statement



ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CVD, cardiovascular disease; EAS, European Atherosclerosis Society; HR, hazard ratio; Lp(a), lipoprotein(a).
Kronenberg F, et al. Eur heart J 2022;43:3925-3946.

Serum Lp(a) levels:

HEART UK consensus

- 32-90 nmol/L - minor increase in CV risk
- 90-200 nmol/L - moderate increase in CV risk
- 200-400 nmol/L - highly increased CV risk
- >400 nmol/L - very highly increased CV risk

CV, cardiovascular; Lp(a), lipoprotein(a); UK, United Kingdom.
Cegla J, et al. Atherosclerosis 2019;291:62-70.

Case study

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Male 63 years, father died of MI aged 47

Medical history:

UA 2013 - 2 stents LAD
Genetics: PH with Lp(a) gene
Lp(a) 284 nmol/L

Current medication:

- Rosuvastatin 40 mgs
- Ezetimibe 10 mgs
- Clopidogrel 75 mgs
- Bisoprolol 1.25 mgs
- Lansoprazole 30 mgs
- Citalopram 40 mgs

Please refer to the respective SmPCs of these therapies for full information.

- ✓ **Discussed results – good diet, vegetarian, BMI 25.6**
- ✓ **Non-smoker, little alcohol**
- ✓ **Switched ezetimibe to bempedoic acid 180 mgs + ezetimibe 10 mgs**

Lab results:

24th May 2023
TC 4.1; LDL-C 2.0; HDL-C 1.4; non-HDL-C 2.7; TGs 0.9

8th November 2023
TC 3.4; LDL-C 1.5; HDL-C 1.6; non-HDL-C 1.8; TGs 0.72

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LAD, left anterior descending artery; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); MI, myocardial infarction; PH, polygenic hypercholesterolaemia; SmPCs, Summary of Product Characteristics; TC, total cholesterol; TGs, triglycerides; UA, unstable angina.
Speaker's own experience.

Serum Lp(a) should be measured:

HEART UK consensus

- Personal or family history of premature ASCVD (aged <60)
- 1st degree relative with increased Lp(a) > 200 nmol/L
- FH or other genetic dyslipidaemia
- Calcific aortic valve stenosis
- Borderline raised (but < 15%) 10-year risk of cardiovascular event

ASCVD, atherosclerotic cardiovascular disease; FH, familial hypercholesterolaemia; Lp(a), lipoprotein(a); UK, United Kingdom.

Yang W and Cegla J. Br J Cardiol 2022;29:S20-S23.

Conclusions[1,2]

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- FH can be diagnosed based on a combination of lipid levels, family history, findings on physical examination and genetic testing
- FH is treatable
  - With early diagnosis and inexpensive statin therapy, excess CVD risk is eliminated
- FH is significantly underdiagnosed and undertreated
  - There are around 220,000 people in England with FH but <8% have been diagnosed
- Because of the dominant inheritance of the disease, when one person in a family is diagnosed with FH, it is vitally important to screen the related family members (known as “cascade testing”)
- Remember other genetic lipid disorders
- Lowering LDL works and is ‘safe’ and cost effective
- Combination therapies using newer agents such as bempedoic acid, inclisiran alongside statins, ezetimibe and PCSK9i may be necessary to achieve targets

CVD, cardiovascular disease; FH, familial hypercholesterolaemia; LDL, low-density lipoprotein; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors.

1. NICE. Familial hypercholesterolaemia: identification and management (CG71). August 2008. Available at: www.nice.org.uk/guidance/cg71. Accessed November 2023; 2. NHS England. Familial hypercholesterolemia (FH). Available at: https://www.england.nhs.uk/london/london-clinical-networks/our-networks/cardiac/familial-hypercholesterolaemia/. Accessed November 2023.