LIPIDS

Lipid / Lipoprotein	Normal Physiological Role	Pathogenesis of Dyslipidaemia	Main Clinical Consequences	Primary Treatments
LDL (Low-Density Lipoprotein)	Delivers cholesterol from liver to peripheral tissues for membrane synthesis and steroid production	Elevated LDL from increased hepatic production, reduced LDL receptor activity (e.g. familial hypercholesterolaemia), diet, diabetes	**Atherosclerosis**, coronary artery disease, stroke, peripheral arterial disease	**Statins (first-line)** → Ezetimibe → PCSK9 inhibitors → Inclisiran → Bempedoic acid; lifestyle modification
HDL (High-Density Lipoprotein)	Reverse cholesterol transport (returns cholesterol to liver); antioxidant and anti-inflammatory effects	Low HDL from obesity, diabetes, smoking, hypertriglyceridaemia, sedentary lifestyle	Marker of increased ASCVD risk (raising HDL pharmacologically has not consistently reduced events)	Exercise, weight loss, smoking cessation; manage LDL and triglycerides rather than targeting HDL directly
Triglycerides (TG)	Energy storage and transport as VLDL and chylomicrons	Increased hepatic VLDL production (obesity, diabetes, alcohol), impaired clearance (LPL deficiency), familial hypertriglyceridaemia	**Pancreatitis** (especially >11.3 mmol/L); contributes to ASCVD	**Fibrates (first-line for severe TG)**, omega-3 fatty acids (icosapent ethyl for selected patients), statins if ASCVD risk, strict low-fat diet, treat secondary causes
VLDL (Very Low-Density Lipoprotein)	Transports endogenous triglycerides from liver to tissues	Overproduced in insulin resistance, obesity, NAFLD, diabetes	Hypertriglyceridaemia, formation of small dense LDL, increased ASCVD risk	Weight loss, glycaemic control, statins, fibrates (if TG predominant)
IDL (Intermediate-Density Lipoprotein)	Transitional particle between VLDL and LDL	Accumulates when remnant clearance is impaired	Atherogenic remnant particles	Statins; lifestyle modification
Chylomicrons	Transport dietary triglycerides and cholesterol from intestine	LPL deficiency, ApoC-II deficiency, familial chylomicronaemia syndrome	**Severe hypertriglyceridaemia**, eruptive xanthomas, lipaemia retinalis, recurrent pancreatitis	**Very-low-fat diet (<10–15% calories)**, avoid alcohol, treat diabetes; fibrates may help if LPL function preserved but have limited benefit in true familial chylomicronaemia
Remnant Lipoproteins	Metabolic remnants of chylomicrons and VLDL	Delayed hepatic clearance due to ApoE abnormalities or insulin resistance	Highly atherogenic; premature ASCVD	Statins, fibrates, lifestyle modification
Lipoprotein(a) [Lp(a)]	LDL-like particle with apolipoprotein(a); role uncertain (possibly wound healing)	Genetically determined elevated synthesis; little affected by lifestyle	Premature ASCVD, calcific aortic stenosis	Aggressive LDL lowering; **PCSK9 inhibitors modestly reduce Lp(a)**; lipoprotein apheresis in selected patients; emerging RNA therapies under investigation
Non-HDL Cholesterol	Represents all atherogenic apoB-containing particles (LDL + VLDL + IDL + remnants + Lp(a))	Elevated when any atherogenic particles are increased	Better predictor of ASCVD risk than LDL in hypertriglyceridaemia	Same as LDL-centred therapy, particularly statins
Apolipoprotein B (ApoB)	One ApoB molecule per atherogenic lipoprotein particle	Increased particle number despite normal LDL concentration	Strong predictor of ASCVD risk	Statins, ezetimibe, PCSK9 inhibitors, lifestyle modification
Apolipoprotein A-I (ApoA-I)	Major structural protein of HDL; activates reverse cholesterol transport	Reduced in metabolic syndrome and diabetes	Associated with lower HDL and increased ASCVD risk	Lifestyle measures; no specific drug target currently recommended

High-yield clinical summary

Predominant abnormality	Likely diagnosis	Best initial drug
High LDL	Hypercholesterolaemia	**Statin**
High TG (>5.6 mmol/L)	Hypertriglyceridaemia	**Fibrate**
Very high TG (>11.3 mmol/L)	Severe hypertriglyceridaemia	**Fibrate + very-low-fat diet ± omega-3; prevent pancreatitis**
High LDL + High TG	Mixed dyslipidaemia	**Statin first** (add fibrate if TG remain markedly elevated)
Elevated Lp(a)	Genetic dyslipoproteinaemia	Intensive LDL lowering (statin ± PCSK9 inhibitor)
Familial hypercholesterolaemia	LDL receptor defect	High-intensity statin → ezetimibe → PCSK9 inhibitor
Familial chylomicronaemia	LPL/ApoC-II deficiency	**Very-low-fat diet**; specialist management (fibrates often ineffective)

Drug targets at a glance

Drug class	Primary lipid lowered	Secondary effects
Statins	LDL ↓↓↓	TG ↓, HDL ↑ slightly
Ezetimibe	LDL ↓↓	Minimal TG effect
PCSK9 inhibitors	LDL ↓↓↓↓	Small Lp(a) reduction
Inclisiran	LDL ↓↓↓	Twice-yearly maintenance dosing
Bempedoic acid	LDL ↓↓	Useful in statin intolerance
Fibrates	TG ↓↓↓	HDL ↑, modest LDL reduction (or transient rise when TG are very high)
Omega-3 fatty acids (icosapent ethyl)	TG ↓↓	ASCVD event reduction in selected high-risk patients
Niacin	HDL ↑, TG ↓	Rarely used due to adverse effects and lack of cardiovascular outcome benefit

CHOLESTEROL FORMATION (CHOLESTEROL BIOSYNTHESIS)

The Mevalonate Pathway

CYTOSOL

Acetyl-CoA from carbohydrate, fatty acid or protein metabolism

1. Acetyl-CoA (2 molecules)

Thiolase

2. Acetoacetyl-CoA

HMG-CoA synthase

3. 3-Hydroxy-3-methyl-glutaryl-CoA (HMG-CoA)

HMG-CoA reductase

SMOOTH ENDOPLASMIC RETICULUM (ER)

4. Mevalonate

Mevalonate kinase

5. Mevalonate-5-phosphate

Phosphomevalonate kinase

6. Mevalonate-5-pyrophosphate

Mevalonate pyrophosphate decarboxylase

7. Isopentenyl pyrophosphate (IPP) (5-carbon unit)

8. Dimethylallyl pyrophosphate (DMAPP) (5-carbon unit)

Isomerization (interconversion)

Prenyltransferases

9. Geranyl pyrophosphate (GPP, 10C) → Farnesyl pyrophosphate (FPP, 15C)

RATE-LIMITING STEP

Inhibited by:
- Statins (e.g., atorvastatin, simvastatin)
- High cholesterol
- Insulin

Activated by:
- SREBP
- Low cholesterol
- Glucagon

SMOOTH ER (MEMBRANE)

10. Squalene (30C)

Squalene epoxidase

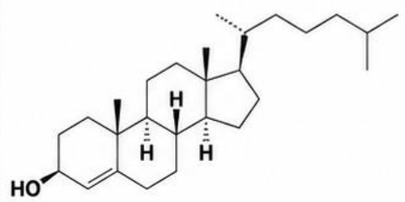
11. 2,3-Oxidosqualene

12. Lanosterol

Multiple enzymatic reactions including demethylation, isomerization and reduction

13. Cholesterol

Cholesterol ($C_{27}H_{46}O$)

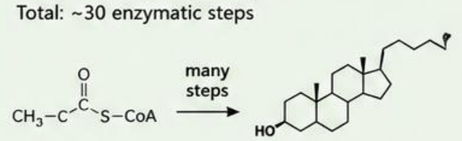


Cholesterol is a sterol with four fused rings (three 6-membered and one 5-membered) and an 8-carbon side chain.

SUMMARY

Acetyl-CoA → (multiple steps) → Cholesterol

Total: ~30 enzymatic steps

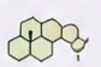


Acetyl-CoA — Cholesterol

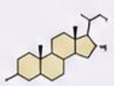
REGULATION (Key points)

- HMG-CoA reductase is the rate-limiting enzyme.
- Controlled by cholesterol levels via SREBP (transcriptional regulation).
- Statins competitively inhibit HMG-CoA reductase.
- High insulin (fed state) stimulates cholesterol synthesis.
- Cholesterol excess inhibits its own synthesis.

Cholesterol is the precursor for:



Bile acids



Steroid hormones (cortisol, aldosterone, estrogen, testosterone)

Vitamin D

Cell membranes and lipoproteins

Statins v Fibrates

Feature	Statins	Fibrates
Primary mechanism	Inhibit HMG-CoA reductase → ↓ hepatic cholesterol synthesis → ↑ LDL receptor expression	Activate PPAR-α → ↑ lipoprotein lipase activity, ↑ fatty acid oxidation, ↓ VLDL production
Primary lipid effect	↓ **LDL cholesterol**	↓ **Triglycerides**
Triglyceride reduction	~10–30%	**30–60%** (greatest effect in severe hypertriglyceridaemia)
LDL reduction	**20–60%** (depends on potency/dose)	5–20%; may increase LDL transiently in very high TG states as chylomicrons clear
HDL increase	5–10%	10–20%
Best indication	Prevention of atherosclerotic cardiovascular disease (ASCVD); elevated LDL cholesterol	Severe hypertriglyceridaemia (especially **TG >5.6 mmol/L**) to reduce pancreatitis risk
Role in familial hypertriglyceridaemia	Adjunct if ASCVD risk or LDL elevation is present	**First-line drug therapy** (along with strict dietary fat restriction and treatment of secondary causes)
Evidence for reducing pancreatitis	Limited	**Preferred lipid-lowering class** when TG are markedly elevated because of greater TG reduction
Evidence for reducing cardiovascular events	**Strong evidence** (primary and secondary prevention)	Modest; greatest benefit in patients with high TG and low HDL
Common examples	Atorvastatin, Rosuvastatin, Simvastatin	Fenofibrate, Bezafibrate, Gemfibrozil
Typical adult doses	Atorvastatin: **10–80 mg PO daily**Rosuvastatin: **5–40 mg PO daily**	Fenofibrate: **145 mg PO daily** (formulation dependent)Bezafibrate MR: **400 mg PO daily** (or **200 mg PO three times daily**)Gemfibrozil: **600 mg PO twice daily**
Major contraindications	Active liver disease, pregnancy, breastfeeding	Severe renal impairment (dose-dependent), active liver disease, gallbladder disease, pregnancy
Important adverse effects	Myalgia, myopathy, rhabdomyolysis (rare), transaminitis	Dyspepsia, myopathy, gallstones, reversible rise in creatinine
Monitoring	ALT before treatment; CK only if symptoms; lipid profile 4–12 weeks after starting	Renal function (eGFR), ALT, lipid profile; CK if muscle symptoms
Drug interactions	CYP3A4 interactions (especially simvastatin/atorvastatin)	Gemfibrozil markedly increases statin levels; fenofibrate/bezafibrate have lower interaction risk but still require caution
Combination therapy	Often combined with ezetimibe or PCSK9 inhibitors	May be combined with a statin in selected patients with persistent severe hypertriglyceridaemia; **fenofibrate is generally preferred** over gemfibrozil when combination therapy is required
Gold-standard use	LDL lowering and ASCVD risk reduction	Triglyceride lowering and prevention of hypertriglyceridaemia-induced pancreatitis

Key clinical pearls

- **High LDL → choose a statin.**
- **High triglycerides (>5.6 mmol/L) → choose a fibrate (or prescription omega-3s), plus lifestyle measures.**
- **Very high triglycerides (>11.3 mmol/L)** are managed urgently to prevent pancreatitis; rapid TG reduction takes priority over LDL reduction.
- Patients with **both elevated LDL and severe hypertriglyceridaemia** often require **both** a statin (for ASCVD prevention) and a fibrate (for TG reduction), with careful monitoring for myopathy.
- In **familial chylomicronaemia syndrome**, fibrates may have limited efficacy because the underlying defect is impaired lipoprotein lipase activity; strict dietary fat restriction is the cornerstone of therapy.