nature REVIEWS
CARDIOLOGY

Dyslipidaemia and its treatment

Robert A. Hegele and Philip Barter

Disorders of plasma lipid and lipoprotein metabolism are well recognized as causative factors in the development of atherosclerotic cardiovascular disease. The rational management of such disorders requires an understanding of the factors that regulate plasma lipid metabolism and how abnormalities of such factors lead to dyslipidaemia. This poster displays the main lipid-metabolism pathways in the body, including synthesis in tissues and the interaction and transfer of lipids between the intestines, liver, blood, and peripheral tissues. The major classes of lipoproteins that transport lipids in blood plasma, and the factors involved in their assembly, interconversion, and catabolism are shown. Points at which monogenetic mutations affect protein concentration, function, and that lead (often in combination with lifestyle factors) to dyslipidaemia are identified. With this knowledge, therapeutic targets can be identified, and we can understand how existing lipid-modifying drugs as well as novel agents under development target these pathways, with the potential to correct the dyslipidaemia and reduce the risk of a major cardiovascular event.[1,2]

Supplement to Nature Publishing Group journals

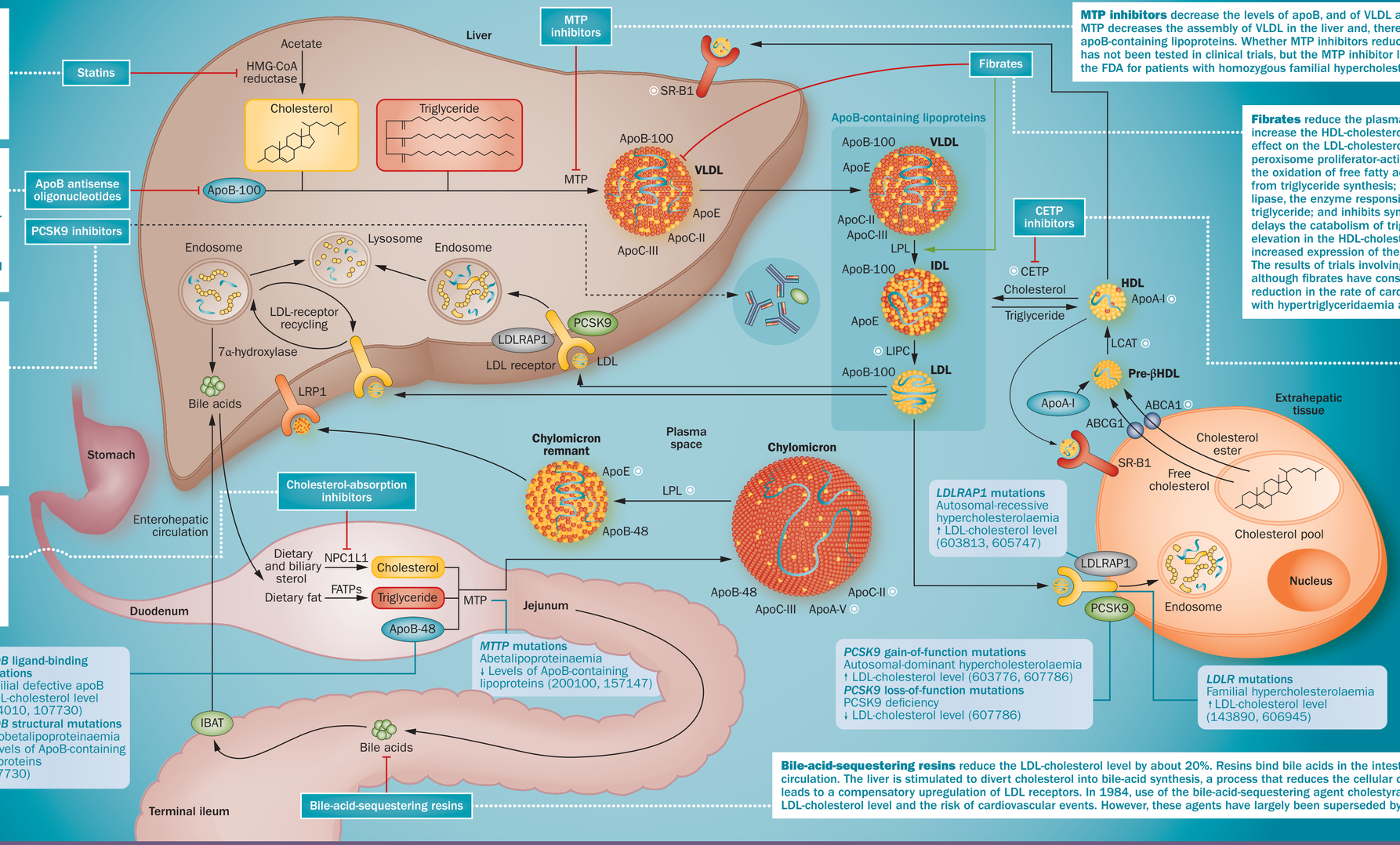
Statins reduce the plasma LDL-cholesterol level by as much as 55%. These drugs inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis. The resulting reduction in cellular cholesterol content leads to compensatory upregulation of LDL receptors and increased uptake of LDL cholesterol by cells. A meta-analysis of 26 clinical trials ($n = 169{,}138$) showed that for every 1.0 mmol/l (40 mg/dl) reduction in LDL-cholesterol level with a statin, the risk of a major cardiovascular event is reduced by about one-fifth.[3]

ApoB antisense oligonucleotides reduce the levels of apoB, LDL cholesterol, and non-HDL cholesterol by 25–30%. These compounds are short, synthetic analogues of natural nucleic acids that bind to mRNA, inhibit the synthesis of apoB and, therefore, decrease the secretion of apoB-containing lipoproteins. Whether apoB antisense oligonucleotides reduce the risk of cardiovascular events has not been tested in clinical trials, but one member of this class, mipomersen, has been approved by the FDA as an orphan drug for patients with homozygous familial hypercholesterolaemia.[4]

PCSK9 inhibitors decrease the LDL-cholesterol level by 40–70% when given either as monotherapy or in addition to a statin. PCSK9 binds to the LDL receptor and enhances its breakdown in lysosomes, reducing receptor recycling back to the surface. Therefore, inhibition of PCSK9 with, for example, monoclonal antibodies increases the expression of the LDL receptor, which results in an increased uptake of LDL cholesterol into cells, primarily hepatocytes. PCSK9 is upregulated by statins, an effect that limits the LDL-cholesterol-lowering potential of these agents, which makes PCSK9 inhibition a rational adjunctive therapy to statins. Clinical trials to test the effects of PCSK9 monoclonal antibodies on cardiovascular events are ongoing.[5]

Cholesterol-absorption inhibitors, such as ezetimibe, decrease the LDL-cholesterol level by about 18%, whether given as monotherapy or in addition to treatment with a statin. Ezetimibe reduces the absorption of cholesterol from the intestine by inhibiting NPC1L1. Reduced delivery of cholesterol to the liver increases hepatic LDL-receptor expression and, therefore, increases clearance of circulating LDL cholesterol. The use of ezetimibe to reduce the risk of cardiovascular events is being tested in the ongoing IMPROVE-IT trial.[6]

Niacin decreases the plasma levels of triglyceride, LDL cholesterol, and proatherogenic lipoprotein(a) by 30–40%, 10–15%, and up to 30%, respectively, and increases the HDL-cholesterol level by 15–30%. The mechanism of action of niacin is not certain, but involves inhibition of adipose tissue lipolysis and hepatic triglyceride synthesis. As monotherapy, niacin reduces the rate of cardiovascular events. In combination with a statin, niacin promotes regression of atherosclerosis. However, in clinical trials involving patients optimally treated with statins, niacin did not reduce the rate of cardiovascular events. The future role of niacin is uncertain.[7]



MTP inhibitors decrease the levels of apoB, and of VLDL and LDL cholesterol. Inhibition of MTP decreases the assembly of VLDL in the liver and, therefore, decreases the level of all apoB-containing lipoproteins. Whether MTP inhibitors reduce the rate of cardiovascular events has not been tested in clinical trials, but the MTP inhibitor lomitapide has been approved by the FDA for patients with homozygous familial hypercholesterolaemia.[8]

Fibrates reduce the plasma triglyceride level by 30–50% and increase the HDL-cholesterol level by 2–20%, but have little effect on the LDL-cholesterol level. Fibrates activate peroxisome proliferator-activated receptor α, which stimulates the oxidation of free fatty acids in the liver, diverting them from triglyceride synthesis; induces expression of lipoprotein lipase, the enzyme responsible for hydrolysing plasma triglyceride; and inhibits synthesis of apoC-III, a protein that delays the catabolism of triglyceride-rich lipoproteins. The elevation in the HDL-cholesterol level might be caused by increased expression of the *APOA1*, *APOA2*, and *ABCA1* genes. The results of trials involving fibrates have been variable, although fibrates have consistently produced a substantial reduction in the rate of cardiovascular events in individuals with hypertriglyceridaemia and a low HDL-cholesterol level.[9]

CETP inhibitors increase the HDL-cholesterol level by up to 140%, decrease the LDL-cholesterol level by up to 35%, and lower the lipoprotein(a) level by >30%. CETP transfers cholesteryl esters from the HDL fraction, where it does not cause atherosclerosis, to the VLDL and LDL fractions, where it can cause atherosclerosis; inhibiting CETP is, therefore, potentially antiatherogenic. However, in a large, randomized trial, dalcetrapib had no effect on cardiovascular outcomes and, in another study, torcetrapib was associated with a significant 25% increase in major cardiovascular events, and a 58% increase in mortality. Large clinical trials are being conducted with anacetrapib and evacetrapib, which do not share the adverse effects of torcetrapib.[10]

***APOB* ligand-binding mutations**
Familial defective apoB
↑ LDL-cholesterol level (144010, 107730)
***APOB* structural mutations**
Hypobetalipoproteinaemia
↓ Levels of ApoB-containing lipoproteins (107730)

***MTTP* mutations**
Abetalipoproteinaemia
↓ Levels of ApoB-containing lipoproteins (200100, 157147)

***LDLRAP1* mutations**
Autosomal-recessive hypercholesterolaemia
↑ LDL-cholesterol level (603813, 605747)

***PCSK9* gain-of-function mutations**
Autosomal-dominant hypercholesterolaemia
↑ LDL-cholesterol level (603776, 607786)
***PCSK9* loss-of-function mutations**
PCSK9 deficiency
↓ LDL-cholesterol level (607786)

***LDLR* mutations**
Familial hypercholesterolaemia
↑ LDL-cholesterol level (143890, 606945)

Bile-acid-sequestering resins reduce the LDL-cholesterol level by about 20%. Resins bind bile acids in the intestine and disrupt their enterohepatic circulation. The liver is stimulated to divert cholesterol into bile-acid synthesis, a process that reduces the cellular content of cholesterol, which leads to a compensatory upregulation of LDL receptors. In 1984, use of the bile-acid-sequestering agent cholestyramine was shown to reduce the LDL-cholesterol level and the risk of cardiovascular events. However, these agents have largely been superseded by newer drugs.[6]

Regeneron is a leading science-based biopharmaceutical company based in Tarrytown, New York, USA, that discovers, invents, develops, manufactures, and commercializes medicines for the treatment of serious medical conditions. Regeneron markets medicines for eye diseases, colorectal cancer, and a rare inflammatory condition, and has product candidates in development in other areas of high unmet medical need, including hypercholesterolaemia, oncology, rheumatoid arthritis, allergic asthma, and atopic dermatitis.

Sanofi, an integrated global health-care leader, discovers, develops, and distributes therapeutic solutions focused on patients' needs. Sanofi has core strengths in the field of health care with seven growth platforms: diabetes mellitus solutions, human vaccines, innovative drugs, consumer health care, emerging markets, animal health, and the new Genzyme.

Since 2007, the Regeneron and Sanofi collaboration has been at the forefront of developing innovative new therapies that seek to address current unmet medical needs. The collaboration brings forth the best of both companies—technology, scientific expertise, commercial experience, and a focus on patient needs.

Abbreviations

ABCA1	ATP-binding cassette sub-family A member 1
ABCG1	ATP-binding cassette sub-family G member 1
Apo	apolipoprotein
CETP	cholesteryl ester transfer protein
FATPs	fatty acid transport proteins
HDL	high-density lipoprotein
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
IBAT	ileal sodium/bile acid cotransporter
IDL	intermediate-density lipoprotein
LCAT	phosphatidylcholine-sterol acyltransferase
LDL	low-density lipoprotein
LDLRAP1	low-density lipoprotein receptor adapter protein 1
LIPC	hepatic triacylglycercerol lipase
LPL	lipoprotein lipase
LRP1	low-density lipoprotein receptor-related protein 1
MTP	microsomal triglyceride transfer protein
NPC1L1	Niemann–Pick C1-like protein 1
PCSK9	proprotein convertase subtilisin/kexin type 9
SR-B1	scavenger receptor class B member 1
VLDL	very-low-density lipoprotein

Information on monogenic dyslipidaemias is formatted:
Gene name | Clinical disorder
Primary biochemical disturbance (OMIM® reference)

References

1. Gotto, A. M. Jr & Moon, J. E. Pharmacotherapies for lipid modification: beyond the statins. *Nat. Rev. Cardiol.* **10**, 560–570 (2013).
2. Watts, G. F., Ooi, E. M. M. & Chan, D. C. Demystifying the management of hypertriglyceridaemia. *Nat. Rev. Cardiol.* **10**, 648–661 (2013).
3. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* **376**, 1670–1681 (2010).
4. Marais, A. D. & Blomm, D. J. Recent advances in the treatment of homozygous familial hypercholesterolaemia. *Curr. Opin. Lipidol.* **24**, 288–294 (2013).
5. Petrides, F. *et al.* The promises of PCSK9 inhibition. *Curr. Opin. Lipidol.* **24**, 307–312 (2013).
6. Couture, P. & Lamarche, B. Ezetimibe and bile acid sequestrants: impact on lipoprotein metabolism and beyond. *Curr. Opin. Lipidol.* **24**, 227–232 (2013).
7. Lavigne, P. M. & Karas, R. H. The current state of niacin in cardiovascular disease prevention: a systematic review and meta-regression. *J. Am. Coll. Cardiol.* **61**, 440–446 (2013).
8. Cuchel, M. & Rader, D. J. Microsomal transfer protein inhibition in humans. *Curr. Opin. Lipidol.* **24**, 246–250 (2013).
9. Jun, M. *et al.* Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet* **375**, 1875–1884 (2010).
10. Barter, P. J. & Rye, K. A. Cholesteryl ester transfer protein inhibition as a strategy to reduce cardiovascular risk. *J. Lipid Res.* **53**, 1755–1766 (2012).

Affiliations and competing interests
Blackburn Cardiovascular Genetics Laboratory, Robarts Research Institute, 100 Perth Drive, London, ON N6A 5K8, Canada (R. A. Hegele).
Centre for Vascular Research, Department of Medicine, University of New South Wales, High Street, Kensington, Sydney, NSW 2052, Australia (P. Barter).
R. A. Hegele declares that he has received research support from Amgen and Merck; and received honoraria from, and is an advisory board member for, Aegerion, Amgen, Genzyme, Merck, and Valeant. P. Barter declares that he has received research support from Merck and Pfizer; honoraria from Amgen, AstraZeneca, Kowa, MSD, Novartis, Pfizer, and Roche; and is an advisory board member for AstraZeneca, CSL, Kowa, Lilly, Merck, Pfizer, and Roche.

Edited by Gregory B. S. Lim; designed by Laura Marshall.
The poster content is peer-reviewed and editorially independent.

http://www.nature.com/nrcardio/posters/dyslipidaemia/