
**International Task Force for Prevention
Of Coronary Heart Disease**



*Clinical management of risk factors
of coronary heart disease and stroke*

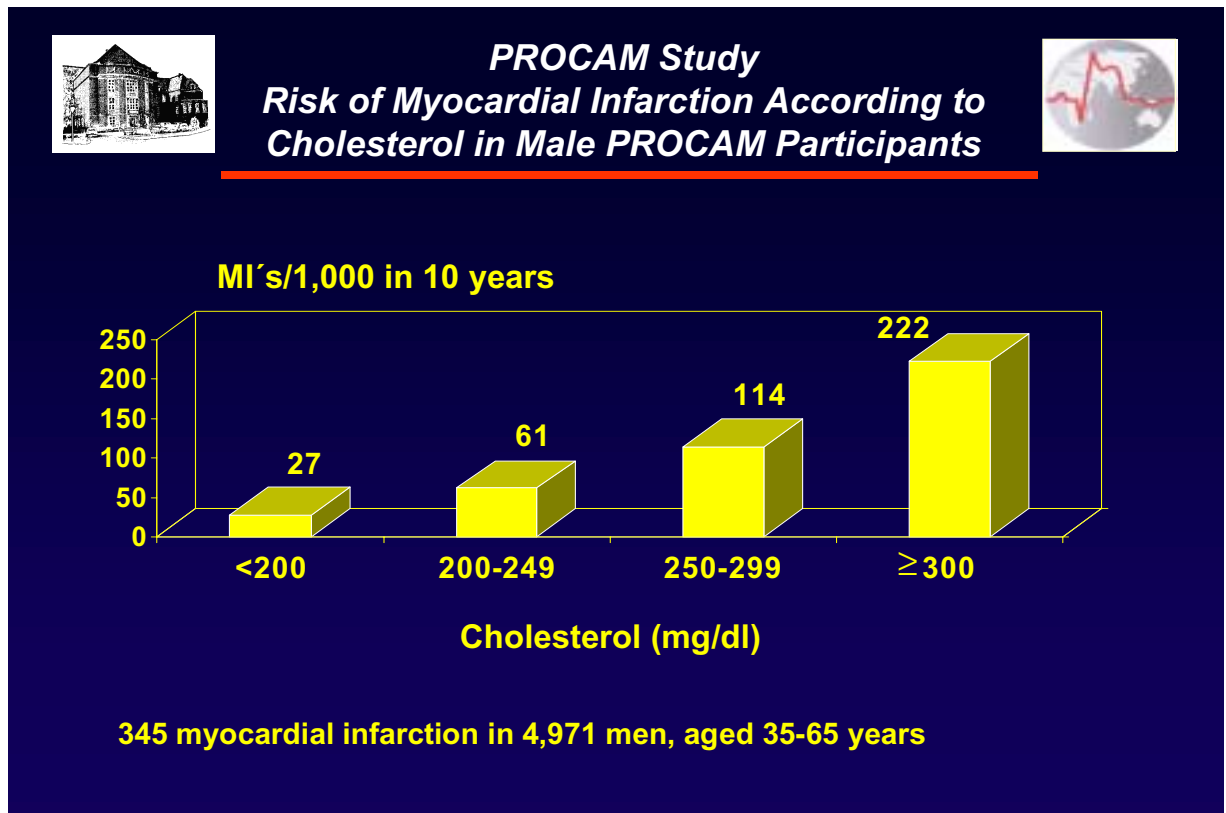
**Intestinal cholesterol absorption
as a drug target for
primary and secondary prevention of CHD**

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Slide 1:

Risk of myocardial infarction according to plasma total cholesterol concentration.

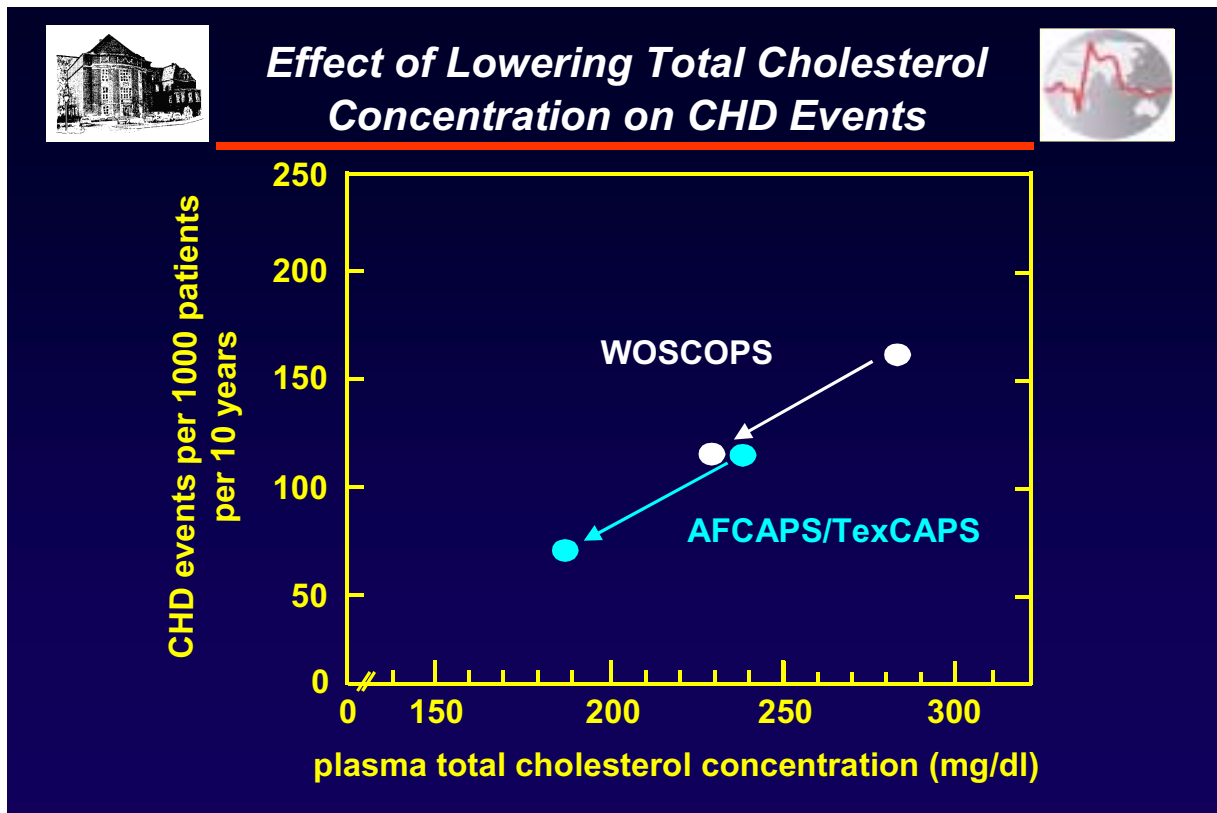


Risk of myocardial infarction according to plasma total cholesterol concentration.

This slide shows the relationship existing between plasma total cholesterol concentration and myocardial infarctions (MI's) per 1000 middle aged men over 10 years of follow-up in the PROCAM study. As can be seen, the incidence of MI's shows a steep increase at total plasma cholesterol concentrations higher than 200 mg/dl.

Slide 2:

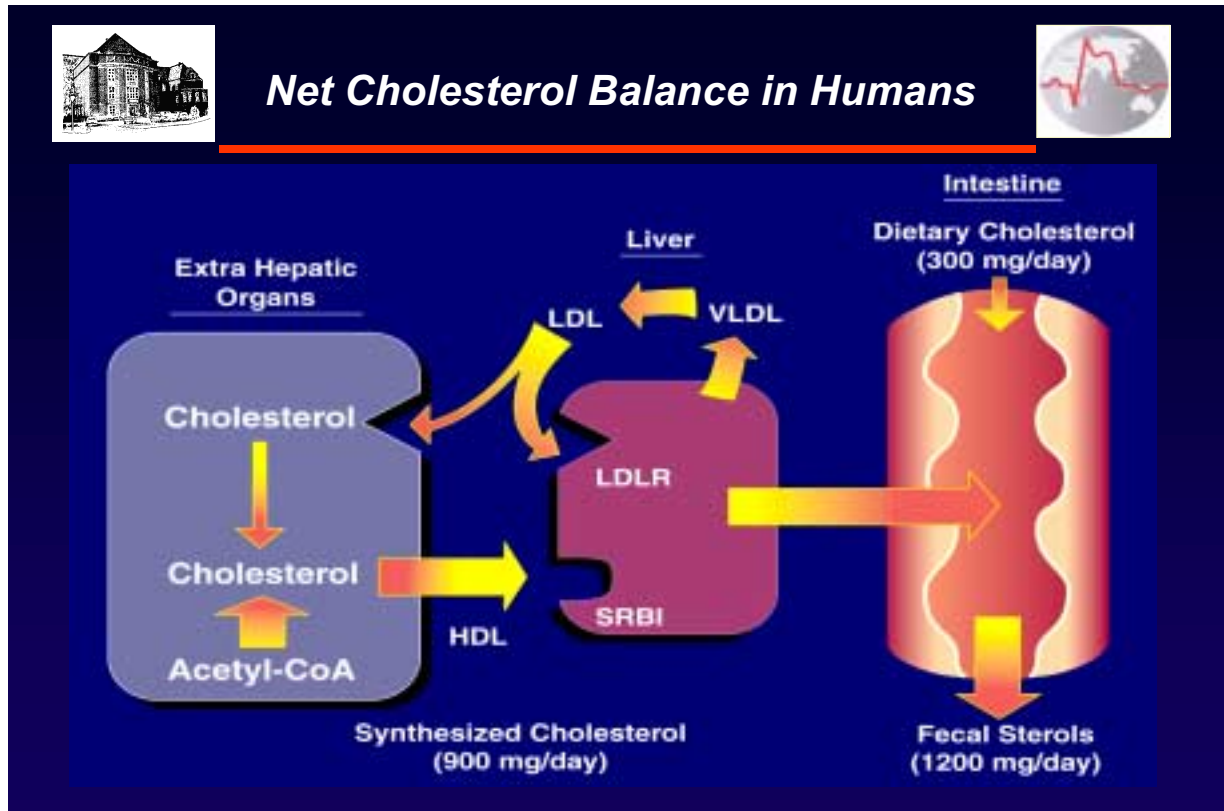
Effect of lowering total cholesterol concentration on CHD events.



Effect of lowering total cholesterol concentration on CHD events.

This slide shows the effectiveness of cholesterol lowering therapy with HMG-CoA reductase inhibitors (statins) in primary prevention. In the West of Scotland coronary prevention study (WOSCOPS), treatment resulted in significant reductions in risks of mortality and coronary events in mildly hypercholesterolemic men. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) demonstrated similar risk reductions in men and women with average cholesterol levels.

Slide 3:
Net cholesterol balance in humans.

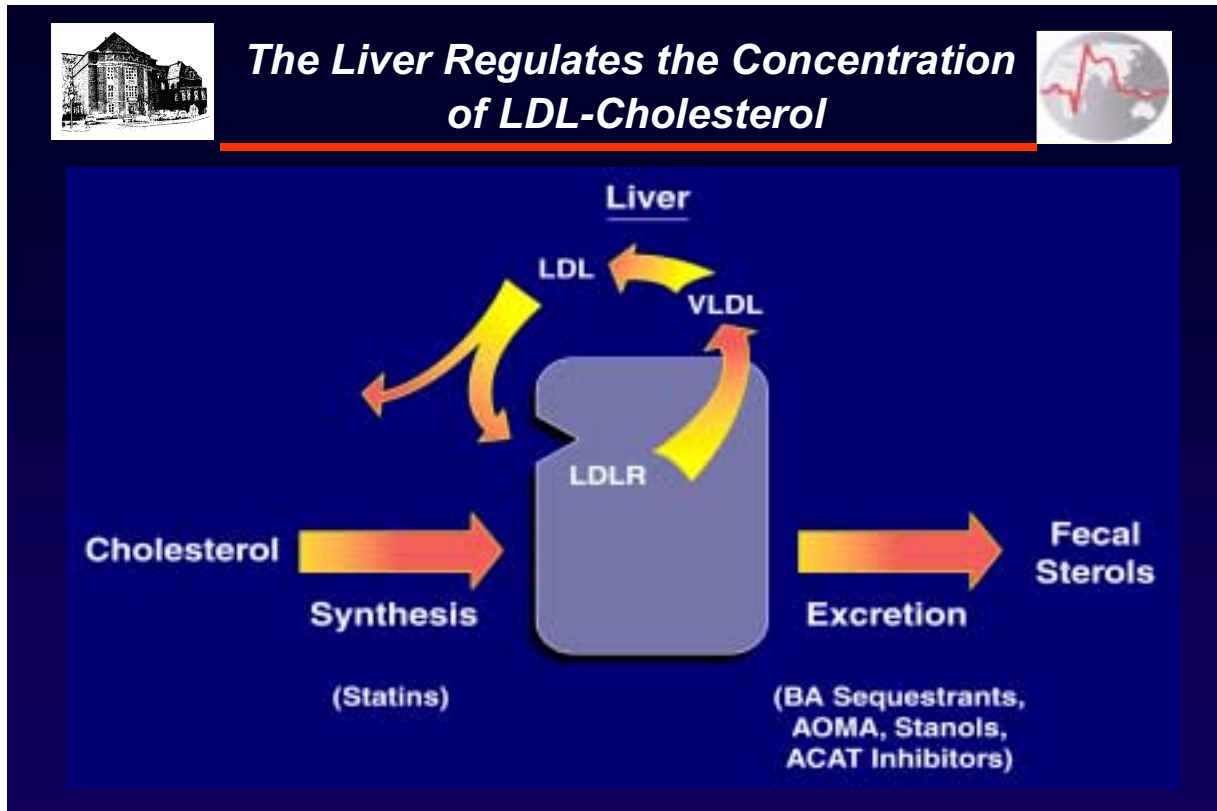


Net cholesterol balance in humans.

Extrahepatic organs synthesize on average ~900 mg of cholesterol per day. In addition, humans take up on average ~300 mg of cholesterol per day with the diet. Under equilibrium conditions, the same amount (1.200 mg/day) is excreted as fecal sterols.

Slide 4:

The liver regulates the concentration of LDL cholesterol.

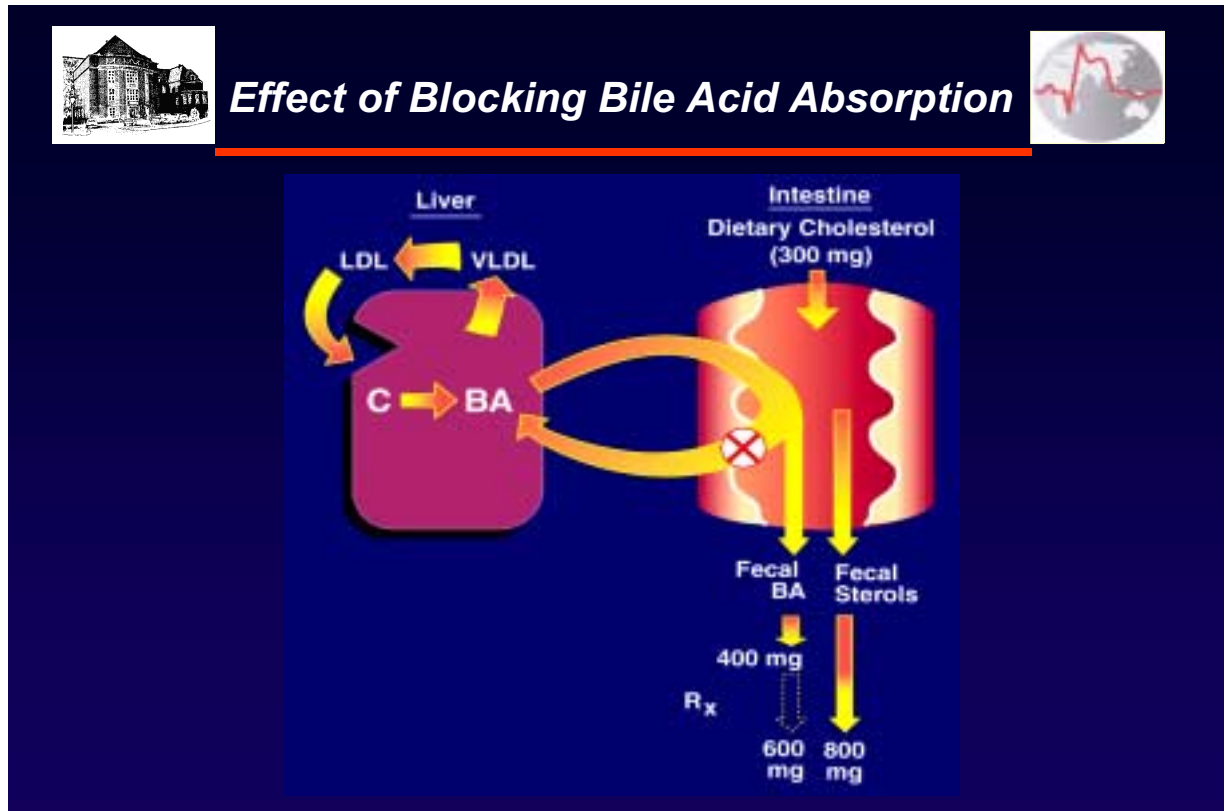


The liver regulates the concentration of LDL cholesterol.

The liver is the sole site of VLDL production, it contains the highest numbers of LDL receptors of all organs and in consequence it regulates the LDL cholesterol concentration by two means: 1) via the rate of VLDL secretion and 2) via the rate of LDL uptake by the LDL receptor. The number of LDL receptors in the liver can be increased by inhibition of cholesterol synthesis with HMG-CoA reductase inhibitors (statins), stimulation of sterol excretion with bile acid sequestrants or inhibition of cholesterol absorption in the intestine with cholesterol absorption inhibitors like a-olefin maleic acid (AOMA), stanols or ACAT inhibitors.

Slide 5:

Effect of blocking bile acid absorption.

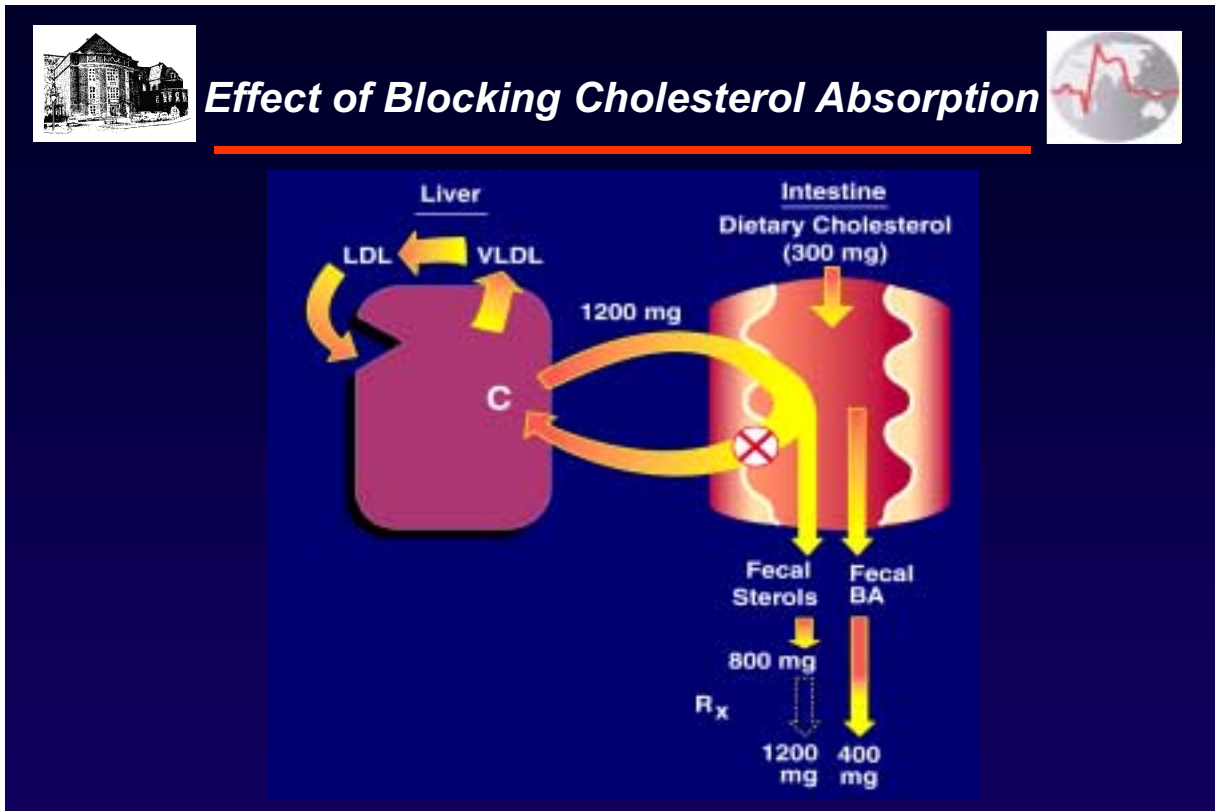


Effect of blocking bile acid absorption.

Blocking bile acid absorption with bile acid sequestrants lowers LDL cholesterol via increasing fecal loss of bile acids which causes enhanced conversion of cholesterol to bile acids, inhibition of VLDL synthesis and stimulation of LDL receptor expression in the liver.

Slide 6:

Effect of blocking cholesterol absorption.

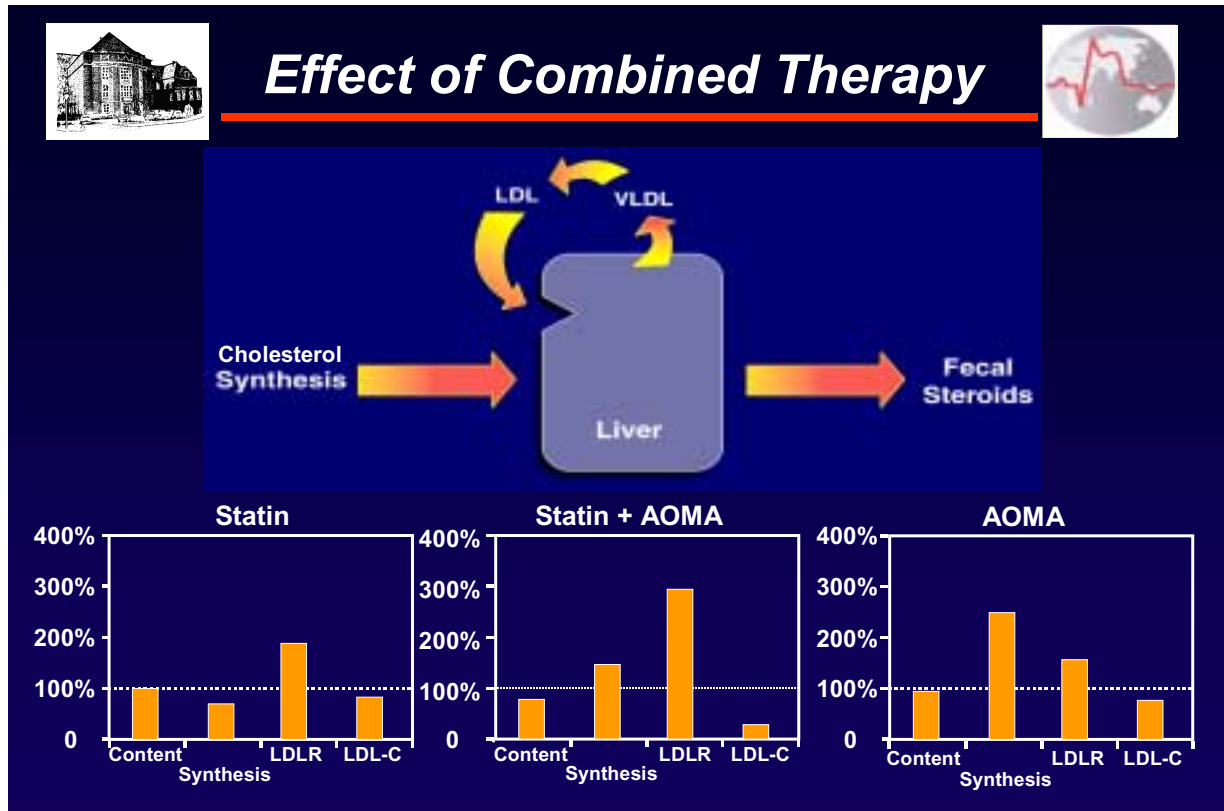


Effect of blocking cholesterol absorption.

Blocking cholesterol absorption in the intestine decreases the uptake of dietary cholesterol and blocks reabsorption of cholesterol which is excreted from the body via the bile duct. However, the effectiveness of the treatment to lower LDL cholesterol is limited by the ability of the body to upregulate cholesterol synthesis.

Slide 7:

Effect of combined therapy.

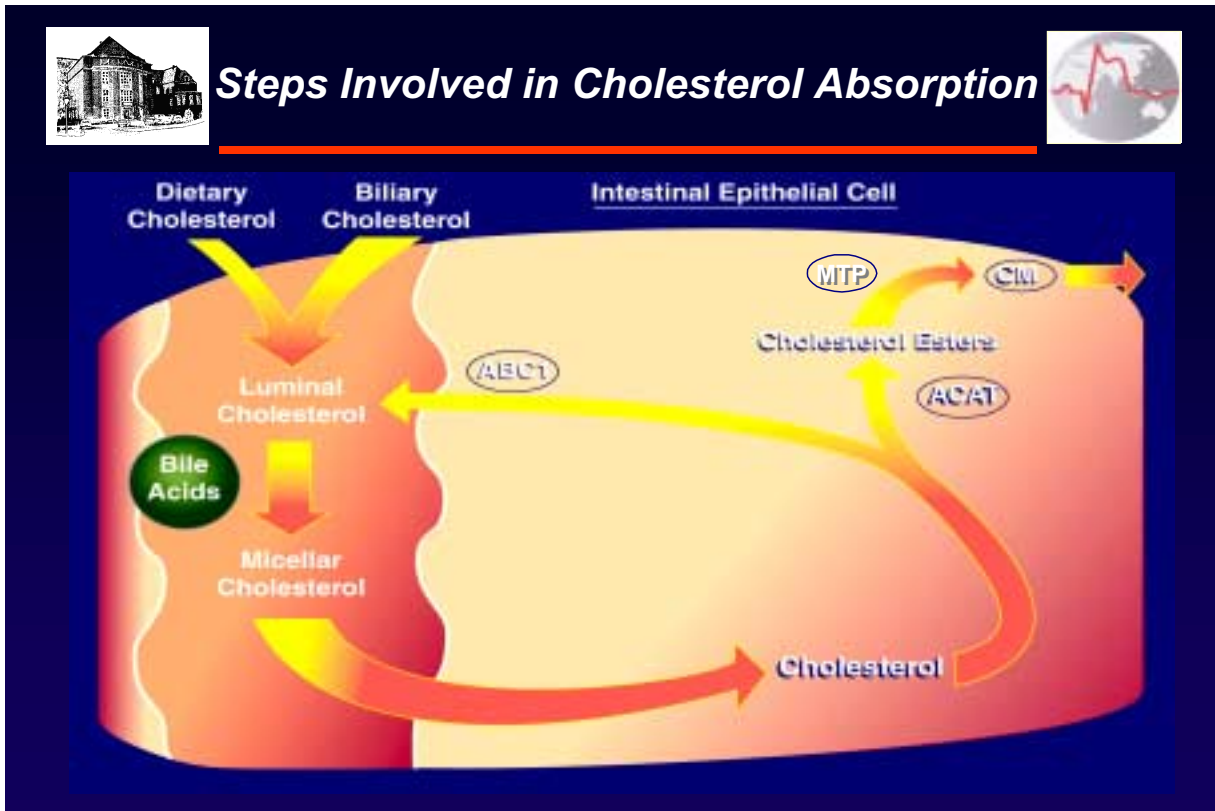


Effect of combined therapy.

Blocking cholesterol absorption in the intestine with a-olefin maleic acid (AOMA) combined with inhibiting cholesterol synthesis with statins provides a very effective cholesterol lowering therapy. Whereas AOMA blocks the uptake of cholesterol by the intestine, statins inhibit the compensatory upregulation of cholesterol synthesis resulting from AOMA treatment alone.

Slide 8:

Steps involved in cholesterol absorption.

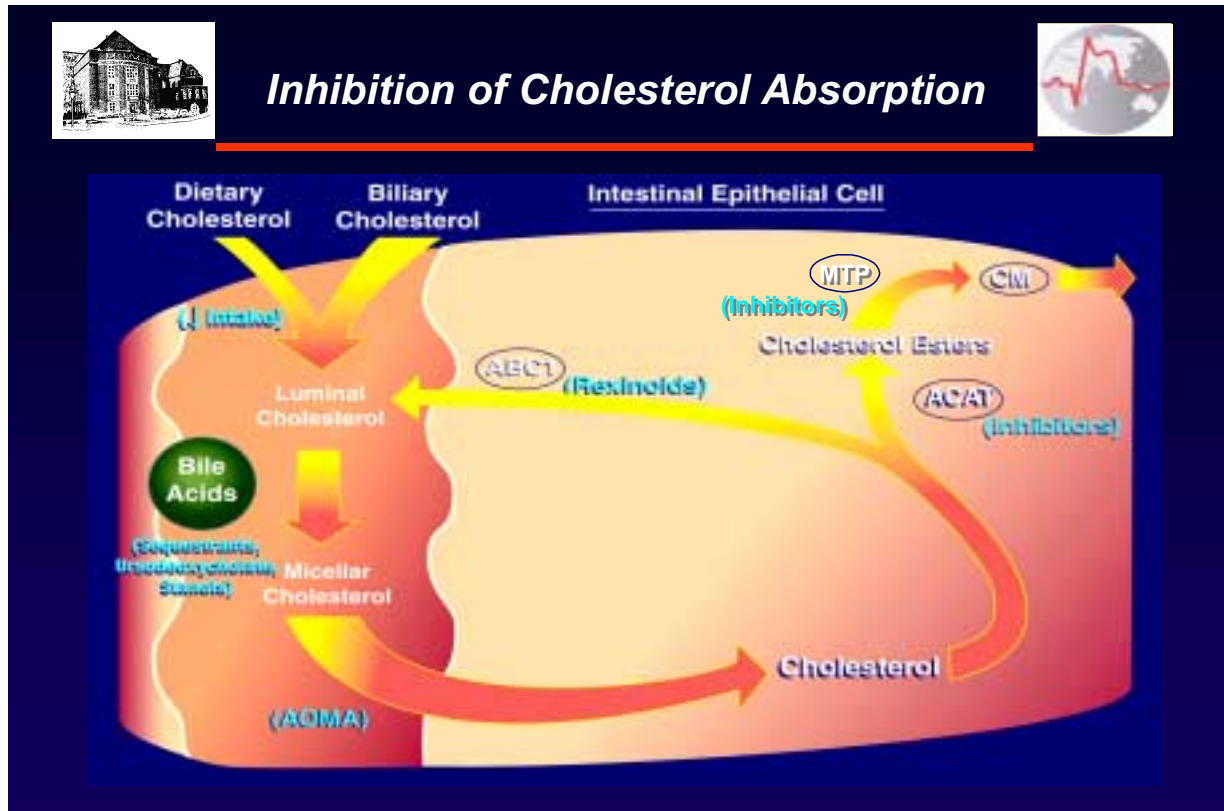


Steps involved in cholesterol absorption.

The slide shows the most important steps which are involved in cholesterol absorption. Bile acids solubilize dietary and biliary cholesterol in micelles which are phagocytosed by intestinal epithelial cells. The phagocytosed cholesterol is esterified with fatty acid by acyl-CoA cholesterol acyl transferase (ACAT, a microsomal enzyme). Cholesterol esters are used by microsomal triglyceride transfer protein (MTP) to assemble chylomicrons which are secreted into the lymph. A significant part of cholesterol that is taken up by the intestinal epithelium is secreted back to the intestinal lumen via the ABC transporter A1 (ABC1).

Slide 9:

Inhibition of cholesterol absorption.

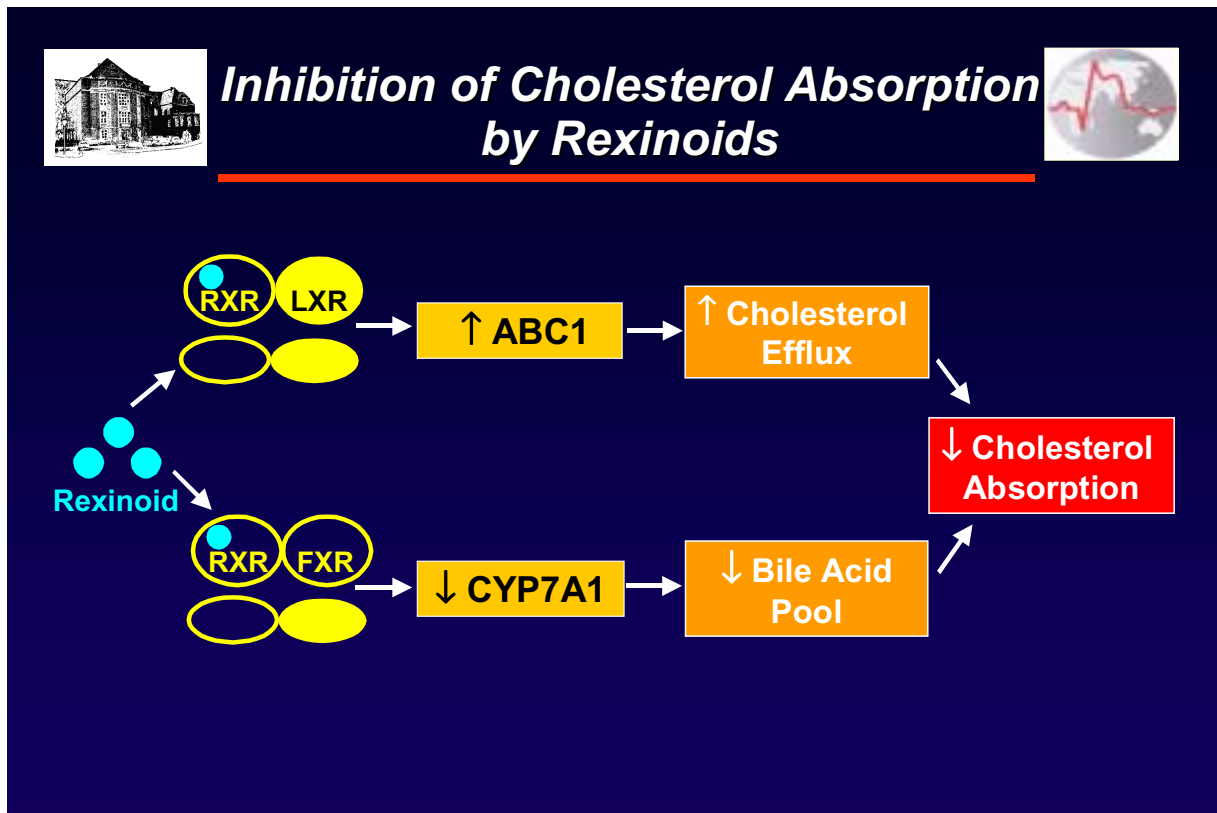


Inhibition of cholesterol absorption.

Inhibition of cholesterol absorption can be achieved by three means: 1) decreasing the bile acid pool size with bile acid sequestrants, ursodeoxycholate or stanols, 2) blocking the uptake of micellar cholesterol by intestinal epithelial cells and 3) stimulation of cholesterol resecretion by ABC1 with rexinoids which activate the retinoid-X-receptor (RXR, a nuclear hormone receptor). α -Olefin maleic acid (AOMA) acts presumably by blocking the uptake of micellar cholesterol.

Slide 10:

Inhibition of cholesterol absorption by Rexinoids.

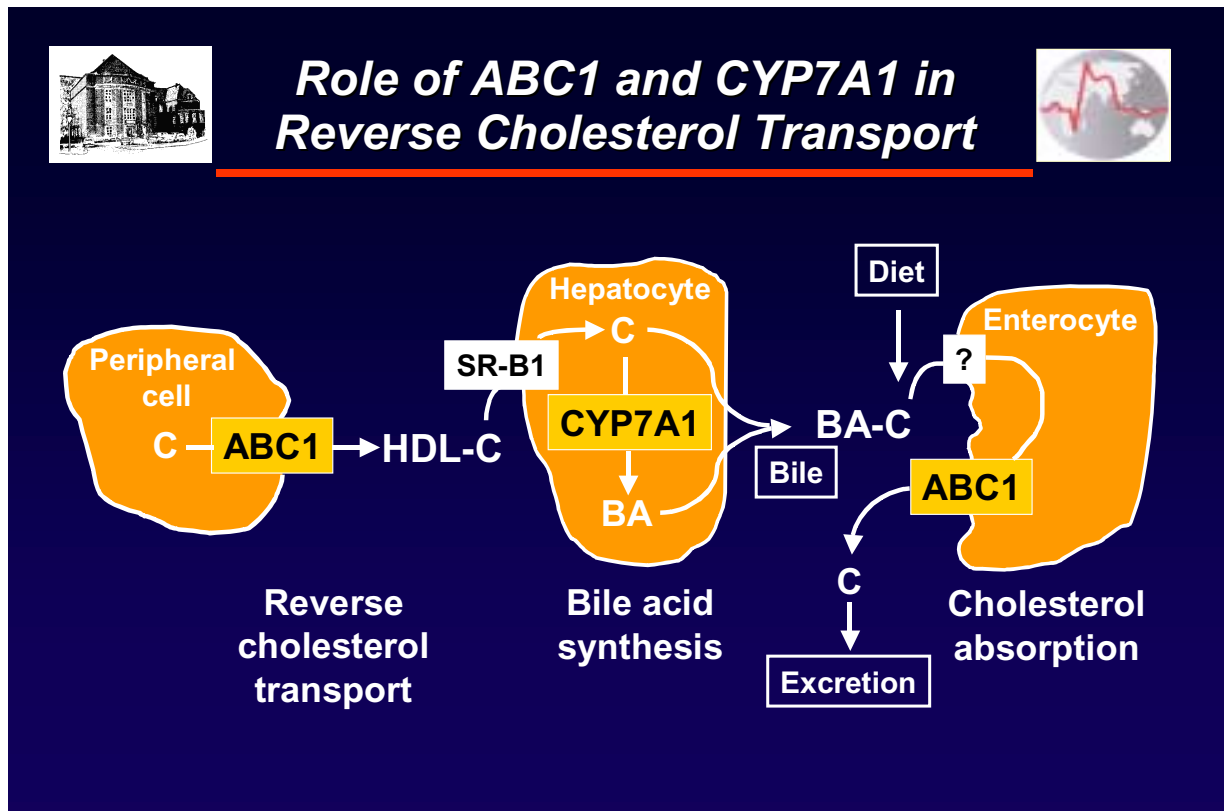


Inhibition of cholesterol absorption by Rexinoids.

Rexinoids stimulate ABC1 gene expression via activation of RXR which leads to heterodimerization of RXR with the liver-X-receptor (LXR, a nuclear receptor which is activated strongly by a number of hydroxylated sterols). RXR/LXR heterodimers promote transcription of the ABC1 gene, thereby increasing cholesterol resecretion into the intestinal lumen. In addition, activated RXR in the liver can form heterodimers with the farnesoid-X-receptor (FXR, a nuclear receptor that is activated by chenodeoxycholic acid). RXR/FXR heterodimers act negatively on transcription of the gene encoding cholesterol 7 α -hydroxylase (CYP7A1), catalyzing the rate limiting step in bile acid production. Activation of RXR/FXR decreases the bile acid pool size thereby inhibiting cholesterol absorption.

Slide 11:

Role of ABC1 and CYP7A1 in reverse cholesterol transport.




Role of ABC1 and CYP7A1 in reverse cholesterol transport.


Reverse cholesterol transport represents a cholesterol transport pathway in which cholesterol derived from peripheral cells is converted to bile acids in the liver which are excreted with the bile. ABC1 mediates secretion of cholesterol from peripheral cells, which is then transferred to HDL. HDL cholesterol is taken up by the liver via selective cholesterol ester uptake involving SR-B1. In the liver, CYP7A1 catalyzes 7 α -hydroxylation of cholesterol, the rate-limiting step in bile acid synthesis. Bile acids are transported from the liver to the intestine where they facilitate cholesterol absorption by promoting the formation of micellar cholesterol. ABC1 expressed in enterocytes limits cholesterol absorption via its resecretion into the intestinal lumen.

Slide 12:

ABC transporter with function in cholesterol metabolism.



ABC Transporter with Function in Cholesterol Metabolism



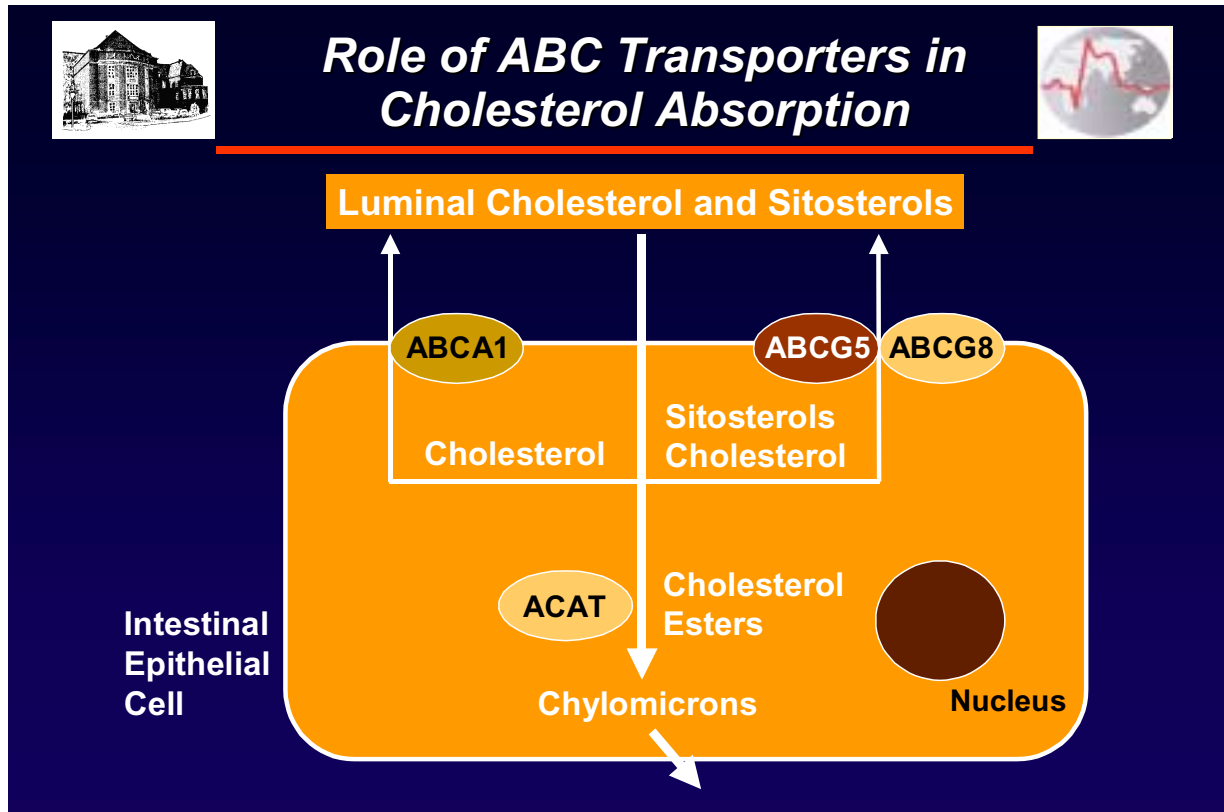
Name	Symbol	Chromosome Human	Chromosome Mouse	RNA	No. of Exons	Remarks
ABC1	ABCA1	9q22-q31	4A5-B3	6.9	48	Tangier Disease
Sterolin-1	ABCG5	2p21	?	2.3	13	Sitosterolemia
Sterolin-2	ABCG8	2p21	?	2.0	13	Sitosterolemia
ABC8	ABCG1	21q22.2-22.3	17A2-B	3.8	15	Sterol sensitive
MDR3	ABCB4	7q21.1	5A2-A3	4.0	28	phospholipids, bile

ABC transporter with function in cholesterol metabolism.

Defects in ABC1 lead to Tangier disease, a monogenic disorder with impaired reverse cholesterol transport and accumulation of cholesterol esters, predominantly in macrophages and Schwann cells. Besides ABC1, other ABC transporters play important roles in cholesterol metabolism. ABCG5 and ABCG8 are heterodimeric transporters which are located at the luminal surface of enterocytes. Defects in each of the two transporters cause familial sitosterolemia, an inherited disorder leading to hyperabsorption of plant and sea food sterols and also of cholesterol. MDR3 (also called ABCB4) is responsible for biliary secretion of phospholipids. The precise function of ABCG1 is still unknown. Its expression is highly dependent upon cellular cholesterol content.

Slide 13:

Role of ABC transporters in cholesterol absorption.



Role of ABC transporters in cholesterol absorption.

This slide shows the overlapping roles of ABC transporters in cholesterol absorption. Both, ABC1 and heterodimeric ABCG5/ABCG8 transporters mediate resecretion of absorbed cholesterol into the intestinal lumen. Whereas ABC1 is selective for cholesterol, ABCG5/ABCG8 is permissive for cholesterol but favors plant and sea food sterols.