Familial Hypercholesterolemia

Dr.Ramzi Al-Mohammadi
Assistant Professor of Medicine
Interventional Cardiologist, Advanced HF and Transplant Consultant

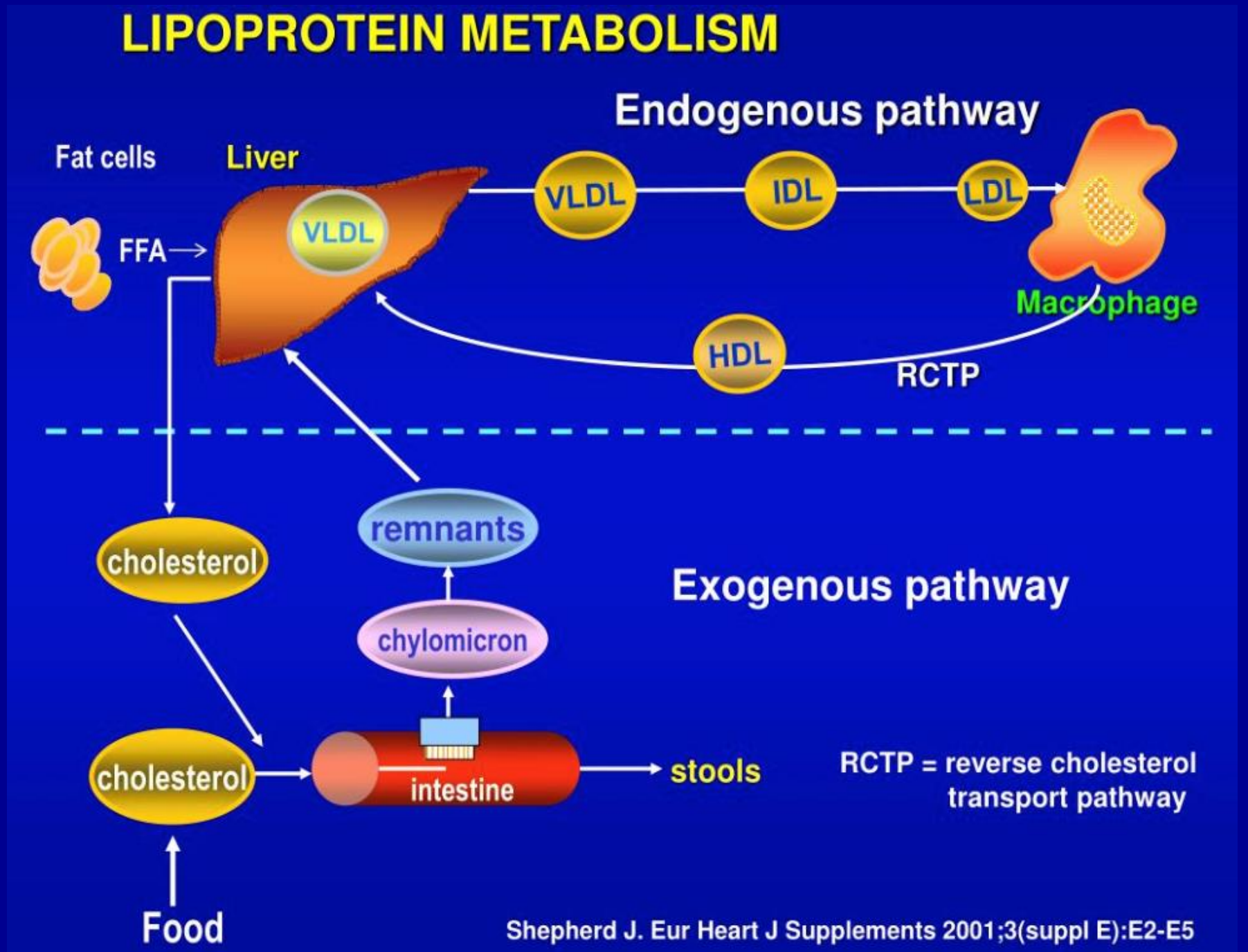
Classification of Hyperlipedemia

- Primary hyperlipedemia: Familial or hereditary

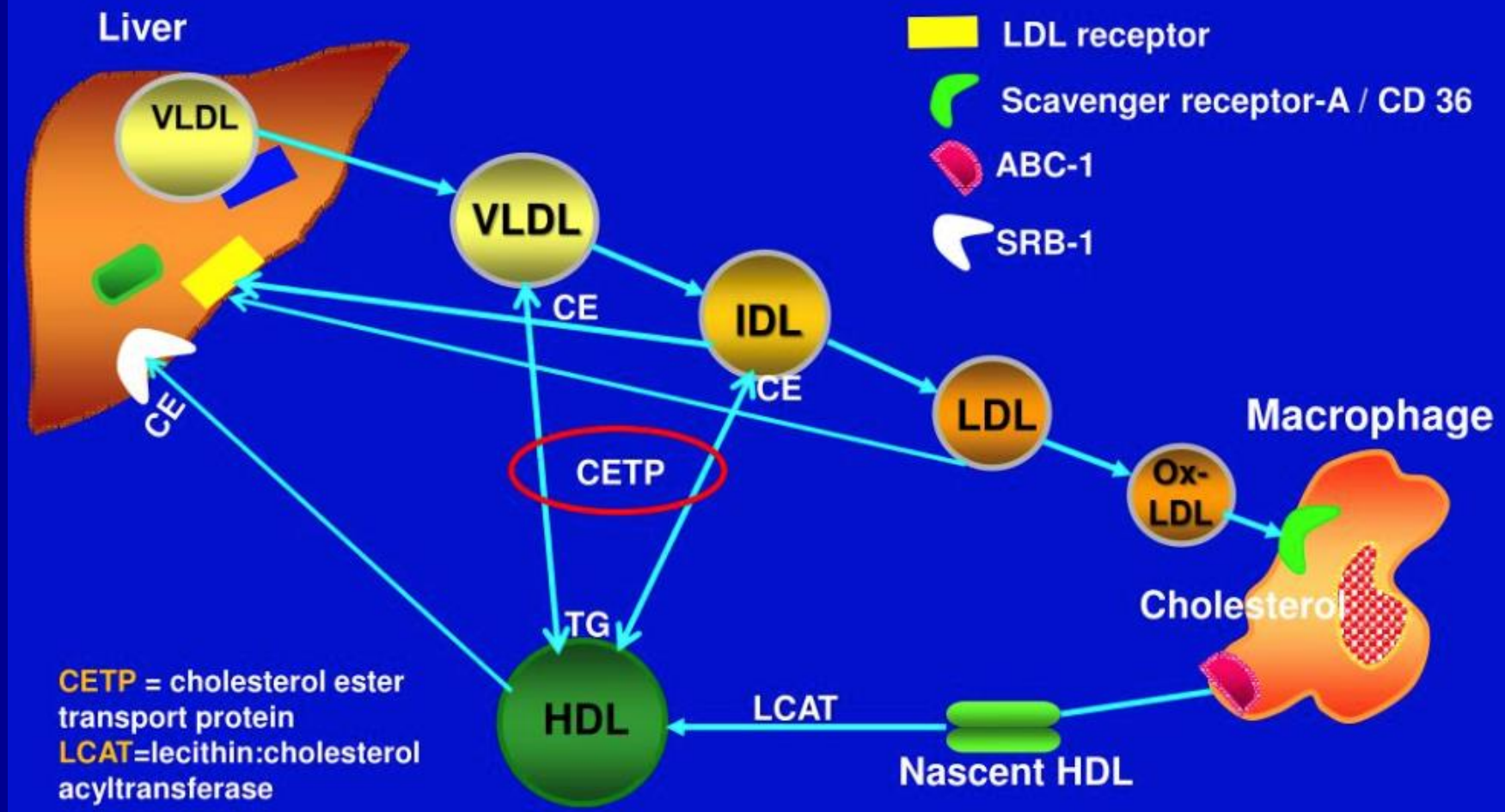
Class	Increased lipoprotein	Synonym
Type I	↑ chylomicrons	Familial chylomicronemia
Type IIa	↑ LDL	Familial hypercholesterolemia
IIb	↑ LDL and VLDL	Familial combined hyperlipidemia
Type III	↑ IDL	Familial dysbetalipoproteinemia
Type IV	↑ VLDL	Familial hypertriglyceridemia
Type V	↑ VLDL and chylomicrons	Familial mixed hyperlipedemia

- Secondary Hyperlipedemia: Acquired

Nephrotic syndrome, Drugs, Hypothyroidism, DM, Alcohol, gout and CRF


LIPOPROTEIN METABOLISM
Endogenous pathway
Fat cells
Liver
VLDL
IDL
LDL
VLDL
FFA
Macrophage
HDL
RCTP
remnants
cholesterol
Exogenous pathway
chylomicron
cholesterol
intestine
stools
RCTP = reverse cholesterol transport pathway
Food
Shepherd J. Eur Heart J Supplements 2001;3(suppl E):E2-E5

LIPOPROTEIN METABOLISM – endogenous pathway



Kwiterovich PO, Jr. The metabolic pathways of high-density lipoprotein, low-density lipoprotein, and triglycerides: A current review. Am J Cardiol 2000;86:5L-10L

Familial Hypercholesterolemia

- Familial hypercholesterolaemia is possibly the most common genetic disease in human

- Medical textbooks have previously reported that heterozygous familial hypercholesterolaemia affects 1 in 500 individuals and that homozygous familial hypercholesterolaemia affects 1 in 1,000,000 individuals

Epidemiology

- country specific surveys that used standardized diagnostic criteria reported a prevalence of heterozygous familial hypercholesterolaemia up to twofold higher (between 1 in 219 and 1 in 300)

- the prevalence of homozygous familial hypercholesterolaemia is now thought to be much higher, namely, 1 in 300,000 individuals

Epidemiology

- Prevalence differs between populations, with higher prevalence in, for example, Afrikaners (1 in 76), French Canadians (1 in 270) and Christian Lebanese individuals (1 in 90)

CVS Risk

- Screening of patients who had a myocardial infarction at <50 years of age showed that ~2% have a molecular diagnosis of familial hypercholesterolaemia

- Early CVD (especially early myocardial infarction), stroke and increased total mortality risk are, therefore, cardinal features of all forms of untreated familial hypercholesterolaemia

Genes associated with LDL cholesterol levels

Disease	Gene/Function	Prevalence
Familial Hypercholesterolemia	*LDLR* / LDL endocytosis	Heterzygous 1:500 (all ethnic groups) homozygous <1:10^6
Familial Defective ApoB100 (ligand defective ApoB)	*APOB* / LDL endocytosis	1:500 to 750 in whites 1:1,250 in all others
Autosomal recessive hypercholesterolemia	*ARH* / LDLR adaptor protein	Sardinia and Lebanon
Autosomal dominant hypercholesterolemia	*CYP7A* / rate limiting enzyme of cholesterol degradation	Very rare
Autosomal dominant hypercholesterolemia	*PCSK9* / serum protease that degrades LDLR	Very rare- activating (better destruction of LDLR) mutations

Management

The goal of management is the primary prevention of atherosclerotic CVD through lipid lowering therapy

- if atherosclerosis is already present, even more intensive lipid lowering treatment becomes crucial

- The causative gene does not seem to have a role in the choice of optimal treatment. Although patients with *PCSK9* mutations might have a superior response to PCSK9 inhibitors4

Management of Hyperlipedemia

- Non drugs therapy
- Low calories diet
- Weight reduction
- Exercise
- Stop smoking and alcohol
- Control risk factors eg DM, CRF
- Avoid drugs that increase plasma lipids, steroids, thiazides and BB

Management of Hyperlipedemia

- Drugs Therapy

Drug Class	Agents	Effects (% change)	Side Effects
HMG CoA reductase inhibitors	Lovastatin Pravastatin	↓**LDL (18-55)**,↑ HDL (5-15) ↓ Triglycerides (7-30)	Myopathy, increased liver enzymes
Cholesterol absorption inhibitor	Ezetimibe	↓ LDL(14-18), ↑ HDL (1-3) ↓Triglyceride (2)	Headache, GI distress
Nicotinic Acid		↓LDL (15-30), ↑ **HDL (15-35)** ↓ **Triglyceride (20-50)**	Flushing, Hyperglycemia, Hyperuricemia, GI distress, hepatotoxicity
Fibric Acids	Gemfibrozil Fenofibrate	↓LDL (5-20), ↑HDL (10-20) ↓**Triglyceride (20-50)**	Dyspepsia, gallstones, myopathy
Bile Acid sequestrants	Cholestyramine	↓ LDL ↑ HDL No change in triglycerides	GI distress, constipation, decreased absorption of other drugs

Pharmacological Therapy

- **Statin Drugs**
- All statins can reduce LDL cholesterol in familial hypercholesterolaemia, and the absolute reductions achieved in heterozygous familial hypercholesterolaemia often exceed those observed in the general population, because of the higher baseline LDL .

- Statins reduce CVD risk in both homozygous and heterozygous familial hypercholesterolaemia

- Statins are generally well tolerated by patients with familial hypercholesterolaemia

Pharmacological Therapy

- **Statin Drugs**
- Statin intolerance occurs in 10–15% of patients with familial hypercholesterolaemia

- The management of statin intolerance in these patients is similar to that in other groups with high CVD risk

Pharmacological Therapy

- **Non-Statin Drugs**
- Most patients with familial hypercholesterolaemia, statins alone are insufficient to normalize LDL cholesterol levels, and ezetimibe and PCSK9 inhibitors should be added

- studies of ezetimibe in familial hypercholesterolaemia have shown that adding this drug to any dose of a statin leads to a 20% additional reduction in LDL cholesterol

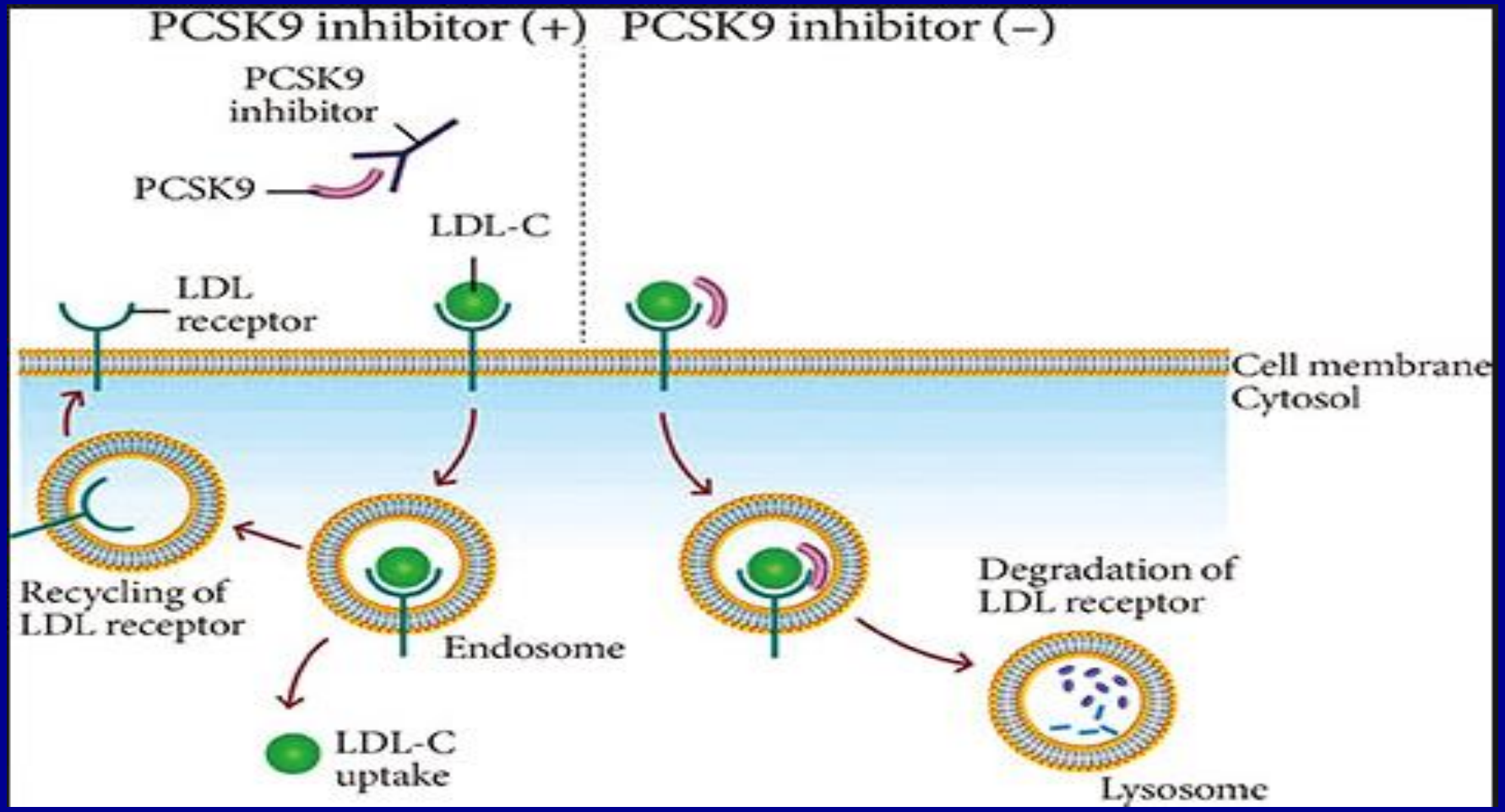
- Triple therapy with a statin, ezetimibe and a bile acid sequestrant can also be used (no data suggest that any of these second line and third line agents reduce CVD events in familial hypercholesterolaemia)

Pharmacological Therapy

- **PCSK 9 Inhibitors:**
- deliver a dose dependent LDL cholesterol reduction of 50–65% in patients with familial hypercholesterolaemia and enable most patients to reach LDL cholesterol levels and prevention targets comparable to those of the general population

- Outcomes data from US national lipid association published in 2017 show that adding PCSK9 inhibitors to statin treatment further reduces CVD events in high risk patients with persistent inadequately controlled LDL cholesterol levels

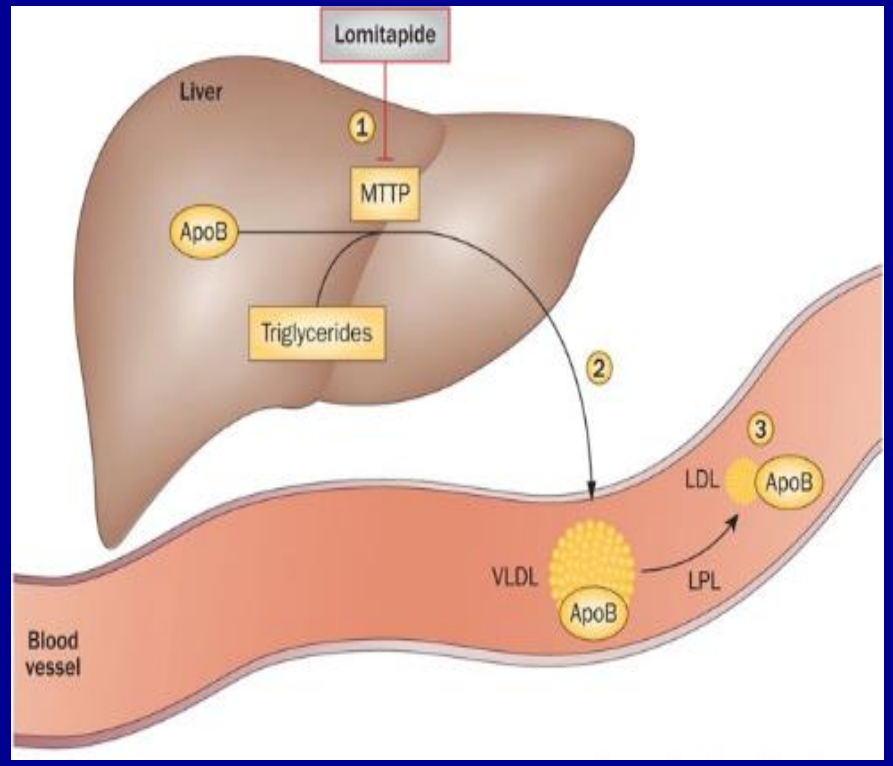
Pharmacological Therapy



Pharmacological Therapy
homozygous familial hypercholesterolaemia

- **Lomitapide**

  Oral inhibitor of microsomal triglyceride transfer protein large subunit (MTTP), which is required for the assembly and secretion of lipoproteins that contain apo B100.

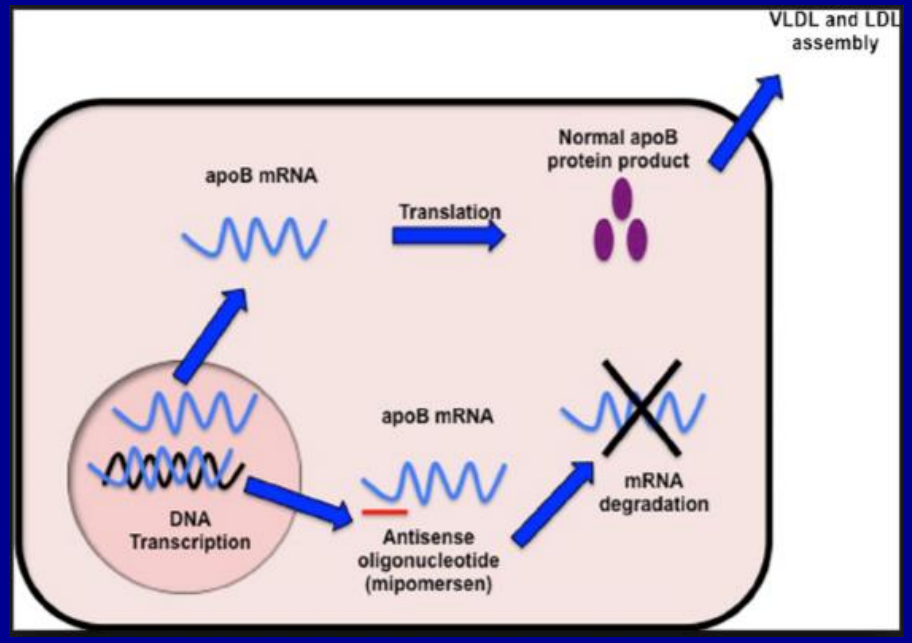


Pharmacological Therapy

homozygous familial hypercholesterolaemia

- **Mipomersen**

  Antisense oligonucleotide that binds to *APOB* mRNA and inhibits its translation, thereby reducing apo B100 synthesis and secretion



Emerging Therapies

- **New LDL lowering agents**
- Antisense oligonucleotide

1. a long acting small interfering RNA inhibitor of PCSK9 synthesis .

2. studied in 501 patients in a phase II study.
3. dose dependent reductions in LDL cholesterol were observed at 6 months: reductions of 28–42% after a single dose of inclisiran and 36–53% after two doses

Emerging Therapies

- **New LDL lowering agents**
- BMS962476

  PCSK9targeted adnectin conjugated to polyethylene glycol, reduced LDL cholesterol by 48% and PCSK9 levels by >90% after subcutaneous injection in a phase I study

Gene Therapy

- An adeno associated virus (AAV) vector encoding *LDLR* cDNA induced a significant reduction of hypercholesterolaemia in a humanized mouse model

- After injection of a low dose of the AAV vector containing *LDLR*, the animals expressed human LDLR and apo B100

THANK YOU