FARMAKOLOGI
OBAT HIPOLIPIDEMI

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Hyperlipidemia

Hyperlipidemia is an increase (*hyper*) in the **lipids** (*lipi*), which are a group of fats or fatlike substances in the blood (*demia*). **Cholesterol** and the **triglycerides** are the two lipids in the blood. Elevation of one or both of these lipids is seen in hyperlipidemia. Serum cholesterol levels above 240 mg/dL and triglyceride levels above 150 mg/dL are associated with atherosclerosis. **Atherosclerosis** is a disorder in which lipid deposits accumulate on the lining of the blood vessels, eventually producing degenerative changes and obstruction of blood flow. Atherosclerosis is considered to be a major contributor in the development of heart disease.

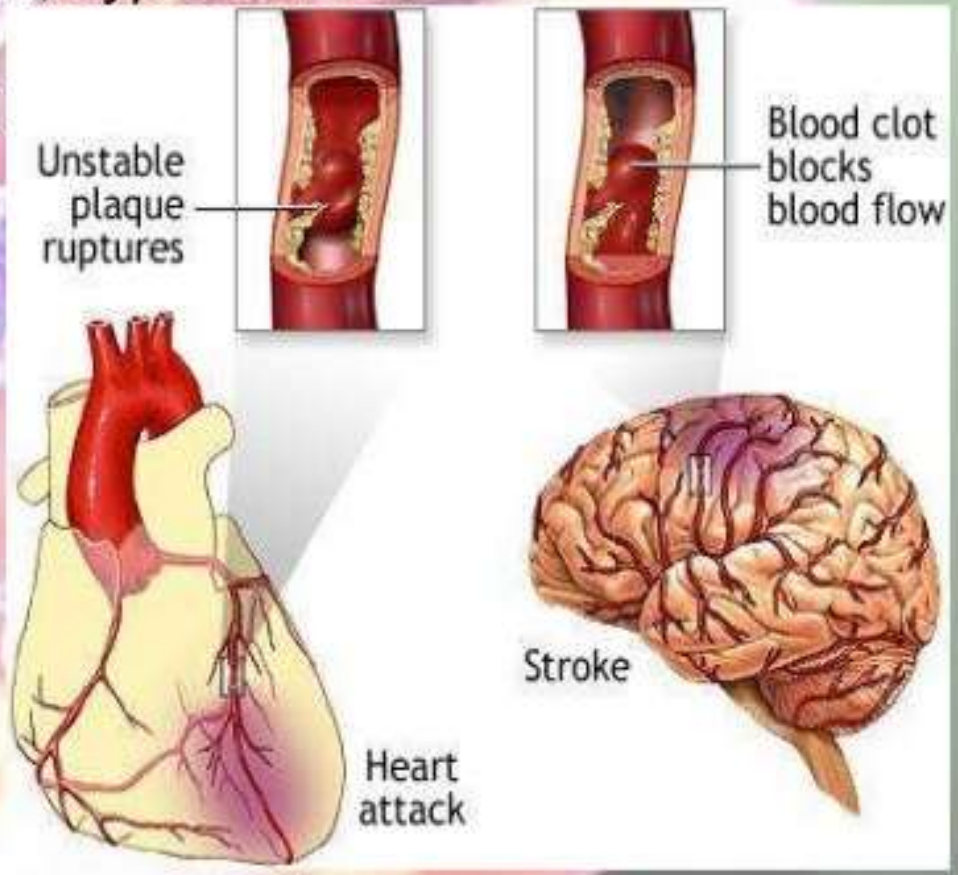
INTRODUCTION

- **Hyperlipidemia Hyperlipoproteinemia** means abnormally increased plasma lipoproteins-one of the risk factors for atherosclerosis (deposition of fats at walls of arteries, forming plaque)

- **Other risk factors**-*Cigarette smoking, Diabetes*, another source of oxidative stress. Also, obesity and, *hypertension*.

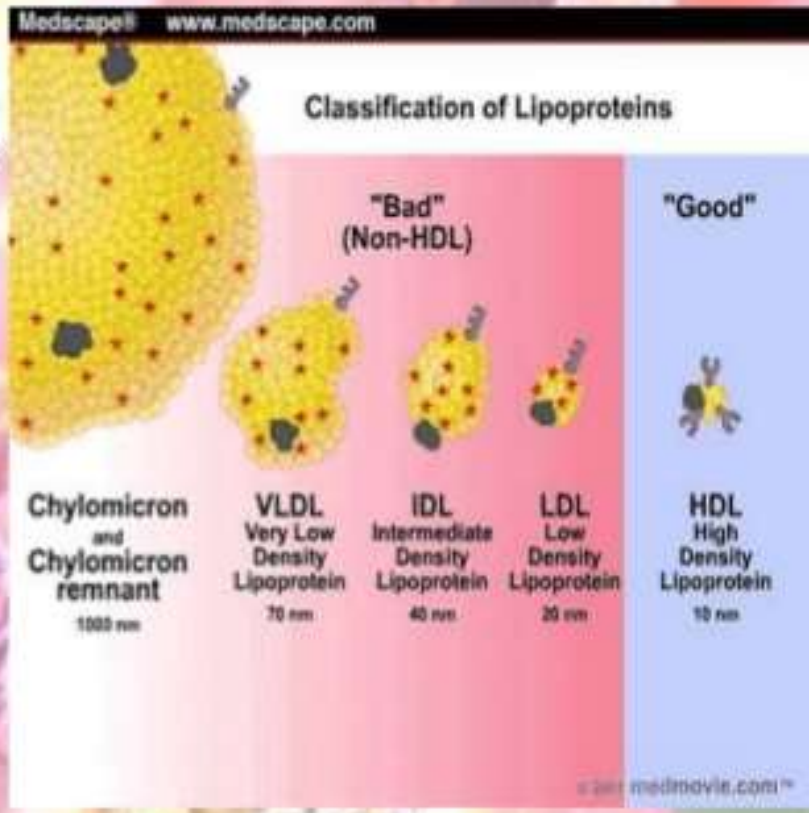
- ***Hyperlipemia*** denotes increased levels of triglycerides.

- Such abnormality is extremely common in general population, regarded as highly modifiable risk factor for cardio vascular diseases, due to influence of cholesterol.



Types of lipoproteins

1. **Chylomicrons (TGs)**: → formed in GIT from dietary TG.
2. **VLDL (TGs and cholesterol)** → endogenously synthesized in liver. Degraded by LPL into free fatty acids (FFA) for storage in adipose tissue and for oxidation in tissues such as cardiac and skeletal muscle.
3. **IDL (TGs, cholesterol)**; **and LDL (cholesterol)** → derived from VLDL hydrolysis by ***lipoprotein lipase.*** Normally, about *70% of LDL* is removed from plasma by hepatocytes.
4. **HDL (protective)** →exert several *anti atherogenic* effects. They participate in retrieval of cholesterol from the artery wall and inhibit the oxidation of atherogenic lipoproteins& removes cholesterol from tissues to be degraded in liver.



	Composition	Density	Size
Chylomicrons	TG >> C, CE	Low	Large
VLDL	TG > CE		
IDL	CE > TG		
LDL	CE >> TG		
HDL	CE > TG	High	Small

CAUSES of hyperlipidemias

Hyperlipidemias can be:

(i)Secondary: associated with diabetes, myxoedema, nephrotic syndrome, chronic alcoholism, drugs (corticosteroids, oral contraceptives, β blockers) (Commonest)

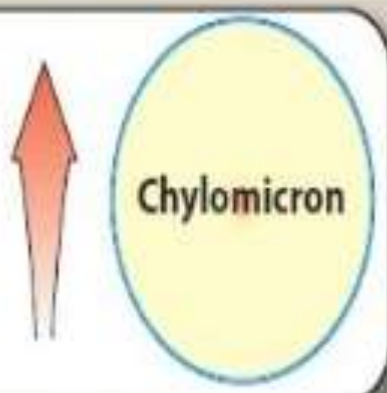
(ii) *Primary: due to:*

(a) A single gene defect: is familial and called 'monogenic' or *genetic*.

(b) Multiple genetic, dietary and physical activity related causes: 'polygenic' or *multifactorial*

Type I (FAMILIAL HYPERCHYLOMICRONEMIA)

- Massive fasting hyperchylomicronemia, even following normal dietary fat intake, resulting in greatly elevated serum TG levels.
- Deficiency of lipoprotein lipase or deficiency of normal apolipoprotein CII (rare).
- Type I is not associated with an increase in coronary heart disease.
- Treatment: Low-fat diet. No drug therapy is effective for Type I hyperlipidemia.



Type IIA (FAMILIAL HYPERCHOLESTEROLEMIA)

- Elevated LDL with normal VLDL levels due to a block in LDL degradation. This results in increased serum cholesterol but normal TG levels.
- Caused by defects in the synthesis or processing of LDL receptors.
- Ischemic heart disease is greatly accelerated.
- Treatment: Diet. Heterozygotes: *Cholestyramine* and *niacin*, or a statin.

Type IIB (FAMILIAL COMBINED [MIXED] HYPERLIPIDEMIA)

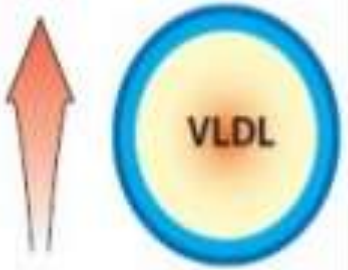
- Similar to Type IIA except that VLDL is also increased, resulting in elevated serum TG as well as cholesterol levels.
- Caused by overproduction of VLDL by the liver.
- Relatively common.
- Treatment: Diet. Drug therapy is similar to that for Type IIA .

Type III (FAMILIAL DYSBETALIPOPROTEINEMIA)

- Serum concentrations of IDL are increased, resulting in increased TG and cholesterol levels.
- Cause is either overproduction or underutilization of IDL due to mutant apolipoprotein E.
- Xanthomas and accelerated vascular disease develop in patients by middle age.
- Treatment: Diet. Drug therapy includes *niacin* and *fenofibrate*, or a statin.

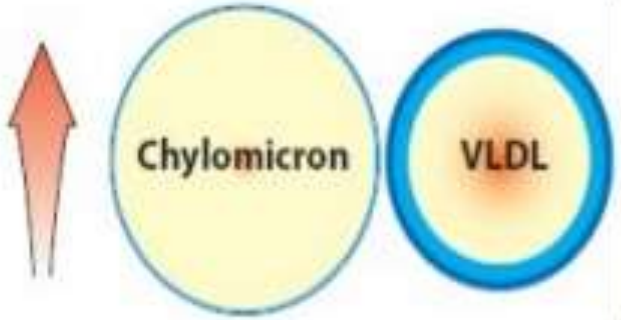
Type IV (FAMILIAL HYPERTRIGLYCERIDEMIA)

- VLDL levels are increased, whereas LDL levels are normal or decreased, resulting in normal to elevated cholesterol, and greatly elevated circulating TG levels.
- Cause is overproduction and/or decreased removal of VLDL and TG in serum.
- This is a relatively common disease. It has few clinical manifestations other than accelerated ischemic heart disease. Patients with this disorder are frequently obese, diabetic, and hyperuricemic.
- Treatment: Diet. If necessary, drug therapy includes *niacin* and/or *fenofibrate*.



Type V (FAMILIAL MIXED HYPERTRIGLYCERIDEMIA)

- Serum VLDL and chylomicrons are elevated. LDL is normal or decreased. This results in elevated cholesterol and greatly elevated TG levels.
- Cause is either increased production or decreased clearance of VLDL and chylomicrons. Usually, it is a genetic defect.
- Occurs most commonly in adults who are obese and/or diabetic.
- Treatment: Diet. If necessary, drug therapy includes *niacin*, and/or *fenofibrate*, or a statin.



Diagnosis of hyperlipidemia

- Diagnosis is typically based on medical history, physical examination and blood test done after overnight fasting.

History and physical examination:

- Presence of cardiovascular risk factors or cardiovascular disease
- Family history of premature cardiovascular disease, hyperlipidemia, or diabetes mellitus
- Diabetes mellitus or glucose intolerance
- Central obesity
- High blood pressure
- Presence or absence of risk factors
- Presence or absence of kidney or liver disease, peripheral vascular disease, abdominal aortic aneurysm, cerebral vascular disease

- LDL-C < 100 mg/dL----------Optimal
  - 100-129 mg/dL ----------Near or above optimal
  - 130-159 mg/dL----------Borderline high
  - 160-189 mg/dL ----------High
  - > or = 190 mg/dL ----------Very high
- Total -C
  - <200 mg/dL---------- Desirable
  - 200-239 mg/dL----------Borderline high
  - > or= 240 mg/dL----------High
- TG-C:
  - <150 mg/dL----------Optimal
  - 150-199 mg/dL ----------Borderline high
  - 200-499 mg/dL ----------High
  - > or = 500 mg/dL ----------Very high
- HDL cholesterol:
  - <40 mg/dL ----------Low
  - >60 or = 60 mg/dL ---------- High

Tata Laksana Hiperlipidemia

Management:

Lipid lowering therapies have a key role in the secondary and primary prevention of CVS disease. Assessment of absolute risk, treatment of all modifiable risk factors and optimization of life style factors especially diet and exercise are central to the management.

Non pharmacological treatment:

1- *Reduce intake of saturated fat to less than 7-10% of total energy.*
2- *Reduce intake of cholesterol to less than 250mg/day.*
3- *Reduce sources of saturated fat and cholesterol by low fat dietary products and low glycemic index carbohydrates.*
4- *Consumption of vegetable, fruits, legumes & fish.*
5- *Supplementary intake of fish oil (contain n3 FA) & dietary fibers.*
6- *Achieve ideal body weight and increase activity and exercise.*
7- *Reduce or stop alcohol intake, also stop smoking.*

HYPOLIPIDAEMIC (Antihyperlipidemic) DRUGS

- These are drugs which lower the levels of lipids and lipoproteins in blood.
- The hypolipidaemic drugs have attracted considerable attention because of their potential to prevent cardiovascular disease by retarding the accelerated atherosclerosis in hyperlipidaemic individuals.

Anti-hyperlipidemic drugs are mainly classified into five types they are:

- **1. HMG CoA REDUCTASE INHIBITORS:**

  E.g.: Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin.

- **2. FIBRATES:**

  E.g.: Fenofibrate, Gemfibrozil, Clofibrate.

- **3. Nicotinic acid:**

  E.g: NIACIN.

- **4. BILE ACID SEQUESTRANTS:**

  E.g.: Colesevelam, Colestipol, Cholestyramine

- **5. CHOLESTEROL ABSORPTION INHIBITORS:**

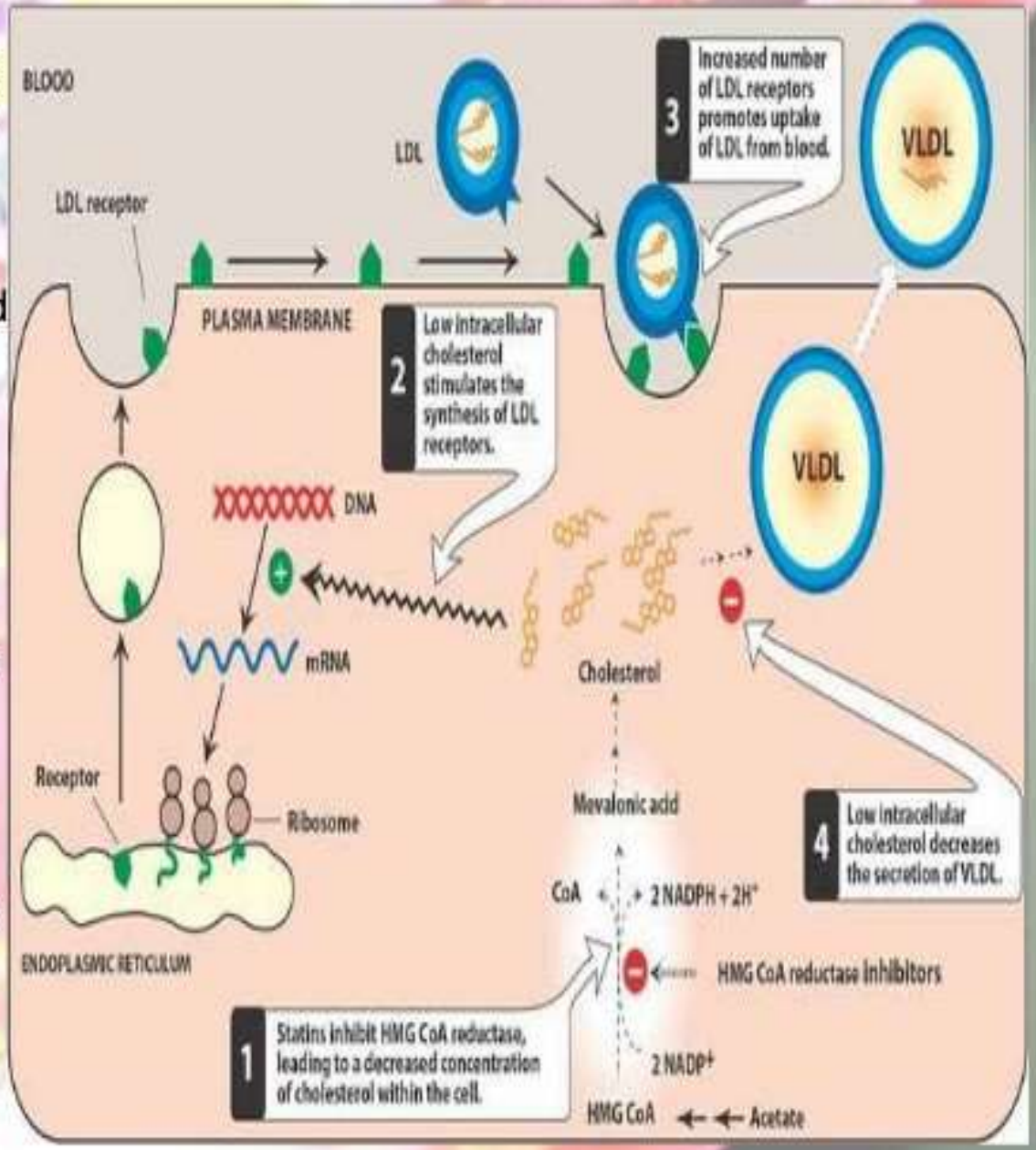
  E.g.: Ezetimibe.

A. HMG CoA reductase (STATIN)

- **Mis. Simvastatin , fluvastatin, atorvastatin, lovastatin, Pravastatin**
- **Mekanisme Kerja :**
  - ✓ **Menghambat enzim 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase** yg mengkatalisa biosintesa kolesterol ⇨ sintesa kolesterol dan VLDL di hepar ↓
  - ✓ **Me ↑ reseptor LDL di hepar** ⇨ clearance LDL-C ↑⇨ LDL ↓
  - ✓ Pd dosis tinggi, atorvastatin dan simfastatin dpt **me ↓ kdr TG**
  - ✓ Beberapa statin dpt **me ↑ kdr HDL-C**
- **Tdk effektif pd keadaan disfungsional reseptor LDL**

Mechanism of action:(statins)

- Structural **analogues of *HMG – COA reductase*** (the rate limiting enzyme in cholesterol synthesis) → reduction of cholesterol synthesis in liver → **compensatory ↑ in synthesis of LDL receptors** on hepatic and extra hepatic tissues →Increase in hepatic **uptake of circulating LDL** which **decreases *plasma LDL*** cholesterol .
- - Decrease TGs to some extent and ↑ **HDL.**
- - Cardio protective: **vasodilators** and **decrease atherosclerosis** (stabilize plaque).
- **Therapeutic uses:**
- - Effective in *all types of hyperlipidemia except* those who are homozygous for familial hypercholesterolemia (lack of LDL receptors).
- Usually combined with other drugs.



Efek Kardioprotektif Statin

- **Pd sel endhotel : me ↑ sintesa NO**
- **Pd stabilitas plaque : me↓ degradasi matriks oleh metalloproteinases**
- **Pd reaksi inflamasi : antiinflamasi?**
- **Pd oksidasi lipoprotein : me↓ oksidasi LDL dan uptake oleh makrofag**
- **Pd koagulasi darah : me ↓ aggregasi platelet dan perubahan kadar fibrinogen**

Potential mechanisms of benefit of statins

HMG Co A reductase inhibitor

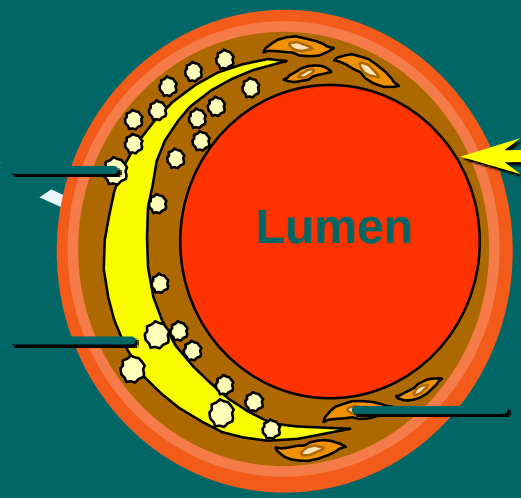
Statins*

Reduction in chylomicron and VLDL remnants, IDL, LDL-C

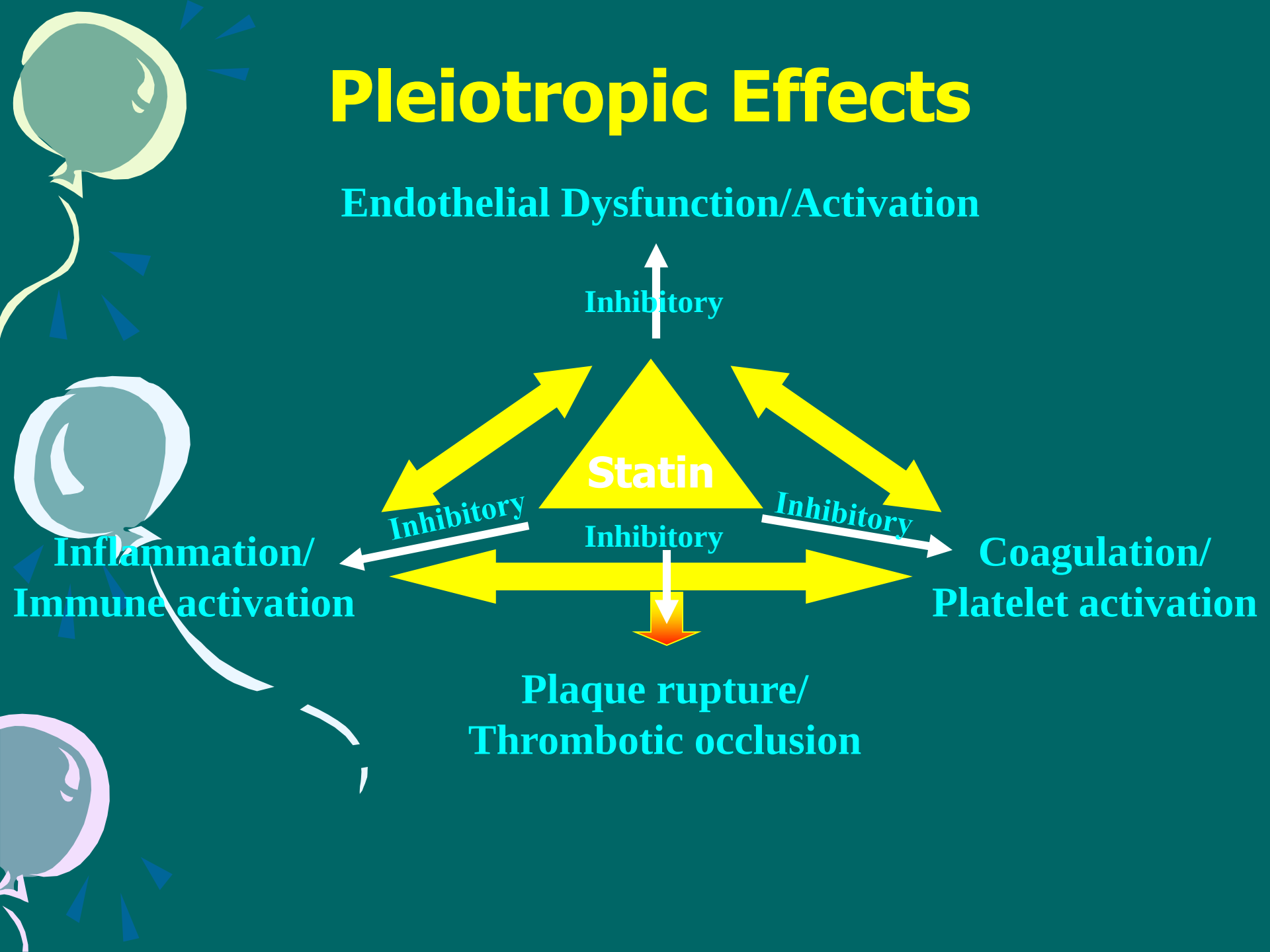
Lipid lowering effect

Pleitrophic effect

1. Anti-inflammatory effects
2. Decreased thrombosis
3. Restore endothelial function
4. Maintain SMC function



Pleiotropic Effects

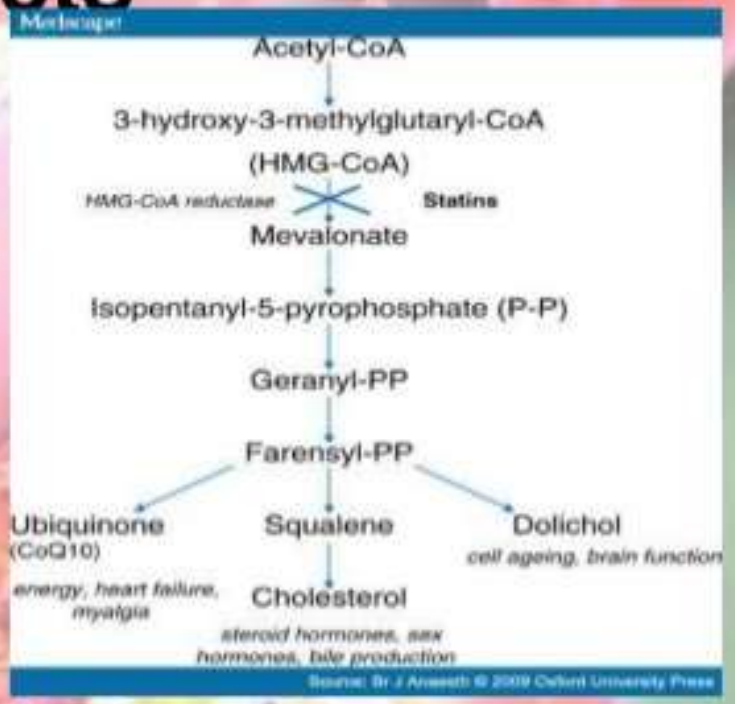


Farmakokinetik Statins

- Mengalami " first pass metabolism"
- Atorvastatin mempunyai T½ lebih panjang (30 jam) drpd statin lain (1-4 jam)
- Diberikan menjelang tidur malam – aktivitas HMG Co-A reductase maksimal pd tengah malam s.d pk 02.00
- KI : ibu hamil dan menyusui
- Baik jk dikombinasi dg resin (cholestyramine & colestipol), niacin atau fibrat

Adverse effects

- 1- Increase in liver enzymes (serum transaminases should be monitored continuously ,**CI** in hepatic dysfunction).
- 2-**Myopathy and muscle damage**Inhibits the production of CoQ10, which is essential for the creation of ATP (energy a cell uses).
- Muscle fatigue and weakness is caused by the disruption of CoQ10 production(95% source of ATP) and resulting lack of ATP production-esp in heart, liver and kidney which have the highest CoQ_{10} concentrations.
- 3- **Cataract** and **GIT** upset.
- 4- Increase in warfarin levels.
- 5- **CI** in pregnancy and nursing mothers (safety in pregnancy is not established), lactation, children and teenagers.



Efek Samping Statins

Jarang :

- Hepatotoksik (perubahan SGPT)
- myopathy (dpt berlanjut menjadi myoglobinuria dan renal failure),

  t.u jk digunakan bersama obat yg dimetabolisme oleh CYP3A4 (erythromycin, azole antifungals, cyclosporine, antidepressants, nefazodone, protease inhibitor)

Effectiveness of statins:

- **Reduce LDL cholesterol by 18-55%**
  Decrease TG by 7-30%
- **Raise HDL cholesterol by 5-15%**
- **Statins are the most effective in lowering LDL cholesterol**
- **Statins are the most effective in patient who has low HDL and high LDL**

Drug- food interaction:

- Grapefruit juice increases concentration of statins
- Pravastatin, rosuvastatin & fluvastatin concentrations are not affected by grapefruit juice

Monitoring:

- Muscle soreness, tenderness, or pain
- Liver function tests : baseline, 4-6 weeks after starting therapy, and then annually
- Muscle enzyme levels when individual has muscle pain

Avoid use in:

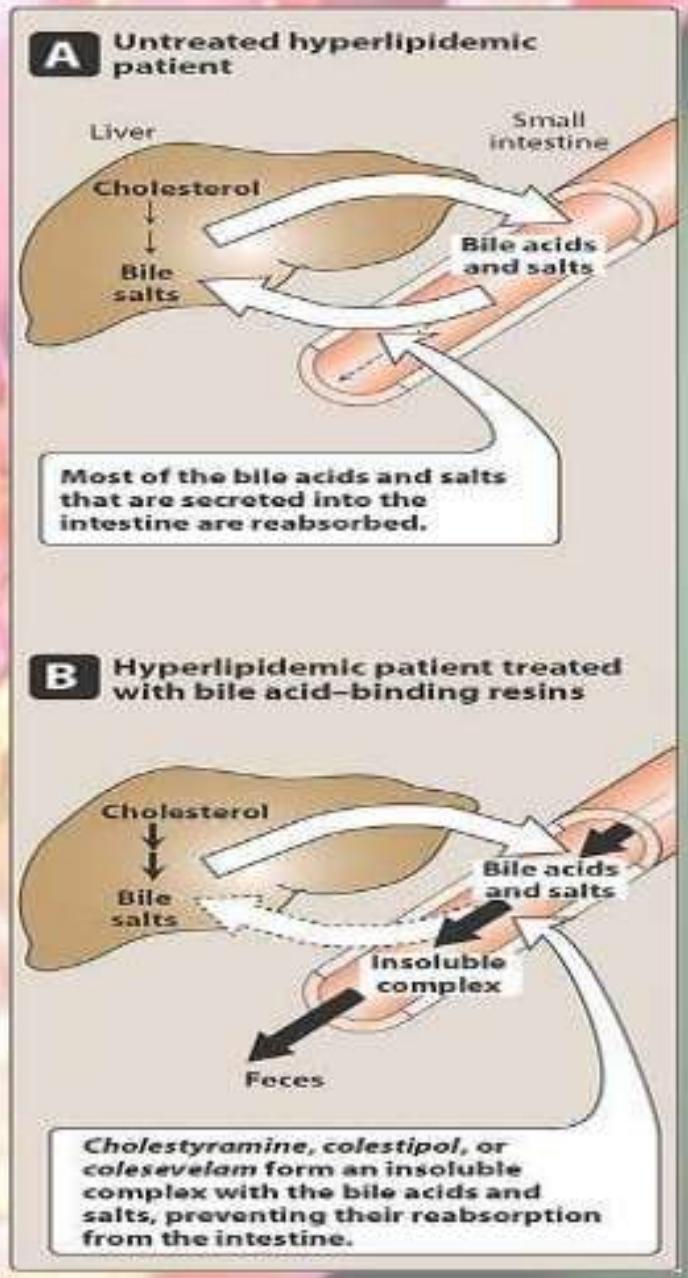
- Active or chronic liver disease and pregnancy

Use with caution with:

- Concomitant use of cyclosporine, macrolide antibiotics, antifungal agents.
  - **For example:** Itraconazole, ketoconazole, erythromycin, clarithromycin, cyclosporine, nefazodone, HIV antiretrovirals
- When statins are used with fibric acids and niacin, appropriate caution should be taken because of increasing incidence of muscle breakdown

B- Bile acids Sequestrants(resins):

- Cholestyramine and colestipol.
- **Mechanism of action:** are **anion exchange resins; bind** bile acids in the intestine forming complex →**loss of bile acids in the stools** →↑ **conversion of cholesterol** into bile acids in the liver.
- Decreased concentration of intrahepatic cholesterol → compensatory **increase in LDL receptors** →↑ hepatic **uptake of circulating LDL** → ↓ **serum *LDL*** *cholesterol levels.*



RESIN (BILE-ACID SEQUESTERAN)

- **Mis : Cholestyramin, Colestipol, Colesevelam**
- **Obat hipolipidemi tertua – second line drugs , dipakai bersama statin.**
- **Satu2-nya obat hiperkolesterol yg direkomendasikan utk anak2 11-20 th**

Therapeutic uses:

- Of choice in treatment of type IIA and IIB hyperlipidemias (along with statins when response to statins is inadequate or they are contraindicated).
- useful for Pruritus in biliary obstruction (↑ bile acids).
- Pharmacokinetics:

Orally given but neither absorbed nor metabolically altered by intestine, totally excreted in feces.

Effectiveness:

- Reduces LDL cholesterol by 15-30%
- Increases HDL cholesterol by 3-5%
- Increases TG

Drug interaction:

- Decreased absorption of fat soluble Vitamins: **A, D, E, K, C and folic acid**
- **Decreased absorption of other drugs:** tetracycline, thiazide diuretics, aspirin, phenobarbital, pravastatin, digoxin

Adverse effects:

- **Constipation** is the most common.
- ↓ **absorption** of fat soluble vitamins (**A, D, K, E)** , ↓ Vit K → hypoprothrombinemia.
- ↓ absorption of **many drugs** as digitoxin, warfarin, aspirin, phenobarbitone.

Side effects:

- Stomach upset, constipation accompanied by heart burn, nausea, and bloating

Avoid use in:

- A disease called dysbetalipoproteinemia
- Triglycerides >400 mg/dL

Use caution if:

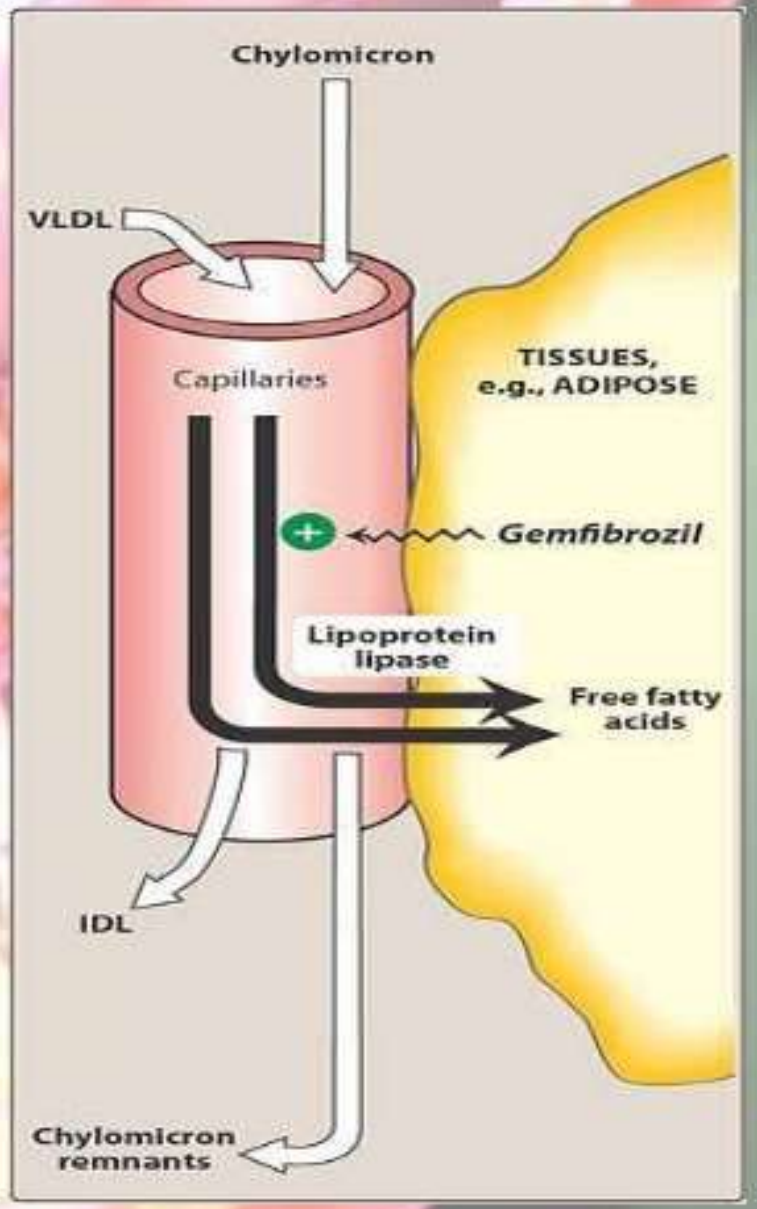
- Triglycerides >200 mg/dL
- Colesevalam is much better tolerated than cholestyramine or colestipol
- Statins and other drugs should be taken 1-2 hours before and 4-5 hours after bile acid sequestrants

C. ASAM FIBRAT

- Mis. Gemfibrozil, Benzafibrat , Clofibrat , Fenofibrat
- Merup obat pilihan (D.O.C) utk hypertriglyseridemia (>1000 mg/dl) ⇨ mencegah pancreatitis
- Sebagai agonis *peroxisomal proliferation activated receptor* (PPAR-α) →transkripsi gen utk LPL →Meningkatkan aktivitas LPL
- Bekerja di hepar dan jar lemak (sedikit pd ginjal, jantung, dan otot skeletal)

C- Fibrates (activators of lipoprotein lipase)

- - Fenofibrate(prodrug) and gemfibrozil.
- **Mechanism of action:** Agonists at **PPAR**(peroxisome proliferator-activated receptor) → expression of genes responsible for increased activity of plasma lipoprotein lipase enzyme → **hydrolysis of VLDL and chylomicrons**→ ↓*serum TGs*
- - Increase clearance of LDL by liver & ↑ HDL.
- **Therapeutic uses:**
- Hypertriglyceridemia (the most effective in reduction TGs) - combined hyperlipidemia (type III) if statins are contraindicated.



Pharmacokinetics:

- - Completely absorbed after oral administration.
- - **Highly bound to plasma proteins(pp)**, extensively metabolized, excreted in urine.
- **Adverse effects:**
- -**GIT disturbances**.
- -**Gall stones** (increased biliary cholesterol excretion).
- - **Muscle pain and myopathy** (patients with renal impairment are at risk).
- - Increase coumarin levels(competitive plasma protien binding)
- -**CI** in pregnancy, lactating women, renal and hepatic dysfunction, gall stones.

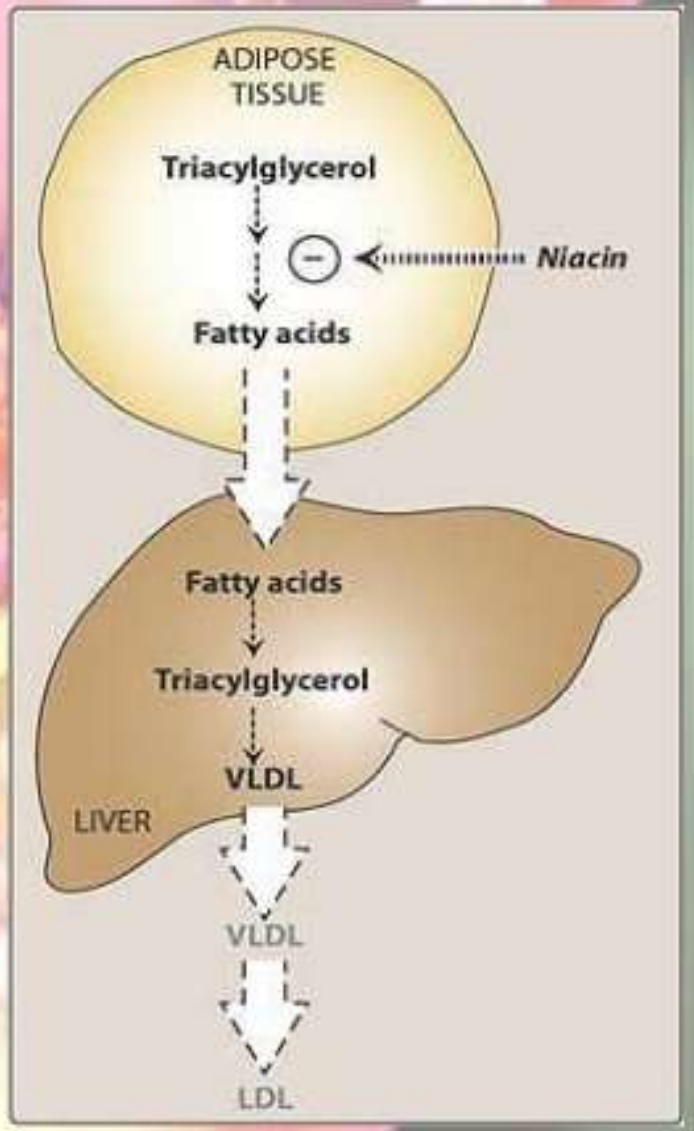
D. NIACIN (ASAM NIKOTINIK)

- **Merup bagian dari vit B kompleks, larut air**
- **Mekanisme Kerja :**
  - ♥ **me ↓ sintesa TG dan VLDL di hepar**
    - ✓ menghambat lipolisis TG di jar lemak ⇨ FFA ↓
    - ✓ kdr LDL ↓ (krn VLDL ↓)
  - ♥ **me ↑ katabolisme TG-VLDL**
    - ✓ aktivitas LPL ↑ ⇨ clearance kilomikron, VLDL, TG ↑
  - ♥ **me ↓ katabolisme apo AI ↓ ⇨ kdr HDL ↑**

- **Efek :**
  - ✓ **me ↓ LDL 20-30% (4.5-6 g/d)**
  - ✓ **me ↑ HDL 30-40%**
  - ✓ **me ↓ TG 35-45% (2-6 g/d)**

D- Niacin; Nicotinic acid (Inhibitor of lipolysis)

- -The first and cheapest anti hyperlipidemic.
- -Decrease both **TGs (VLDL) and cholesterol (LDL) levels.**
- **Mechanism of action:**
- It is a potent ***inhibitor of lipolysis*** in adipose tissues → ↓ **mobilization of FFAs** (major precursor of TGs) to the liver → ↓ **VLDL** (after few hours).
- Since LDL is derived from VLDL so ↓ VLDL → ↓ **LDL** (after few hours).
- - **↑ HDL levels** (*the most potent antihyperlipidemic).*
- **↓ endothelial dysfunction →↓** thrombosis.



- **Pharmacokinetics:**
- - Orally given, converted to nicotinamide which does not decrease plasma lipids alone(must be incorporated with NAD Co).
- **Therapeutic uses:**
- -Familial hyperlipidemias (type IIB) (↑VLDL and↑ LDL).
- - Sever hypercholesterolemia, combined with fibrates or cholestyramine.
- **Adverse effects:**
- - **Cutaneous flush** (PG- mediated, ↓ by aspirin) and pruritus.
- **- GIT** disturbances.
- **- Glucose** intolerance.
- **- Gouty** arthritis (hyperurecemia).
- **- Myopathy** (rare).

Efek Samping & KI Niacin

Efek Samping : Sering dan dapat menyebabkan ketidakpatuhan penderita dalam berobat:

- ✓ Flushing (tekanan darah↓ ⇨ sinkope)
- ✓ Dyspepsia (shg pembrian stl makan)
- ✓ Pruritis, skin rashes.
- ✓ Hiperglikemi
- ✓ Hiperurisemi
- ✓ Hepatotoksik (paling serius)

Kontraindikasi :

- Pasien peptic ulcer & gout
- Diabetes yg memburuk
- Ibu hamil

E. EZETIMIBE

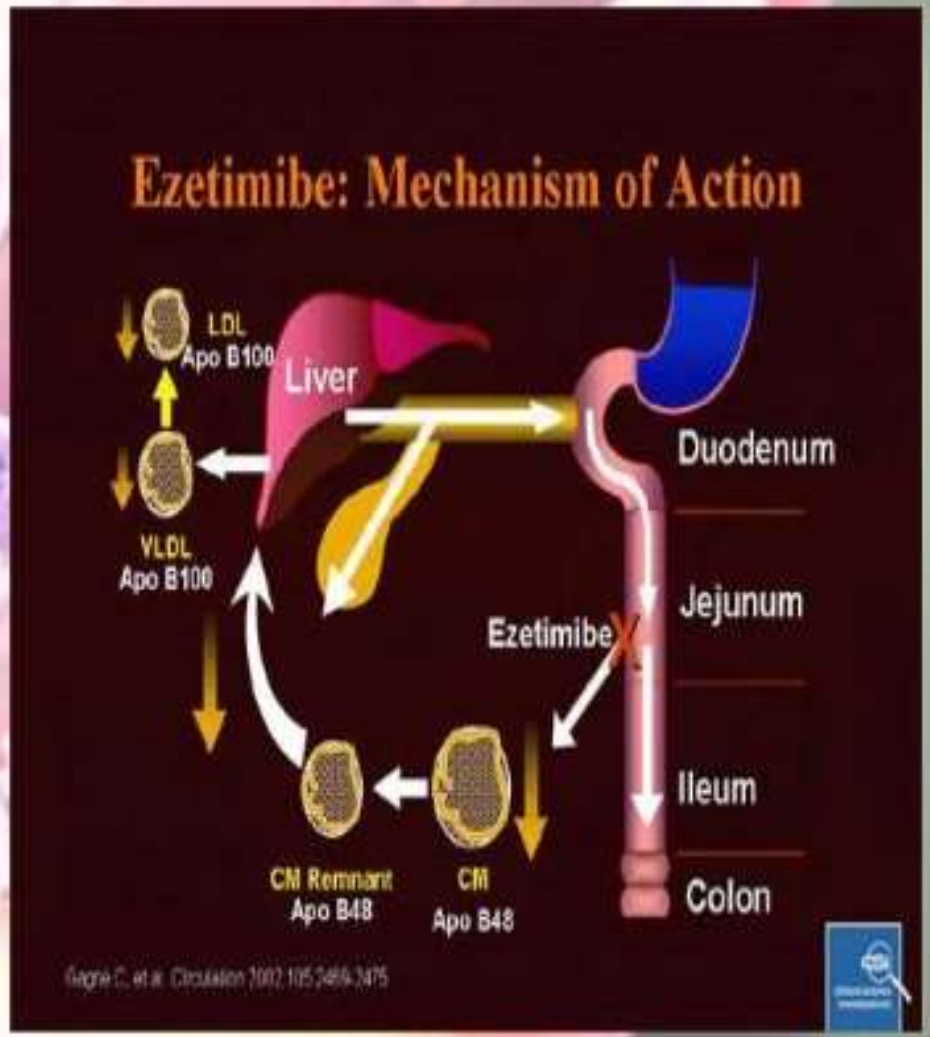
- Mek kerja :

  hamb absorbsi kolesterol di *brush border* usus halus ➔kolest yg ke hepar ↓ ➔ cadangan kolest di hepar ↓ & clearance kolest di plasma ↑

- First – line therapy
- Tdk mempengaruhi absorbsi TG

E- Ezetimibe (cholesterol absorption inhibitors)

- Inhibits **intestinal cholesterol absorption** → ↓ concentration of intrahepatic cholesterol→ **compensatory ↑ in LDL receptors** →↑ **uptake of circulating LDL** →↓ serum LDL cholesterol levels.
- - **Used** in hypercholesterolemia together with statins & diet regulation.
- - **Adverse effects**: diarrhea and abdominal pain.
- **CI** in patients with liver dysfunction.



FISH OIL
(asam lemak omega-3)

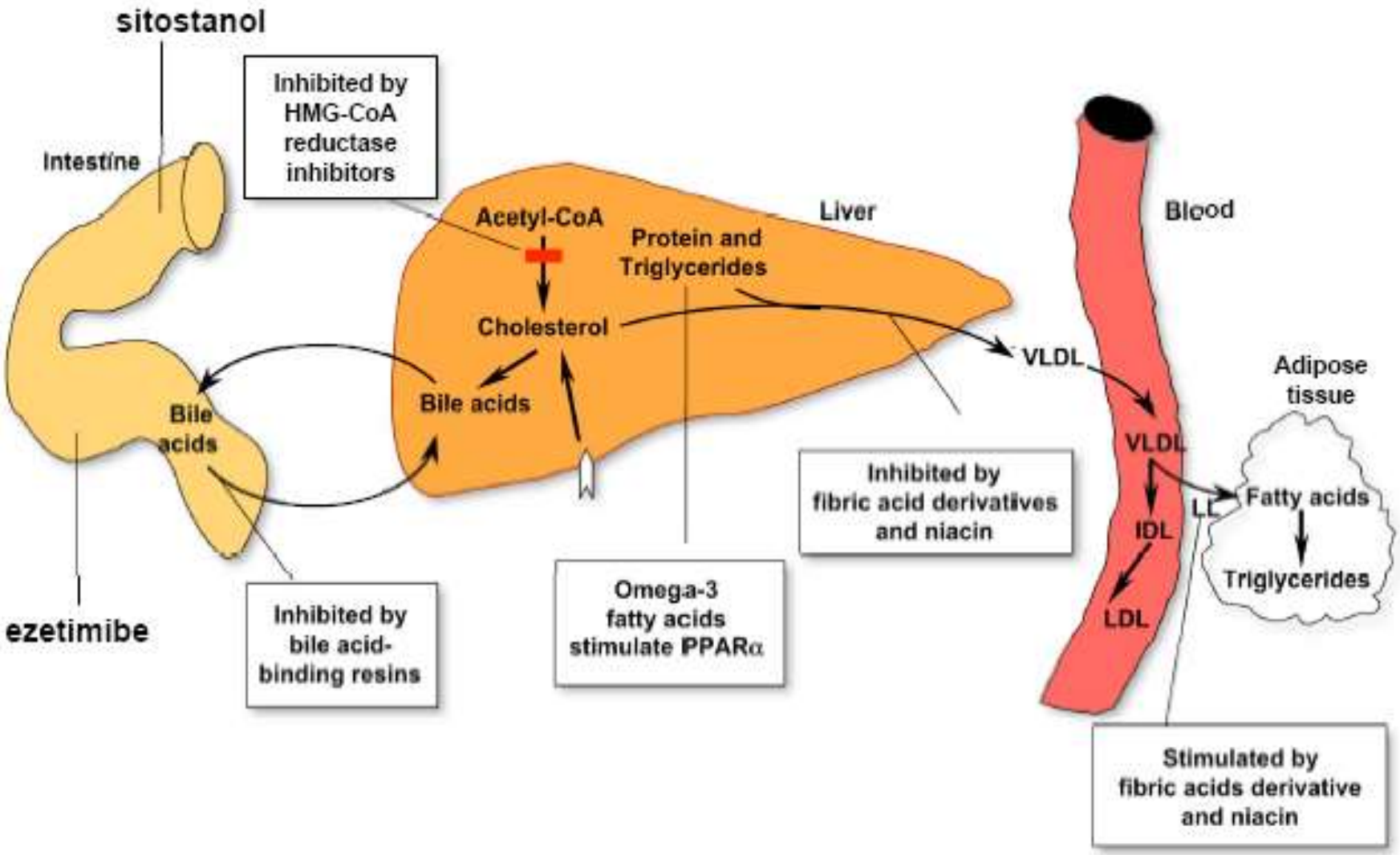
- Manfaat : me↓ TG
  - ✓hambat lipogenesis
  - ✓me ↑oksidasi asam lemak (mel. aktivasi PPAR-α)
- Dipakai sbg suplemen diet pd pasien hiper-TG
- Sumber : mackerel, lake trout, herring, ardines, albacore tuna and salmon (tinggi kadar eicosopentaenoic acid (EPS) & ocosahexaenoic acid (DHA)
- Tahu/soybeans; canola, walnut & flaxseed oils mengandung alpha-linolenic acid (LNA) dlm tubuh dikonversi menjadi as lemak omega-3

Efek Obat Hipolipidemi pada Serum Lipid

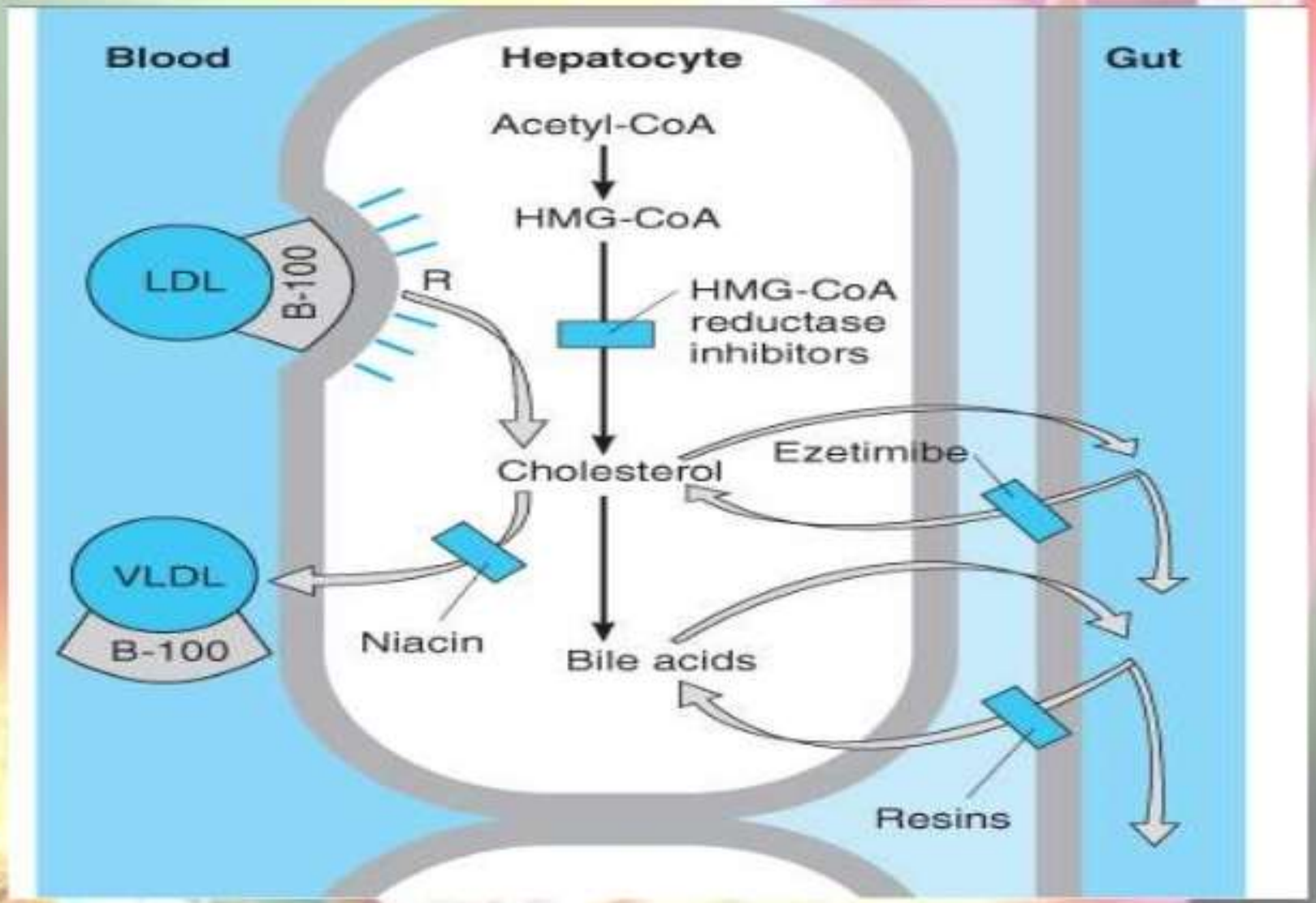
	TC	LDL	HDL	TG
Resins	↓20%	↓10%–20%	↑3%–5%	Variable
Ezetimibe	↓20%	↓10%–20%	↑3%–5%	Variable
Nicotinic acid	↓25%	↓10%–15%	↑15%–35%	↓20%–50%
Fibrates	↓15%	Variable	↑6%–15%	↓20%–50%
Statins	↓15%–60%	↓20%–60%	↑3%–15%	↓10%–40%
Fish Oil (PUFA)	None	None	?? ↓ 3%	↓25%–35%

Adapted from Gotto AM Jr. Management of lipid and lipoprotein disorders. In: Gotto AM Jr, Pownall HJ, eds. *Manual of lipid disorders*. Baltimore: Williams & Wilkins; 1992; Rubins HB, et al. *N Engl J Med.* 1999;341:410–418.

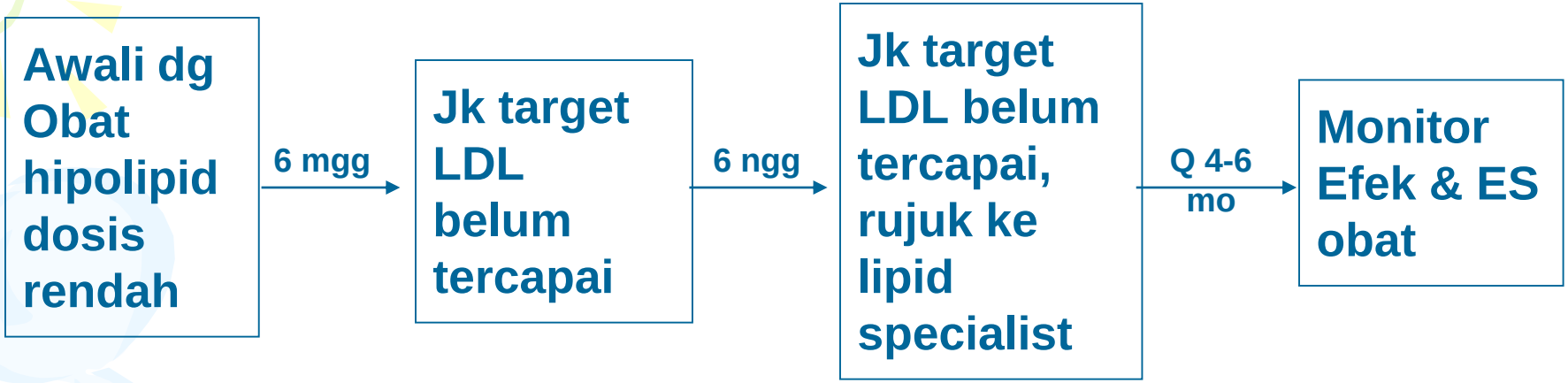
Sites of Drug Action in Hyperlipidemia



Sites of action of HMG-CoA reductase inhibitors, niacin, ezetimibe, and resins used in treating hyperlipidemias. LDL receptors (R) are increased by treatment with resins and HMG-CoA reductase inhibitors.



Tahapan Terapi Hiperlipidemi



- Mulai dg statin / ezetimibe/ bile acid sequestrant / nicotinic acid
- Pertimbangkan statin dosis tinggi / kombinasi (statin + ezetimibe/ bile acid sequestrant / nicotinic acid)
- Tx faktor resiko lipid yg lain (hiper TG, hipo HDL)

Combination drug therapy

- If **no improvement** within **6 weeks** with a single drug therapy, the **dose** should be **increased.** If no improvement **after 3 months** change the drug or consider combination therapy:
- - **Bile acid resins** can be safely combined with **statins** or **nicotinic acid** (↓ LDL, VLDL cholesterol levels respectively).
- **- Ezetimibe + statins → synergistic** effects.
- - Fibrates and statins are **CI** → myopathy**.**
- - Nicotinic acid and statins (must be **cautiously** used) → **myopathy.**