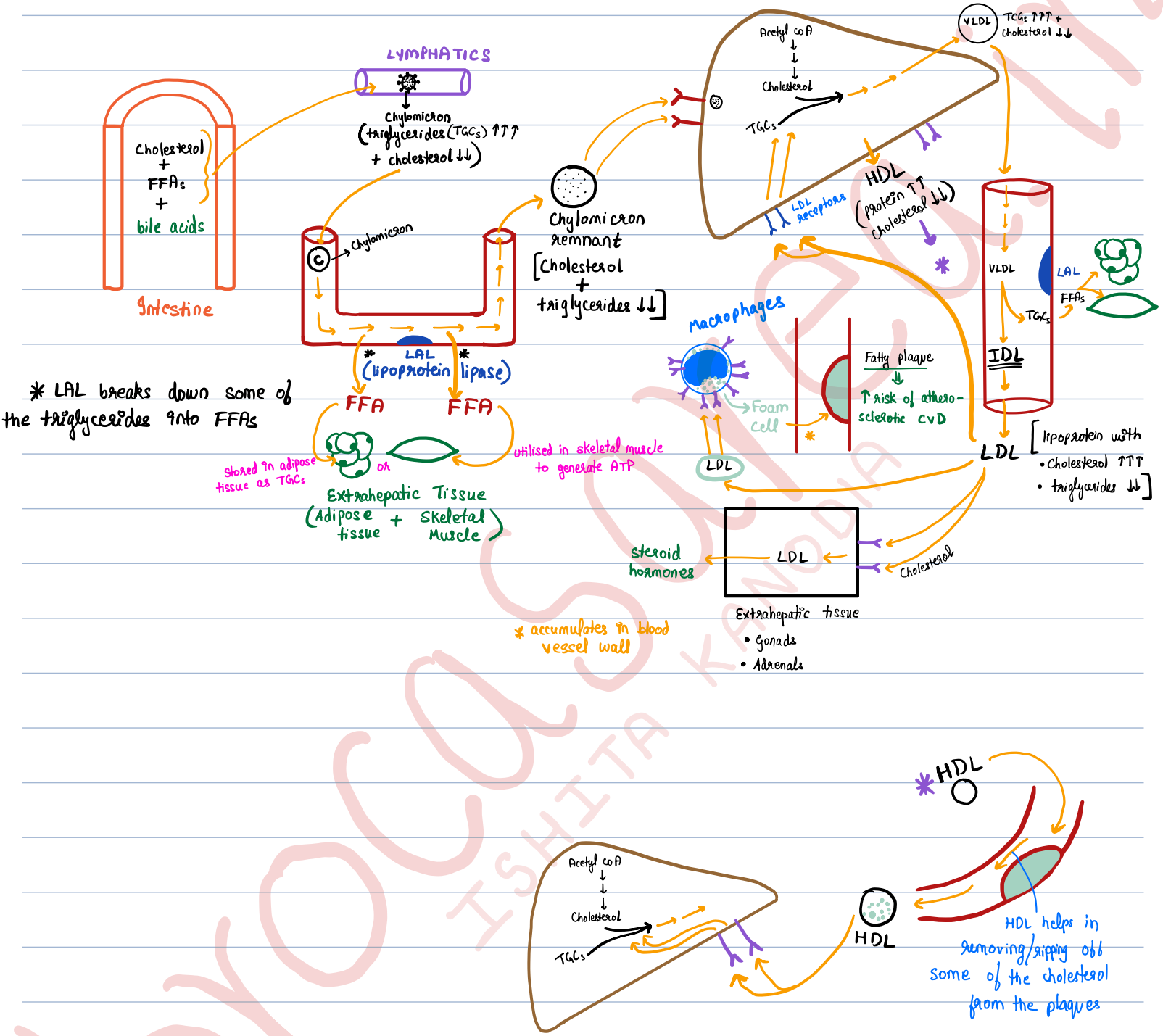
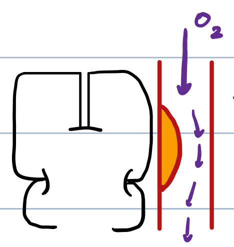
Pathophysiology of Hyperlipidemia:



Hyperlipedemia: LDL, cholesterol, TGCs deposition in vessel wall & solid organs.

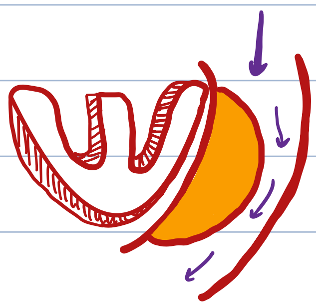
- ↑↑ LDL
- ↑↑ TGCs
- ↓↓ HDL

- Xanthoma → deposition in skin
- Xanthalasma → fat deposition around medial portion of eye
- Corneal arcus → " " " the cornea
- NASH → fatty changes in liver
- Pancreatitis (seen with ↑↑↑↑ TGCs (>1000 mg/dL)) → fatty deposition in pancreas
- Plaques → deposition of high cholesterol & TGCs & their non-removal due to low HDL.
  - → ↑ risk of atherosclerotic CVD



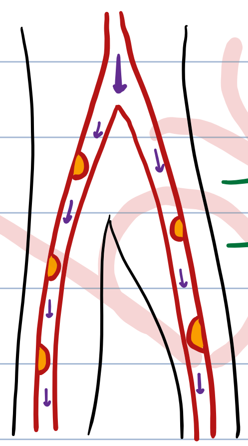
→ TIA
→ CVA

Brain



→ NSTEMI
→ STEMI
→ CAD, angina

Heart



Peripheral

→ PAD
→ Acute Limb Ischaemia

Lipid Lowering Agents:

- ↓↓ LDL &/or
- ↓↓ TGCs &/or
- ↑↑ HDL

[I] HMG coA reductase inhibitors

[II] Niacin

[III] Fibrates

[IV] Bile acid Sequestrants

[V] Cholesterol Absorption inhibitors

[VI] PCSK-9 inhibitors.

HMG CoA Reductase Inhibitors: (Statins) 1st Line Hyperlipidemia drugs

→ action: ↓↓ LDL in bloodstream (minorly ↓TGCs, ↑HDL)

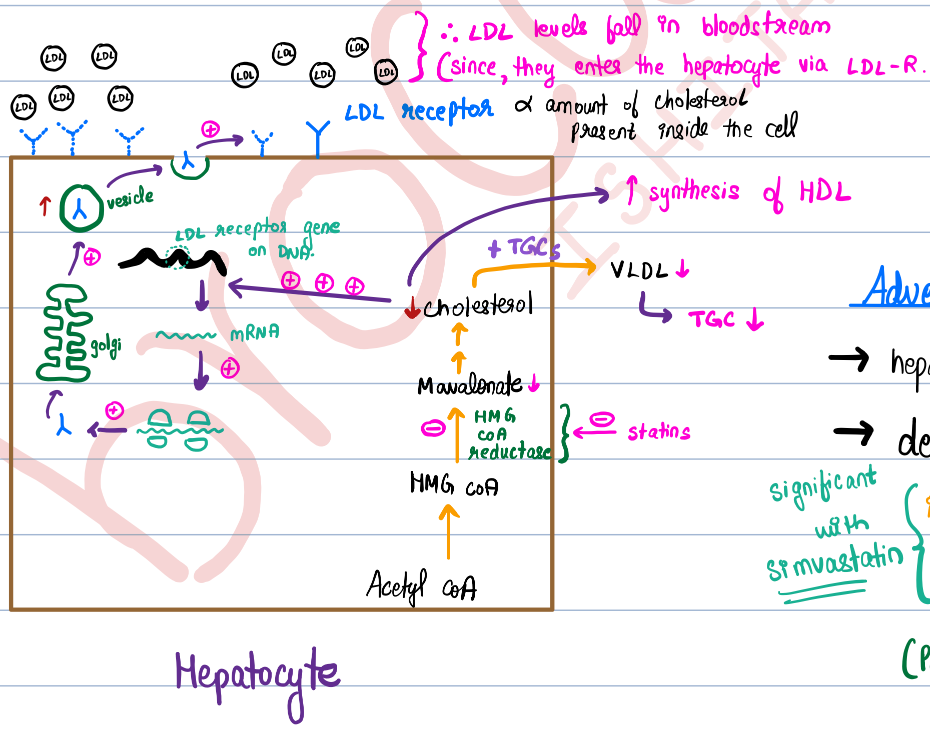
High Intensity Statins

- Rosuvastatin (20 mg+)
- Artorvastatin (40 mg+)

Moderate Intensity Statins

- Rosuvastatin (< 20 mg)
- Artorvastatin (< 40 mg)
- Lovastatin
- Fluvastatin
- Simvastatin
- Pravastatin

(pink) = effect of statins



Adverse Effects of Statins:

→ hepatotoxicity (mild) ⇒ increased LFTs

→ deplete CoQ in skeletal muscle cell (important component of ETC)

significant with simvastatin

⇓

less ATP synthesis ⇒ Myopathies

(Pain, weakness, Rhabdomyolisis, elevated creatine kinase, myoglobin)

↓

affects kidney to cause an acute kidney injury.

Niacin : (c/I - gout)

Adipose Cell

TGCs
↓
HSL (hormone sensitive lipase)
↓
FFA ↓↓

Niacin ⊖ HSL

FFA ↓↓↓

hepatocyte

FFA ↓↓
↓
TGCs ↓↓
Cholesterol
↓↓ VLDL → IDL → LDL ↓
TGCs ↓↓

Extrahepatic tissue

synthesis in hepatocyte → HDL

HDL ↓ ↓ HDL

∴ HDL ↑↑ in bloodstream ↓↓

Niacin ⊖ HDL

Macrophage [Foam cell]

Scavenger receptors

HDL successfully rips off some plaque

Niacin ⊖

Catabolism of HDL

HDL ↓↓↓ ↑↑

Niacin

- ↑↑↑ HDL
- ↓↓ TGCs
- ↓↓ LDL

Adverse Effects of Niacin :

OAAT = Organic acid anion transporter

① Gout

Niacin ⊖ → OAAT ⊖ → uric acid (U) ⊖ → PCT

increased uric acid in urine

∴ less uric acid in urine

more uric acid in bloodstream

↑ hyperuricemia

↑ Gout

② Niacin → Insulin resistance

(reduced insulin secretion & insensitivity to released insulin)

rise in blood glucose

↓ hyperglycemia

③ Arachidonic acid

Niacin ⊕

- synthesis of leukotrienes
- synthesis of prostaglandins ↑↑↑
  - ⇓ Vasodilation, increased capillary permeability
    - flushing, itching
    - histamine release → pruritis

Treat with Aspirin

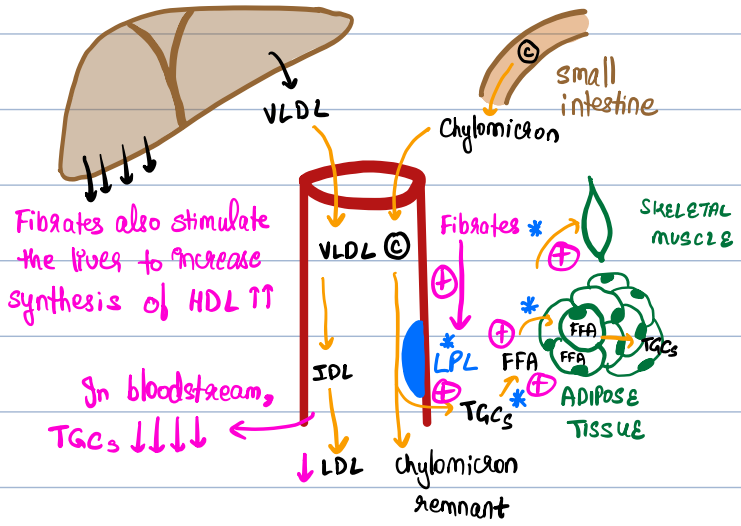
Fibrates: stimulate LPL

→ better than niacin in lowering TGCs

TGC ↓↓↓

HDL ↑↑

- Fenofibrate
- Gemfibrozil



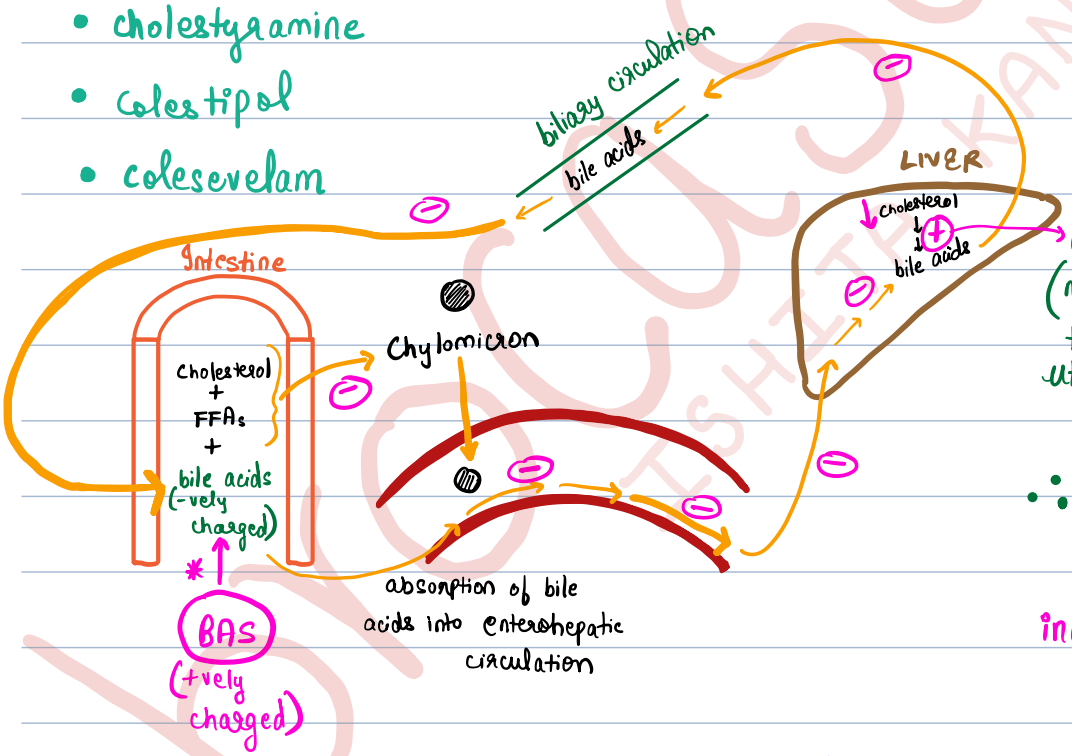
Adverse Effects:

- Patient on statins (statins are metabolized by CYP450 in liver); Fibrates inhibit CYP450
  ∴ statin action ↑↑
  → CoQ ↑↑ ⇒ ↑ in myopathy
- increase in LFTs
- Gallstones (cholelithiasis/cholecystitis)
  Fibrates inhibit 7α-hydroxylase in bile acid synthesis pathway
  ∴ bile acids ↓ cholesterol ↑ (relatively)
  precipitation to form gallstones

Bile Acid Sequestrants: (BAS)

LDL ↓↓
cholesterol ↓↓
TGCs ↑↑

- cholestyramine
- colestipol
- colesevelam



(more cholesterol in the liver is utilized for synthesis of bile acids)

∴ Cholesterol ↓↓↓

↓

increased LDL receptors

↓

LDL ↓↓↓

* BAS binds to bile acids ⇒ bile acid is depleted

⇓ excreted into faeces

⇓ decreased absorption of fats

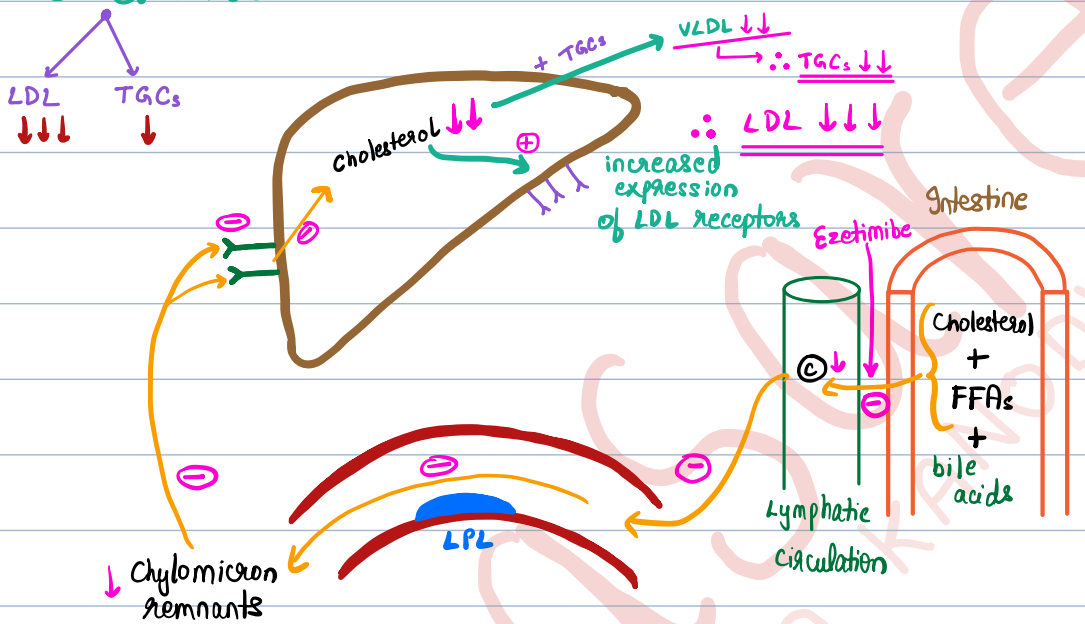
Adverse effect of BAS:

- TGCs ↑↑↑ (mechanism not properly understood)
- Due to ↓ in bile acids ⟹ ↓ absorption of fat & fat soluble vitamins (A, D, E, K)
- Digoxin, Warfarin } BAS binds onto these drugs & inhibits their absorption [∴ BAS can be used as an antidote in warfarin or digoxin toxicity (overdose)]

Cholesterol Absorption Inhibitors: (Second Line Drugs)

[© = chylomicron]

- Ezetemibe



Adverse effects:

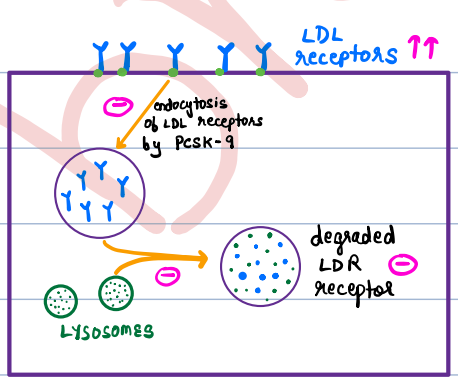
- Mild increase in LFTs (rare)
- Diarrhoea (mild)

PCSK-9 inhibitors: (PCSK9-I)

- alirocumab
- evolocumab

PCSK9-I → helps in endocytosis of LDL receptors

● = PCSK-9 protein



⟹ ∴ LDL ↓↓↓ (in blood)

Adverse Effects:

- painful injection (given s.c.)
- myalgia
- rarely causes upper respiratory tract infections

Approach to Lipid Lowering Therapy:

- Any type of clinical atherosclerotic CVD (CVA/MI/PAD) ⇒ Statins
  - > 75 y/o → moderate intensity statin (considering adverse myopathic effect)
  - < 75 y/o → high intensity statin
- LDL > 190 mg/dL ⇒ high risk of atherosclerotic CVD ⇒ High Intensity Statins
- DM + 45-70 y/o
  - ↳ increased risk of atherosclerotic CVD & hyperlipidemia ⇒ ↑ LDL plaques
  - ASCVD > 7.5 % → high intensity statin
  - ASCVD < 7.5 % → moderate intensity statin
- ~~DM~~, 45-70 y/o + ASCVD > 7.5 % → moderate intensity statin

(already on statins)

Combo Therapy:

In cases of:
- adverse drug reactions / intolerance to statins
- statins not offering adequate therapeutic effect

- ↓↓↓ LDL → PCSK-9 inhibitors
  - → Cholesterol absorption (ezetimibe) inhibitors → if intolerant to ezetimibe ⇒ Add: BAS, Niacin
- ↓↓↓ TGCs → Niacin
  - → Fibrates (Better than niacin)
- ↑↑↑ HDL → Niacin
  - → Fibrates