Coronary artery disease, Hypertension and Lipids In Diabetes

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Case 1

58-year-old Mr.A presented to the emergency with worsening dyspnoea of 24 hr duration. Two days ago he was referred to an orthopedician by his family doctor when he had presented with acute onset neck pain, shoulder pain and vague discomfort.

He was on irregular drugs for diabetes for last 8 years. He had quit smoking 1 year ago subsequent to the development of right leg claudication.

On examination his BP was 100/60 mm Hg, had crepts over lung base and absent right leg pulse. ECG showed fully evolved MI with Q-waves in the anterolateral leads. RBS was 326 mg/dl and urine ketone was trace positive.

Case 2

- A 55 year old obese woman came to the OPD for check up.She had stopped her anti-diabetic medications for last 6 months.Her BP was 160/100, HbA1c 8.2 %,FPG - 210,2hr PPBG-300,TC- 256,LDL-151,TGL- 286 & HDL - 48mg/dl.
- What is the appropriate line of management?

The problem…

- CAD -the main cause of mortality in diabetes.
- Diabetes increasing in epidemic proportions..
- The increasing life expectancy
  - so the numbers are expected to go up significantly.
- Dyslipidemia and hypertension -the common co-morbid conditions in diabetes significantly affect the outcome.

- ***The crucial role of physician in screening and management is important.***

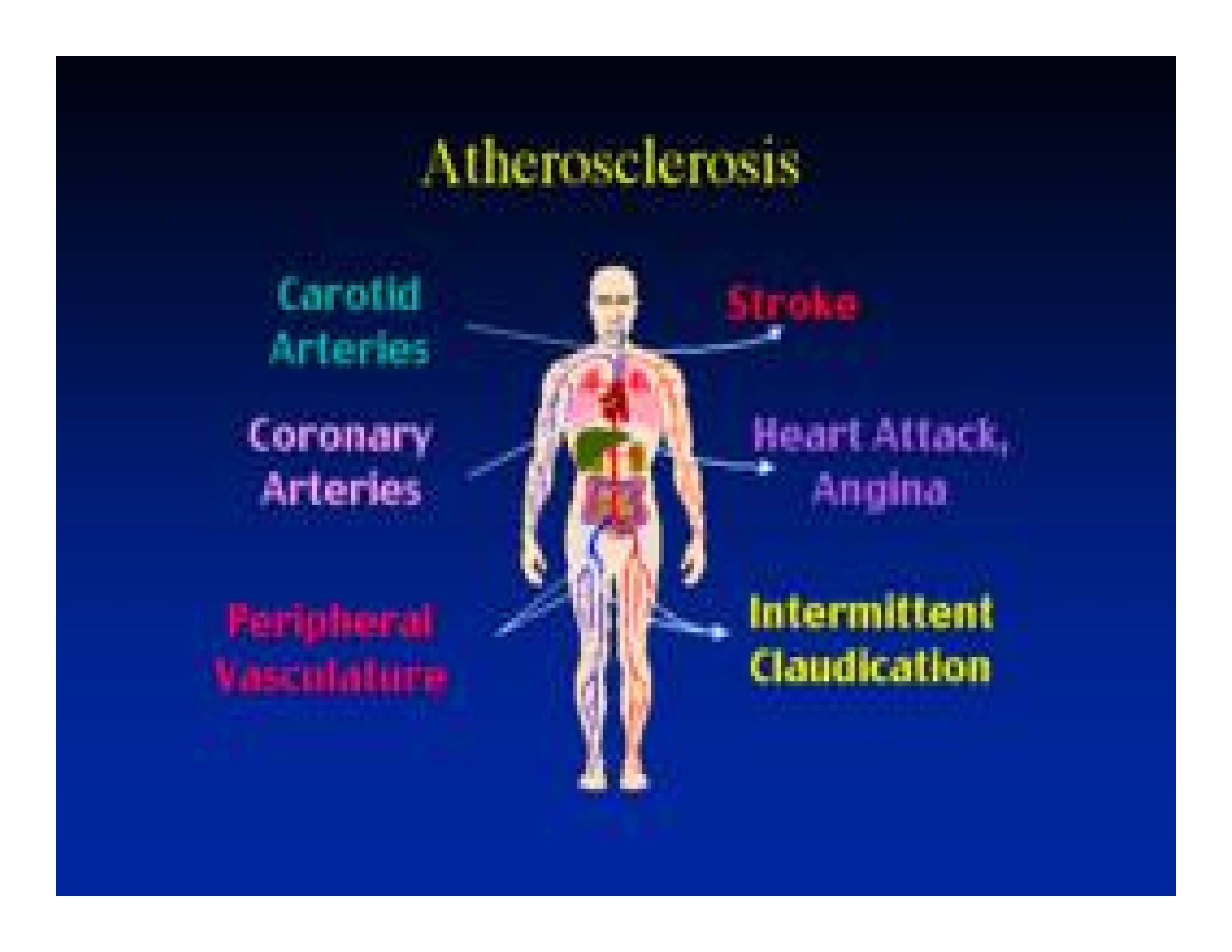
What is different with diabetes ?

- Coronary artery disease is **3-4** times more common.
- Sudden death is higher by **50%** in males and **100%** in females.
- **Loss of** premenopausal **protection** in females.
- Triple vessel disease, multiple lesions per patients and **more** distal involvement of coronary arteries.
- **Atypical presentation** delays diagnosis.
- LV **dysfunction** is more common.

the difference…

- Coexisting diabetic cardiomyopathy worsens the outcome.
- Revascularization procedures have less favorable outcome.
- Restenosis is more common.
- Defective lipid metabolism in diabetes.
- Autonomic neuropathy in diabetes worsens the outcome.

Atherosclerosis



Pathogenesis of accelerated atherosclerosis

- Hyperglycemia
- Obesity
- Dyslipidemia of diabetes
- Hypertension
- Altered hemorheology
- Oxidative stress
- Hyperinsulinemia – selective MAPK pathway

Clinical Manifestations …

- With the **classical symptoms** of stable angina, unstable angina or myocardial infarction.
- ***Silent or painless ischemic symptoms*** -dyspnoea, hypotension,sweating,syncope or asymptomatic.
- **Complications** like shock, conduction disturbances, cardiac failure, re-infarction and ketoacidosis.
- ***Atypical symptoms*** - dyspepsia, arm pain, toothache, sudden falls, vomiting, and giddiness.

Evaluation

- **Resting ECG -** has a low sensitivity

  A normal resting ECG does not rule out an acute coronary syndrome **unless** - a combination of

  a) Clinical features,

  b) Serial cardiac enzyme and ECGs and

  c) Significant relief with treatment of non-cardiac illness

Further evaluation

- **Stress ECG -** excludes triple vessel disease but not single or double vessel disease.
- **Stress Echo -** valuable, reliable and cost-effective but does not give information on the nature of the lesion.
- **Angiography -** describes the nature and site of the lesion but does not give 3D image and eccentric lesions are not visualized.
- **Nuclear imaging -**widespread availability is a problem. SPECT and PET assess viable myocardium.

Glycaemic control – CAD

- **Role of optimal glycaemic control in preventing or retarding complications of diabetes applies to cardiovascular diseases also.**
- ACCORD/ADVANCE and VADT STENO-2
- Metabolic memory/Legacy effect

Hypertension -the problem statement

- Affects 20–60% of patients with diabetes.
- Substantially increases the risk of both macro vascular and micro vascular complications.
- Increases mortality by 7 folds.
- In diabetic nephropathy increases mortality by 37 folds.
- 85% of nephropathy patients have hypertension.

How crucial is BP control ?

- Each 10-mmHg decrease in mean Sbp
  - = 12% reductions in risk for any complication
  - =15% for deaths related to diabetes
  - =11% for myocardial infarction
  - =13% for micro vascular complications.

What is the target BP?

- Blood pressures lower than 125/75 mmHg are recommended for people who have proteinuria higher than 1gm/day and renal insufficiency regardless of etiology.

- A target blood pressure goal of <130/80 mmHg is reasonable if it can be safely achieved.

Non-pharmacological management

- Moderate sodium restriction
- Weight reduction
- Moderately intense physical activity
- Smoking cessation and moderation of alcohol intake

Pharmacotherapy of hypertension

- **ACE inhibitors** and **ARBs** have a favorable effect on renal and cardiovascular systems.
- **Diuretics** are recommended when BP control is still uncontrolled.
- **ß-blockers** along with ACE inhibitors help in reducing myocardial infarction and heart failure.
- **Non-DCCBs** (i.e., Verapamil and Diltiazem) may reduce microalbuminuria. **DCCBs (**i.e.,Amlodipine**)** in combination with ACE inhibitors, ß-blockers, and diuretics help in controlling blood pressure.

When to start therapy?

- Bp should be measured at every visit both in the sitting and lying down positions.
- SBP >130, DBP > 80 - needs repeated readings.
- SBP of 120–139 mmHg or a DBP of 80–89 mmHg requires lifestyle/behavioral therapy for a maximum of 3 months.
- SBP > 140 mmHg or DBP> 90 mmHg should receive drug therapy in addition.

Special situations

- **Ischemic Heart Disease**

  Stable angina – beta blockers or long acting CCBs

  Unstable angina/MI – beta blockers +ACE Inhibitors

  Post MI CCF–ACE-Is + beta blockers + aldosterone antagonists

- **Pregnancy**

  Alpha methyldopa, vasodilators and calcium channel blockers are safe

Cardio protective drugs

- **Anti-platelet drugs:** Aspirin and Clopidogrel
- **ACE inhibitors:**

  reduce cardiac remodeling, infarct size, improve endothelial function and fibrinolysis.
- **Beta-blockers:**

  cardio-selective drugs reduce sympathetic load on the heart and improve the outcome.
- As a **primary prevention** strategy aspirin is recommended **in those with risk factors** like hypertension, smoking and dyslipidemia.

Surgical intervention

- **PTCA** (Percutaneous Transluminal Coronary Angioplasty)

  less effective due to extensive disease and re-stenosis

- **CABG (**Coronary bypass grafting) with internal mammary artery

  -is better than bypass grafting with the saphenous vein and more effective than PTCA.

Dyslipidemia in Diabetes

Mechanisms of Dyslipidemia in the Metabolic Syndrome

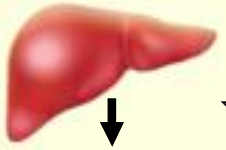
FACTORS:

Environmental
Biological
Inherited

Abdominal fat → Hypertrophic adipocytes → Defect in the incorporation of FFAs into TG

Insulin resistance → ⇩FFA trapping and retention by adipose tissue

⇧FFA in plasma



⇩ Clearance LPL, APO CIII

⇩Proteolysis of Apo B-100

⇧ TG

⇧ VLDL apo B

TG
⇧*CETP*
CE

⇧ TG in HDL

⇧ *Catabolism HDL-C*

⇩ HDL-C levels

TG
⇧*CETP*
CE

⇧ TG in LDL-C

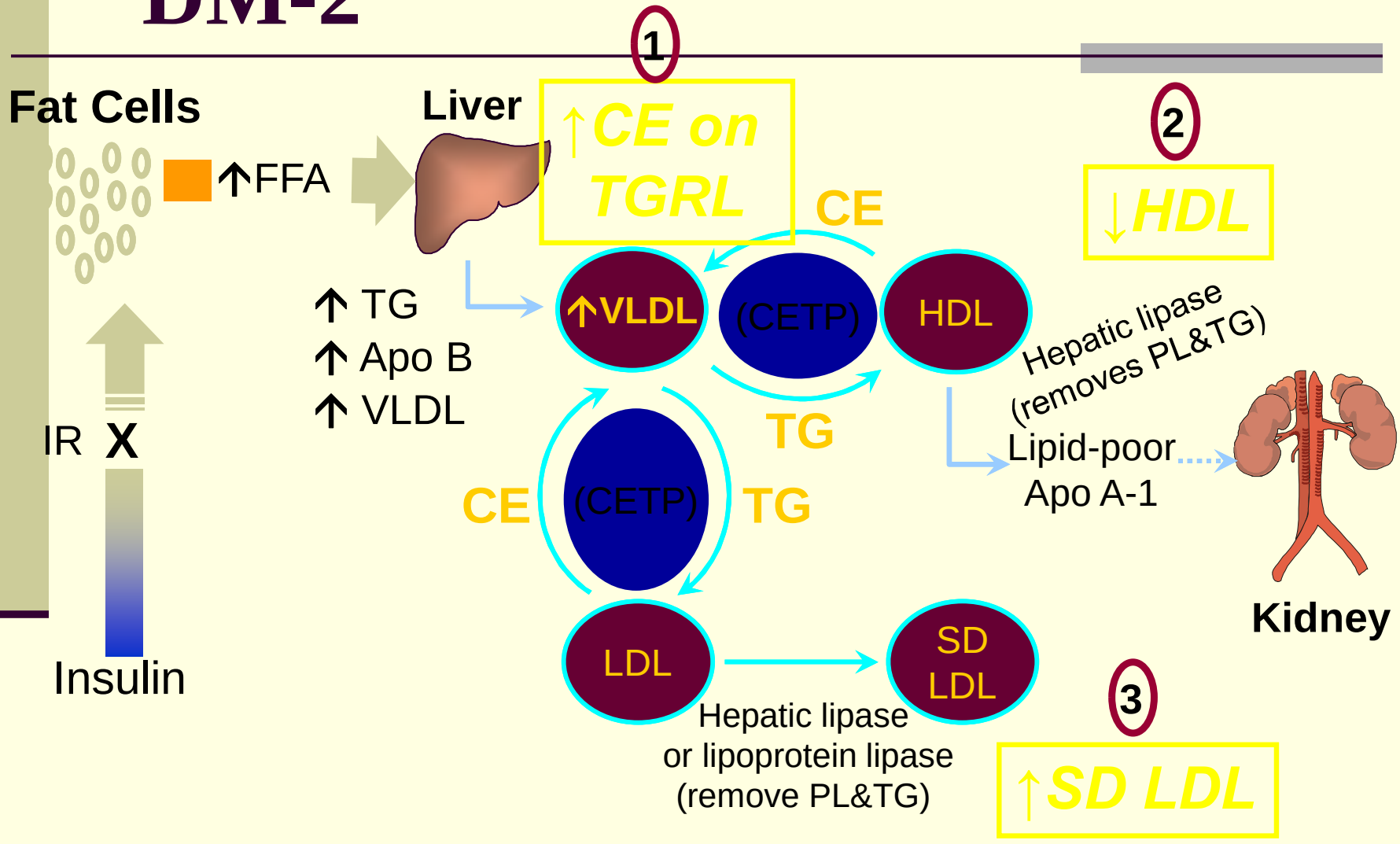
⇧ *Hepatic Lipase*

⇧ Small dense LDL-C

FFA: free fatty acids
TG: triglycerides
LPL: lipoprotein lipase
HDL: high density lipoprotein
CETP: cholesterol ester transfer protein
CE: cholesterol ester
VLDL: very low density lipoprotein

Kolovo GD. *Postgrad Med J.* 2005;81;358-366.

"Atherogenic Dyslipidemia" of DM-2



CETP=cholesterol ester transfer protein.

Ginsberg HN. *J Clin Invest*. 2000;106(4):453-457.

“Atherogenic Dyslipidemia” (=~~Dyslipidemia of Diabetes Mellitus/~~ Insulin Resistance)

- Hypertriglyceridemia (HTG)
- Low HDL-C
- Small, dense LDL
- (Increased VLDL-C)
- (Non–HDL-C)

NCEP Guidelines-TG and Non–HDL-C as Important Parameters for Lipid Management

Treatment Objectives for Elevated Triglycerides

"Very High" TG ≥500

- *Primary Objective*: TG reduction
- *Secondary Objective*: LDL-C and non HDL reduction

"High" TG 200-499

- *Primary Objective*: LDL-C goal
- *Secondary Objective*: non-HDL C reduction (VLDL-C[a] and LDL-C)

[a]VLDL-C levels are influenced by triglyceride levels

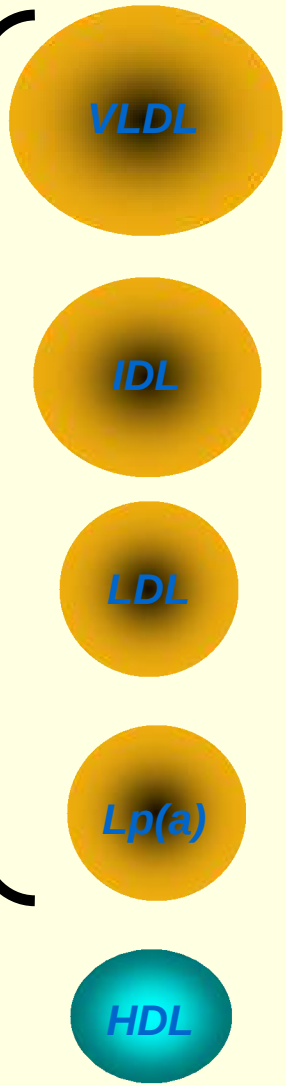
Prescription Omega-3 is indicated for the reduction of very high triglycerides, in addition to diet, in adult patients with triglycerides ≥500 mg/dL

HDL-C = high-density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; NCEP = National Cholesterol Education Program; TG = triglyceride; VLDL-C = very low-density lipoprotein cholesterol

Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III). *Circulation*. 2002;106:3143-3421.

Non-HDL Includes *All* Atherogenic Lipoprotein Classes

Atherogenic **Lipoproteins**
Non-HDL; Apo B100-containing



Very low-density lipoprotein

- Made in the liver
- TG >> CE
- Carries lipids from the liver to peripheral tissues

Intermediate-density lipoprotein

- Formed from VLDL due to loss of TG
- Also known as a VLDL remnant

Low-density lipoprotein

- Formed from IDL due to loss of TG
- CE>>TG

Lipoprotein (a)

- Formed from LDL w/ addition of apo (a)?
- Very atherogenic

High-density lipoprotein

- Removes cholesterol from peripheral tissues

- **Non–HDL-C = Total C – HDL-C (*all* atherogenic lipids)**
- **Non–HDL-C goal = LDL-C goal + 30:**

- Non–HDL-C is a stronger predictor of CHD risk than LDL-C

	Goals		
	LDL-C	Non–HDL-C	Apo B
Highest-Risk Patients ■ Known CVD ■ Diabetes plus ≥1 additional major CVD risk factor[a]	<70 mg/dL	<100 mg/dL	<80 mg/dL
High-Risk Patients ■ No diabetes or known CVD but ≥2 major CVD risk factors[a] ■ Diabetes but no other major CVD risk factors[a]	<100 mg/dL	<130 mg/dL	<90 mg/dL

Management of dyslipidemia

- In all patients with diabetes and IGT check lipid profile at diagnosis and during annual screening.
- R/o alcohol, estrogen use, physical inactivity, renal impairment, hypothyroidism, steroids, diuretics and familial hyperlipidemia.

Drugs available:

- Life style modification
- Glycaemic control
- Statins
- Fibrates
- Niacin
- Ezetimibe
- Bile acid resins

Dietary modification

- Diet - reduces LDL cholesterol 15–25 mg/dl.
  carbohydrate - 50 to 60%
  fat - 24 to 28%
  protein 10 to 15%
  Saturated fat< 7%
  mufa and pufa 10% each of the total fat.
- The total cholesterol intake <200 mg / day.

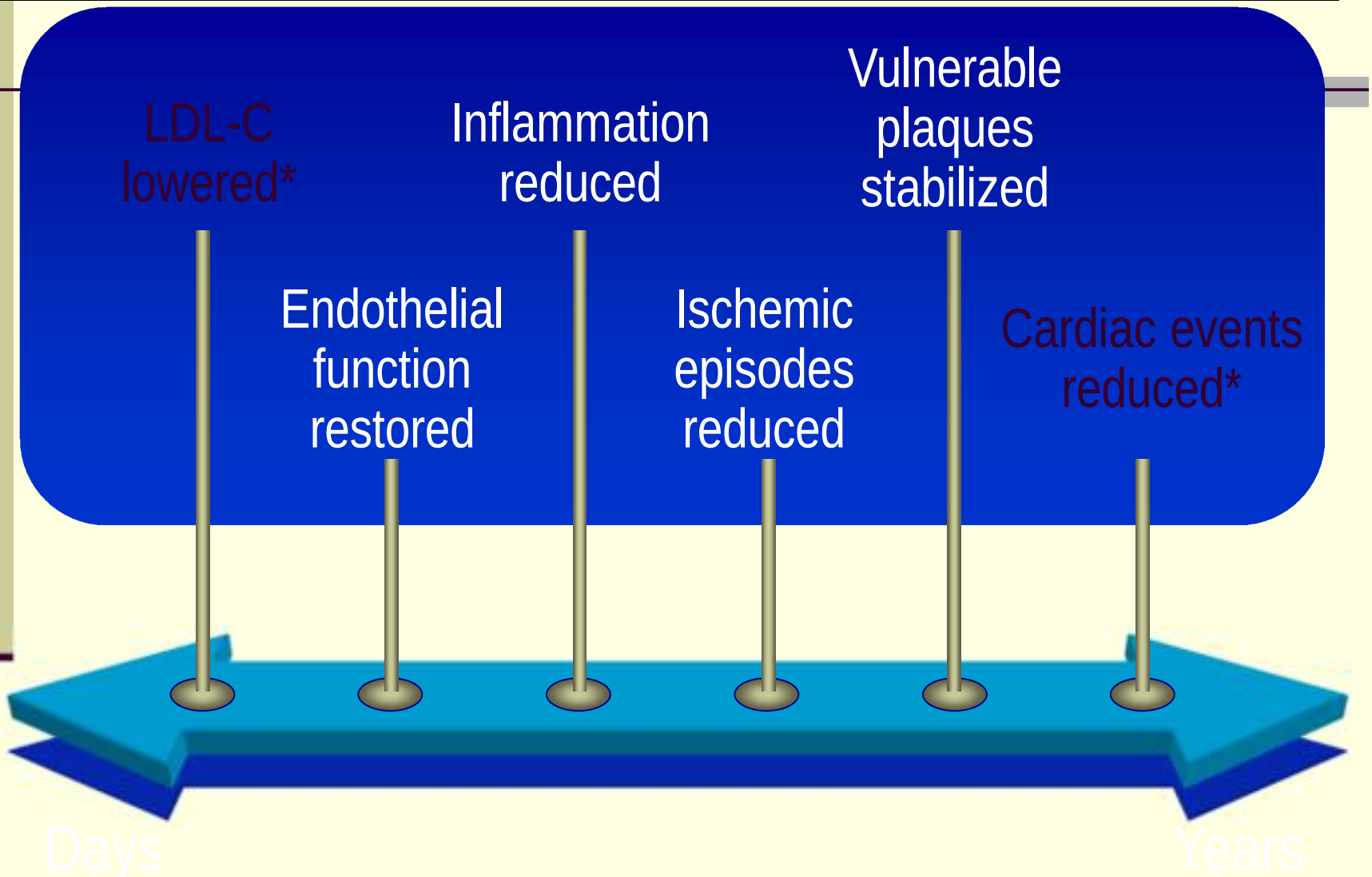
Management of dyslipidemia

- **Physical activity**: help in reducing TGL & LDL levels and in increasing the HDL levels.
- Increase in the HDL is a predominantly seen with exercise.
- **Diabetic control** improves lipids in Type1 DM but in Type2 DM,some lipid abnormalities persist.
- Glucose-lowering oral agents have main effect on TGL **;** only a minimal effect on HDL levels.

Statin therapy

Lovastatin	20–80 mg
Pravastatin	20–40 mg
Fluvastatin	20–80 mg
Simvastatin	20–80 mg
Atorvastatin	10–80 mg
Rosuvastatin	5–20 mg
Cerivastatin	0.4–0.8 mg

Time course of Statin effects



* Time course established

- Common side effects
  - Headache, Myalgia, Fatigue, GI intol. Flu-like symptoms
- Increase in liver enzymes – serious problems are very rare
  - Occurs in 0.5 to 2.5% of cases in dose-dependent manner
- Myopathy occurs in 0.2 to 0.4% of patients
  - Rare cases of Rhabdomyolysis
  - We can reduce this risk by
  - Cautiously using statins in impaired renal function
  - Using the lowest effective dose
  - Cautiously combining statins with fibrates
  - Muscle toxicity requires the discontinuation of statin

Cholesterol Treatment Trialist Collaboration Findings

- Prospective meta-analysis from 90,056 patients in 14 randomized trials of statins demonstrated:
  - Decreasing LDL-C with a statin by 1 mmol/L in patients with and without established cardiovascular disease, decreased the following:
    - All cause mortality – 12%
    - CHD – 19%
    - Major vascular event – 21%
    - Non-fatal MI – 26%
    - CHD death – 19%
    - Need for revascularization – 24%
    - Stroke – 17%

Lancet 2005;366:1267-78

Fenofibrate

- Enhances the activity of lipoprotein lipase
- Reduces hepatic fatty acid synthesis
- Inhibits HMG co-enzyme A reductase activity
- Reduces the CETP activity
- Increases the LCAT activity
- Increases the production of Apo AI and Apo A II

Fibric Acid Derivatives

- Major actions
  - Lower TG 20–50%,↓VLDL synthesis
  - Raise HDL-C 10–20%
  - ↓ LDL (TG is N), ↑ LDL (TG is ↑)
  - Increase the SDL particle size (less athero)
- Side effects

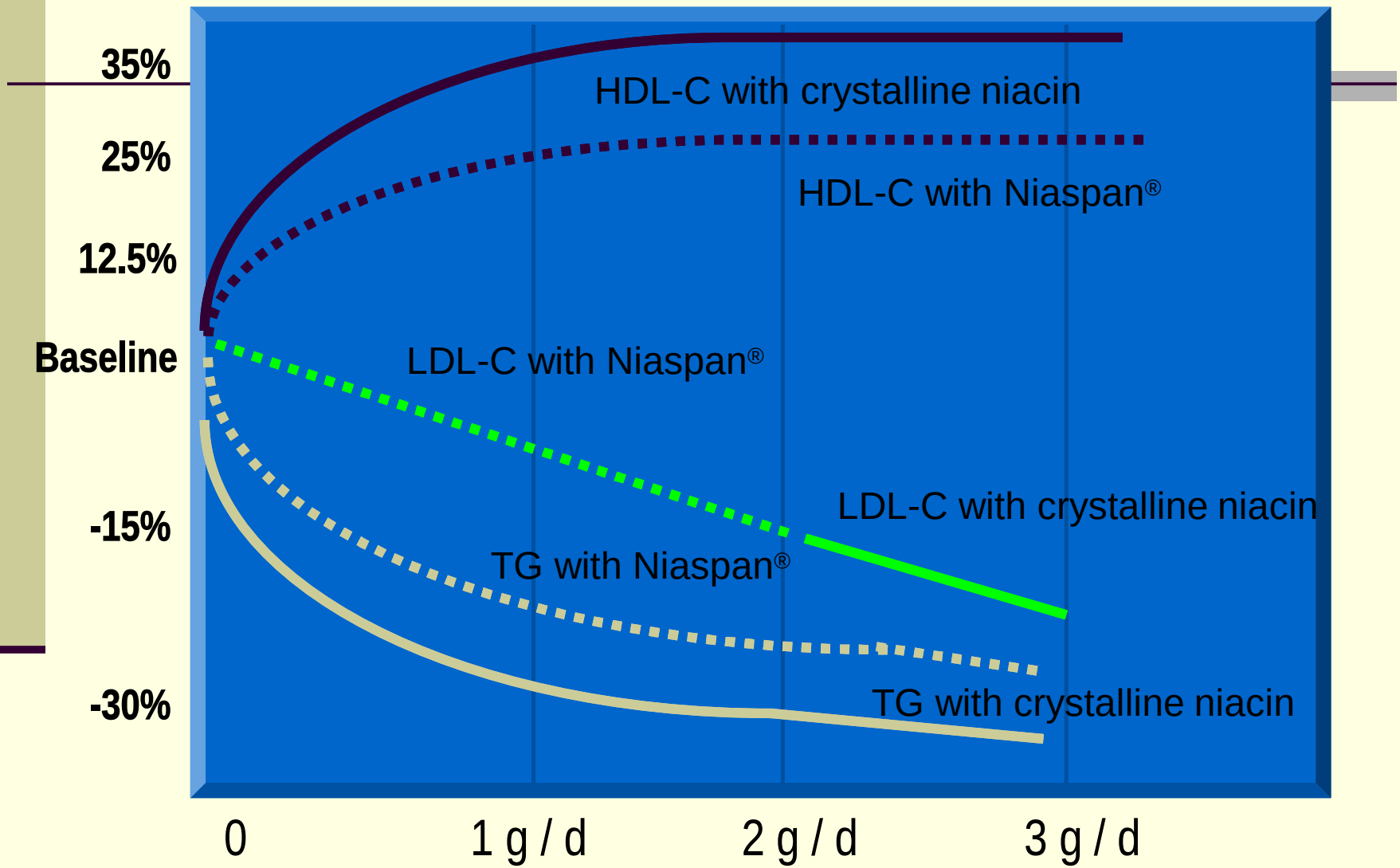
  Dyspepsia, gallstones, myopathy, Abn. LFT
- Contraindications

  Severe renal or hepatic / biliary disease

Fibric Acid Derivatives

Drug	Dose
Clofibrate	1000 mg BID
Bezafibrate	200 mg BID
Gemfibrozil	600 mg BID
Fenofibrate	200 mg OD
Fenofibrate micronized	160 mg OD

Effect of Niacin on Lipoproteins



Adapted from Knopp RH. N Engl J Med 1999;341:498-511..

Nicotinic Acid

- Products available
  - Immediate-release, 2–4 g/d, Sustained Release 3 g /d
  - Extended-release (Niaspan®) 1–2 g/d
- Best agent to raise HDL-C
- Reduces coronary events
- Adverse effects
  - Flushing, itching, headache (immediate-release, Niaspan®)
  - Hepatotoxicity, GI (sustained-release)
  - Activation of peptic ulcer
  - Hyperglycemia and reduced insulin sensitivity
- Contraindications
  - Active liver disease or unexplained LFT elevations
  - Peptic ulcer disease

Bile Acid Resins (BAR)

Major actions

- Reduce LDLc by 15–30%
- Raise HDLc by 3–5%
- May increase TG

Side effects

- GI distress / constipation / nausea
- Decreased absorption of other drugs

Contra indications

- Dysbetalipoproteinemia,
- Biliary Obstruction
- Raised TG (especially >400 mg/dL)

Bile Acid Resins

Drug	Dose Range
Cholestyramine	4–16 g
Colestipol	5–20 g
Colesevelam	2.6–3.8 g

How do we treat ?

Increased LDL	Statins +/- EZ
Increased TG	Fibrates
Decreased HDL	Niacin
Increased Lp(a)	Niacin
Increased LDL + TG	Statin + Fibrate
↑ LDL + ↓HDL	Statin + Niacin
↑TG + ↓HDL	Fibrate + Niacin

Agents That Raise HDL-C

Agent	HDL-C ↑	Primary Use
Nicotinic acid	15-35%	↑ **HDL**
Fibrates	5-20%	↓ TG
Statins	5-15%	↓ LDL
Rx omega-3[a]	*5-10%*	↓ *TG*
Bile-acid resins[a]	*2-5%*	↓ *LDL*
Ezetimibe[a]	*1-3%*	↓ *LDL*
Pioglitazone[a]	*5-20%*	↓ *Glucose*
Estrogens[a]	*10-25%*	↓ *Hot flashes*
α-blockers[a]	*10-20%*	↓ *BPH*
*Alcohol**	*5-10%*	*Social*

After Belalcazar LM, et al. *Prog Cardiovasc Dis.* 1998;41:151-174.
Insull W, et al. *Mayo Clin Proc*. 2001;76:971-982.
McKenney JM, et al. *Pharmacotherapy.* 2007;27:715-728.

Monitoring

Targets (in mg/dl)

HDL **>40 (>50 in women)**

TGL **< 150**

LDL **<100**

Total cholesterol **< 180.**

Therapy is monitored with muscle enzymes and liver enzyme estimation.Discontinue if liver enzymes are increased by 10 times the basal values.

Reduce dose of drugs and monitor renal functions while combining with fibrates.