Dyslipidaemias

- Clinical Discussion Series DH Dompe.
- 2016 November.

Short definition

- Dyslipidemias are disorders of lipoprotein metabolism, including lipoprotein overproduction or deficiency. These disorders may be manifested by elevation of the serum total cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride concentrations, and a decrease in the high-density lipoprotein (HDL) cholesterol concentration.

Good and bad fats.

- Bad fats- trans fats (risk of atherosclerosis is high)

  Artificial **trans fats** (or **trans fatty** acids) are created in an industrial process that adds hydrogen to liquid vegetable oils to make them more solid

- Good-monounsaturated and polyunsaturated fats (including omega-3s)

  Because risk of atherosclerosis is very less.

Why we have a strong concern about dyslipidemias

- There is a strong relationship between elevated serum cholesterol levels and the genesis of coronary heart disease. Coronary artery disease yet remains one of the major killers in current society.

- There are variety of other diseases which have closer relation with dyslipidemias. dyslipidemia remains major etiological factor of those diseases.

Classification of Dyslipidaemia

- Primary and secondary
  - 1)Primary-Familial Dyslipidaemias.
  - 2)secondary-acquired

Familial Hypercholesterolemia

- Also known as primary Hypercholesterolemia(dyslipidaemias)
- They are classified in to few classes which is based on the pattern of lipoproteins on electrophoresis or ultracentrifugation

TABLE 356-3 Fredrickson Classification of Hyperlipoproteinemias

Phenotype	I	IIa	IIb	III	IV	V
Lipoprotein, elevated	Chylomicrons	LDL	LDL and VLDL	Chylomicron and VLDL remnants	VLDL	Chylomicrons and VLDL
Triglycerides	↑↑↑	N	↑	↑↑	↑↑	↑↑↑
Cholesterol (total)	↑	↑↑↑	↑↑	↑↑	N/↑	↑↑
LDL-cholesterol	↓	↑↑↑	↑↑	↓	↓	↓
HDL-cholesterol	↓↓↓	N/↓	↓	N	↓↓	↓↓↓
Plasma appearance	Lactescent	Clear	Clear	Turbid	Turbid	Lactescent
Xanthomas	Eruptive	Tendon, tuberous	None	Palmar, tuberoeruptive	None	Eruptive
Pancreatitis	+++	0	0	0	0	+++
Coronary atherosclerosis	0	+++	+++	+++	+/−	+/−
Peripheral atherosclerosis	0	+	+	++	+/−	+/−
Molecular defects	LPL and ApoC-II	LDL receptor, ApoB-100, PCSK9, LDLRAP, ABCG5 and ABCG8		ApoE	ApoA-V	ApoA-V and GPIHBP1
Genetic nomenclature	FCS	FH, FDB, ADH, ARH, sitosterolemia	FCHL	FDBL	FHTG	FHTG

Type	Synonym	Defect	Serum abnormality	Clinical Features	Treatment	Serum appearance
Type 1	Familial Hyperchylomicronemia	Low LDL Altered ApoC2	Chylomicron ↑	Pancreatitis, Lipemia retinalis, skin eruptions, Xanthoma, Hepatosplenomegaly	Diet	Creamy top layer
Type IIa	Familial Hypercholestrolemia	↓LDL receptor	LDL↑	Xanthelasma, Arcus senilis, Tendon xanthomas	Cholestyramine or Cholestipol, Statins, Niacin	Clear
Type IIb	Familial Combined Hypercholestrolemia	↓LDL receptor & ↑Apo B	LDL & VLDL↑		Statins, Niacin, Fibrate	Clear
Type III	Familial dysbetalipoproteinemia	Apo E2 synthesis defect	IDL↑	Tubo-eruptive xanthomas, palmar xanthoma	Fibrate, Statins	Turbid
Type IV	Familial Hyperlipemia	↑VLDL production, ↓elimination	VLDL↑		Statins, Niacin, Fibrate	
Type V	Endogenous hypertriglyceridemia	↑VLDL production, ↓LPL	VLDL & Chylomicron↑		Niacin, Fibrate	Creamy top layer & Turbid bottom

Secondary causes of hyperlipidemia (dyslipidemias)

- Medical conditions - eg, hypothyroidism, obstructive jaundice, Cushing's syndrome, anorexia nervosa, nephrotic syndrome, diabetes mellitus, and chronic kidney disease.
- Drugs - eg, thiazide diuretics, glucocorticoids, ciclosporin, antiretroviral therapy, beta-blockers, combined oral contraceptive pill, atypical antipsychotics, and retinoic acid derivatives.
- Pregnancy.
- Pregnancy.
- Alcohol abuse.

Diagnosis

- **Clinical features-**
- 1) Premature arcus senilis - a white or gray opaque ring in the corneal margin
- 2) Tendon xanthomata - these are hard, non-tender nodular enlargement of tendons. They are most commonly found on the knuckles and the Achilles tendons.
- 3) Xanthelasmas - fatty deposits in the eyelids.

Lipid profile

- Traditionally, most laboratories have required patients to fast for 9–12 hours before screening. However, recent studies have questioned the utility of fasting before lipid panels, and some diagnostic labs now routinely accept non-fasting samples.
- **The lipid profile typically includes:**
- Low-density lipoprotein (LDL)
- High-density lipoprotein (HDL)
- Triglycerides
- Total cholesterol
- **Using these values, a laboratory may also calculate**:
- Very low-density lipoprotein (VLDL)
- Cholesterol:HDL ratio

Cholesterol:HDL ratio

- Your cholesterol ratio is calculated by dividing your total cholesterol by your HDL number. For instance, if your total cholesterol is 180 and your HDL is 82, your cholesterol ratio is 2.2. According to the American Heart Association (AHA), you should aim to keep your ratio below 5, with the ideal cholesterol ratio at 3.5. this number represents the risk of a CV disease. Risk increase with the number.

Total cholesterol levels in a lipid profile

- A total cholesterol level of less than 200 mg/dL (5.17 mmol/L) is **normal**.
- A total cholesterol level of 200 to 239 mg/dL (5.17 to 6.18 mmol/L) is **borderline high**.
- A total cholesterol level greater than or equal to 240 mg/dL (6.21 mmol/L) is **high**.

TG levels

- **Triglycerides** — High triglyceride levels are also associated with an increased risk of cardiovascular disease
- Normal - less than 150 mg/dL (1.69 mmol/L)
- Borderline high - 150 to 199 mg/dL (1.69 to 2.25 mmol/L)
- High - 200 to 499 mg/dL (2.25 to 5.63 mmol/L)
- Very high - greater than 500 mg/dL (5.65 mmol/L)

HDL levels

- A level greater than or equal to 60 mg/d is exelent level.
- while levels of HDL cholesterol less than 40 mg/dL lower than desired.

Familial hypecholesterolaemia

- **Familial hypercholesterolaemia**
- Suspect familial hypercholesterolaemia where:
- Adults have a raised TChol concentration (typically >7.5 mmol/L) and there is a personal or family history of premature CHD.
- Rule out secondary causes of hypercholesterolaemia.
- Do not rule out familial hypercholesterolaemia simply because physical signs such as tendon xanthomata are not present.
- Make a diagnosis using the Simon Broome criteria
- Check two fasting LDL-C measurements to confirm the diagnosis.

The Simon Broom diagnostic criteria for diagnosing familial hypercholesterolemia

- *Definite* familial hypercholesterolaemia is diagnosed if an individual has:
  - A TChol level in an adult of >7.5 mmol/L (>6.7 mmol/L in a child) and an LDL-C of >4.9 mmol/L (>4.0 mmol/L in a child); PLUS
  - Tendon xanthomata or evidence of these signs in a first-degree or second-degree relative; OR
  - DNA evidence of an LDL receptor mutation, familial defective apo-B-100 or a PCSK9 mutation.
- *Possible* familial hypercholesterolaemia should be diagnosed if the cholesterol concentrations fit these criteria and the individual has at least one of the following:
  - A family history of myocardial infarction in a second-degree relative aged 50 years or younger, or in a first-degree relative aged 60 years or younger.
  - A family history of raised TChol greater than 7.5 mmol/L in adult first-degree or second-degree relatives or greater than 6.7 mmol/L in a child, brother or sister aged younger than 16 years.

Familial combined hyperlipidaemia

- This is the most common genetic dyslipidaemia, occurring in about 1 in 100 people but is usually polygenic in origin.
- Lipid phenotypes in familial combined hyperlipidaemia vary considerably but suspect where:
- There is family history of hyperlipidaemia or premature CHD not due to familial hypercholesterolaemia.
- Moderate-to-severe mixed hyperlipidaemia (typically TChol 6.5-8.0 mmol/L and TG 2.3-5.0 mmol/L).

Short description about lipoproteins

- **VLDL Very-low-density lipoprotein**
- Makes up 10%-15% of total cholesterol
- With LDL, the main form of "bad" cholesterol
- A precursor of LDL.
- **LDL Low-density lipoprotein**
- Makes up 60%-70% of total cholesterol
- Main form of "bad" cholesterol
- Causes build up of plaque inside arteries.

continued

- **HDL High-density lipoprotein**

- Makes up 20%-30% of total cholesterol
- The "good" cholesterol
- Moves cholesterol from arteries to the liver.

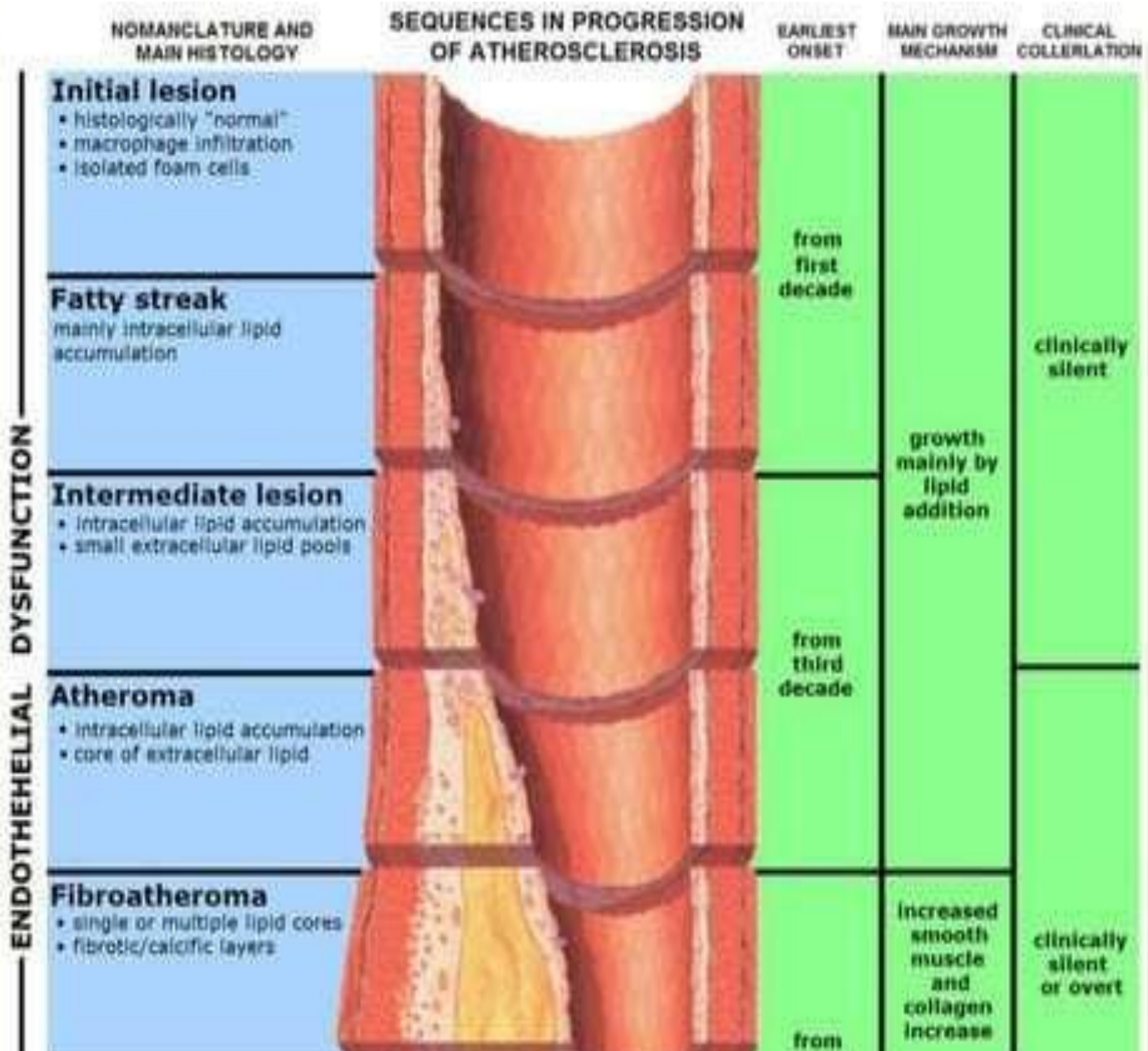
Atherosclerosis

- Atherosclerosis, or hardening of the arteries, is a condition in which plaque builds up inside the arteries. Plaque is made of cholesterol, fatty substances, cellular waste products, calcium and fibrin (a clotting material in the blood).

Atherosclerosis is a type of *arteriosclerosis*. *Arteriosclerosis* is a general term for the thickening and hardening of arteries.

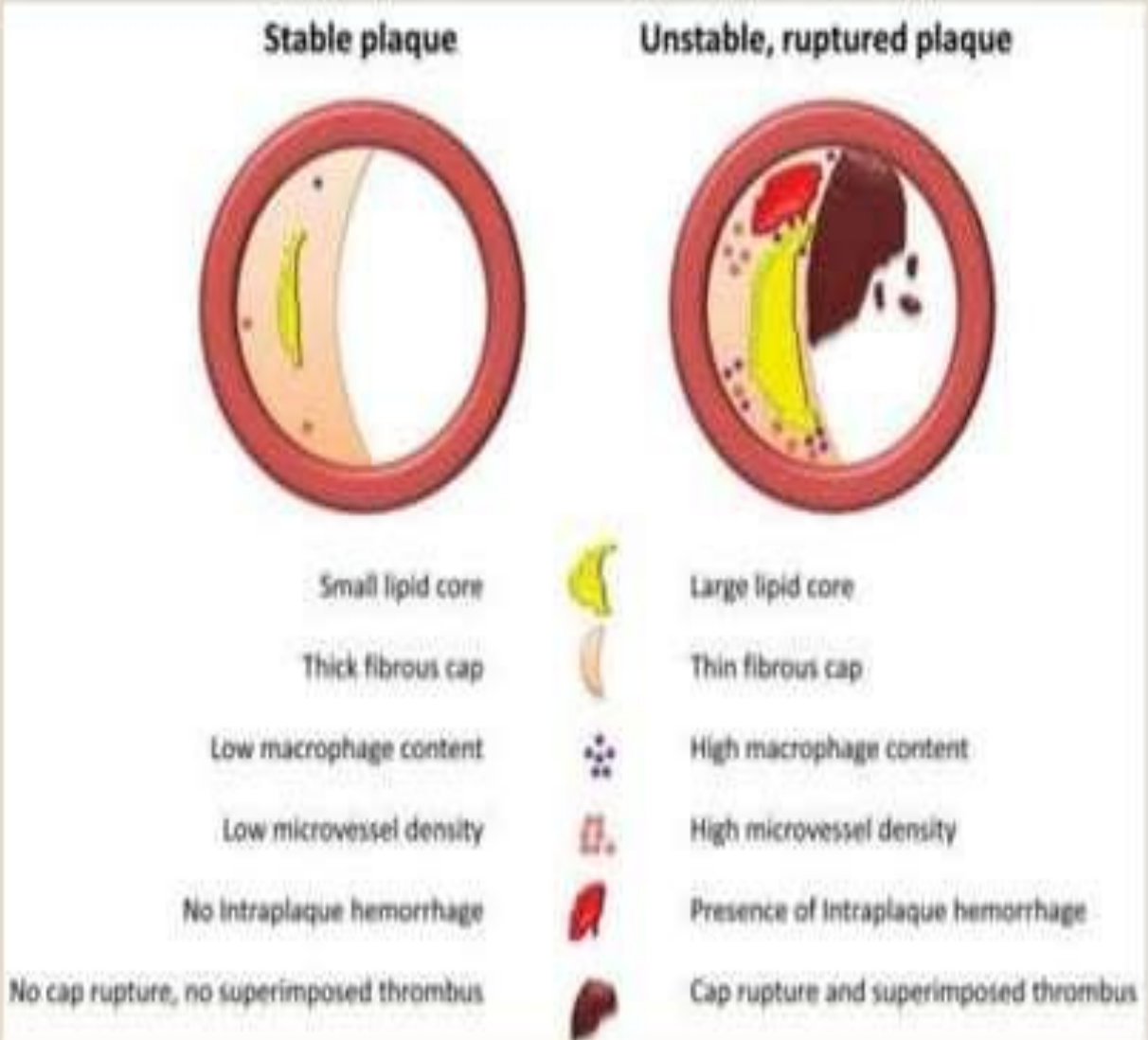
Pathology

- 1)endothelial damage-(smoking,hypertension,elevated blood cholesterols.)
- 2)fatty streak formation in the vessel wall.
- 3) These accumulations contain both living, active WBCs (producing inflammation) and remnants of dead cells, including cholesterol and triglycerides.
- 4)Calcification of the lesion.
- 5)reduction in the arterial wall diameter and elasticity.


NOMANCLATURE AND MAIN HISTOLOGY
SEQUENCES IN PROGRESSION OF ATHEROSCLEROSIS
EARLIEST ONSET
MAIN GROWTH MECHANISM
CLINICAL COLLERLATION
ENDOTHEHELIAL DYSFUNCTION
Initial lesion
• histologically "normal"
• macrophage infiltration
• isolated foam cells
Fatty streak
mainly intracellular lipid accumulation
Intermediate lesion
• intracellular lipid accumulation
• small extracellular lipid pools
Atheroma
• intracellular lipid accumulation
• core of extracellular lipid
Fibroatheroma
• single or multiple lipid cores
• fibrotic/calcific layers
from first decade
from third decade
from
growth mainly by lipid addition
increased smooth muscle and collagen increase
clinically silent
clinically silent or overt

Atherosclerotic plaque

- Stable plaques-Less symptomatic or asymptomatic.
- Unstable plaques-High risk of rupture and causing an ischemic event.


Stable plaque
Unstable, ruptured plaque
Small lipid core
Large lipid core
Thick fibrous cap
Thin fibrous cap
Low macrophage content
High macrophage content
Low microvessel density
High microvessel density
No intraplaque hemorrhage
Presence of intraplaque hemorrhage
No cap rupture, no superimposed thrombus
Cap rupture and superimposed thrombus

Risk factors for atherosclerosis

- increasing age
- gender (At younger ages, males are more at risk. Premenopausal women are relatively protected; after menopause the risk in women increases and eventually exceeds the risk in males.)
- family history
- genetic abnormalities (yet fully not explained)
- Hyperlipidemia
- Hypertension
- Cigarette smoking (smoking potentiates the other risk factors)
- Diabetes
- C-reactive protein level (increased in atherosclerosis)

Lesser or uncertain risk factors

- Obesity
- Physical inactivity
- Stress
- Postmenopausal estrogen deficiency
- High carbohydrate intake
- Lipoprotein (a) (an altered form of LDL that seems to be independently associated with increased risk of atherosclerosis)
- Trans-fat intake

Diseases associated with atherosclerosis

- Most common disease is IHD
- Carotid artery disease.
- PVD+/_leriche Xd
- Chronic kidney disease due to atherosclerosis of renal artery.

Total cardiovascular risk assessment.

- Total cardiovascular risk estimation means the likelihood of a person developing an atherosclerotic CV event over a defined period of time.
- Most guidelines use risk estimation systems based on either the **Framingham** or the **SCORE(Systemic Coronary Risk Estimation)** projects

Basics-when to use a risk estimation system

(1) Those with

- † known CVD
- † type 2 diabetes or type 1 diabetes with
- microalbuminuria
- † very high levels of individual risk factors
- † chronic kidney disease (CKD)

They are automatically categorized in high risk group. While they need prompt medical management to cover all the risk factors.

Basics-when to use a risk estimation system

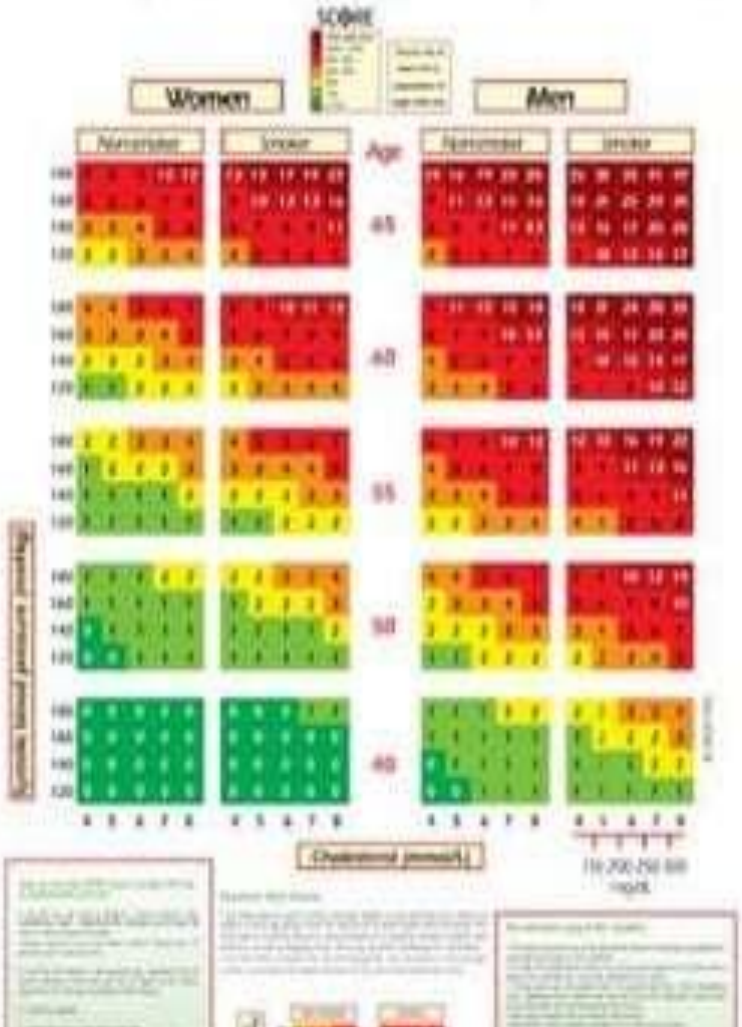
- All the other patients not falling in above mentioned criteria should assessed with a risk estimation system like SCORE.

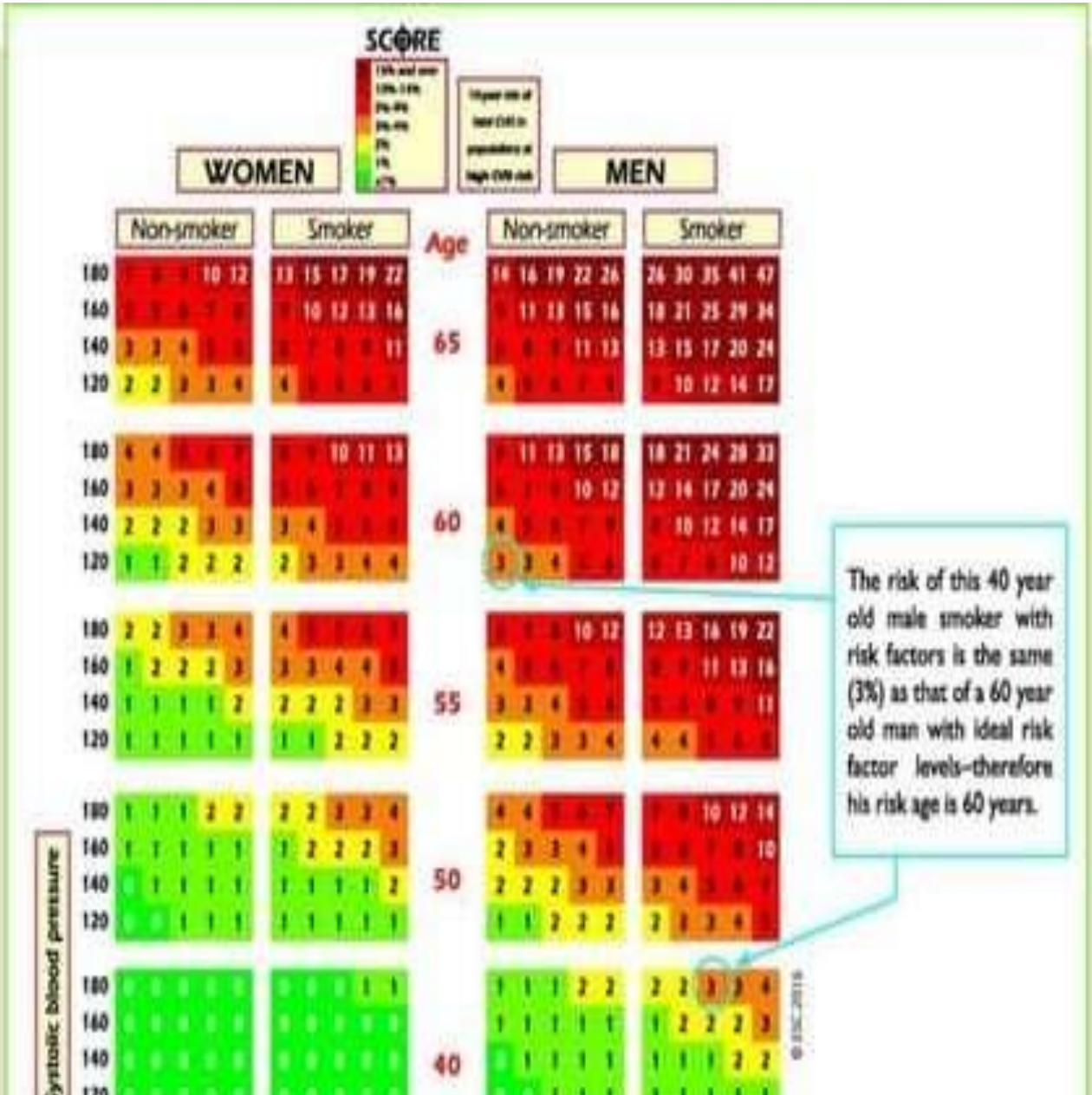
- Risk estimation systems including firmingham and SCORE are somewhat similar. Once you are familiar with one system you can easily adapt other system. As an example here we are using SCORE system to calculate risk.(risk estimation systems will change with the dynamics of the medical knowledge and newer recommendations by clinicians)

SCORE (developed in EU)

- The SCORE system estimates the 10 year risk of a first fatal atherosclerotic event, whether heart attack, stroke, or other occlusive arterial disease, including sudden cardiac death.

SCORE - European High Risk Chart




SCORE
WOMEN
MEN
Non-smoker
Smoker
Non-smoker
Smoker
Age
65
60
55
50
40
Systolic blood pressure
The risk of this 40 year old male smoker with risk factors is the same (3%) as that of a 60 year old man with ideal risk factor levels–therefore his risk age is 60 years.

SCORE

- The SCORE data indicate that the total CVD event risk is about three times higher than the risk of fatal CVD for men, so that a SCORE risk of 5% translates into a CVD risk of 15% of total (fatal plus non-fatal)

SCORE

- Clinicians often ask for thresholds to trigger certain interventions, but this is problematic since risk is a continuum and there is no threshold at which, for example, a drug is automatically indicated,

Risk groups depending of SCORE system-Very High Risk

- **Subjects with any of the following falls this category.**
- Documented CVD by invasive or non-invasive testing (such as coronary angiography, nuclear imaging, stress echocardiography, carotid plaque on ultrasound), previous myocardial infarction (MI), ACS, coronary revascularization [percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG)] and other arterial revascularization procedures, ischaemic stroke, PAD.
- Patients with type 2 diabetes, patients with type 1 diabetes with
- Patients with moderate to severe CKD
- A calculated 10 year risk SCORE ≥10%.

Risk groups depending of SCORE system-High Risk

- **Subjects with any of the following:**
- † Markedly elevated single risk factors such as familial dyslipidaemias and severe hypertension.
- † A calculated SCORE ≥5% and ,10% for 10 year risk of fatal CVD.

Risk groups depending of SCORE system-Moderate Risk

- Subjects are considered to be at moderate risk when their SCORE is ≥1% and ,5% at 10 years.

Risk groups depending of SCORE system-Moderate Risk

- The low risk category applies to individuals with SCORE ,1%.

About What the patient should be adviced?

- 1)lifestyle-diet, exercise
- 2)Controlling the causes of secondary hyperlipidemia.
- 3)Controlling DM.
- 4)timely medical assessments.
- 5)importance of drug compliance.
- 6)well know side effects of therapy.
- 7)adequate knowledge about IHD.

Which patients should be treated?

- The most important factor to consider is a person's long-term risk of experiencing a heart attack or stroke. If the risk is very low, there is probably no need for statins, unless the LDL is above 190 mg/dL (4.9 mmol/L). If the risk is very high — for example, someone who has had a heart attack in the past — the person may benefit from statins, even if his or her cholesterol is not elevated.

New guidelines from the American College of Cardiology

- **People who already have cardiovascular disease.** This group includes people who have had heart attacks, strokes caused by blockages in a blood vessel, mini-strokes (transient ischemic attacks), peripheral artery disease, or prior surgery to open or replace coronary arteries.
- **People who have very high LDL (bad) cholesterol.** This group includes adults who have LDL cholesterol levels of 190 mg/dL (4.9 mmol/L) or higher.
- **People who have diabetes.** This group includes adults who have diabetes and an LDL between 70 and 189 mg/dL (1.8 and 4.9 mmol/L), especially if they have evidence of vascular disease.
- **People who have a higher 10-year risk of heart attack.** This group includes people who have an LDL above 100 mg/dL (1.8 mmol/L) and whose 10-year risk of a heart attack is 7.5 percent or higher.

Manage hypertriglyceridaemia

- Controlling triglyceride levels decrease risk of IHD.
- Also prevents Pancreatitis.
- (elevated triglycerides also cause hepatomegaly and splenomegaly)

- Treatment options-Fibrates, Niacine, Omega-3 fatty acids.
- Statins may use as a combined therapy. (statin and a
- fibrate, particularly fenofibrate, bezafibrate, or ciprofibrate)
- **Better management of triglycerides helps to lower the VLDL levels.**

How to manage low HDL levels.

- Low HDL levels increase the risk of IHD.
- Low HDL levels can be treated with-
  - 1) Statins produce modest elevations in HDL-C
  - 2)nicotinic acid-Nicotinic acid appears to increase HDL-C by partially reducing HDL catabolism and mainly by increasing apo A1 synthesis by the liver.
  - (fibrates has a small ability to elevate HDL levels though there is no therapeutic advantage)
  - 3)Cholesteryl ester transfer protein inhibitors(new drug group and very effective) **torcetrapib, dalcetrapib, and anacetrapib**

Management of LDL levels

- Statins-Statins reduce synthesis of cholesterol in the liver by competitively inhibiting HMG-CoA reductase activity.
- Commonly used statins-
  - atorvastatin (Lipitor),
  - fluvastatin (Lescol, Lescol XL),
  - lovastatin (Mevacor, Altoprev),
  - pravastatin (Pravachol),
  - rosuvastatin (Crestor),
  - simvastatin (Zocor), and
  - pitavastatin (Livalo).

Statins are widely used in sri lanka. What do we need to know about statins?

- Usually statins are metabolized in liver.
- There are two serious sideeffects which a clinican must be aware of.
  - 1)myopathy which may progress in to rhabdomyolysis. (myoglobin levels will be increased causing acute renal failure.) one of the signs of myopathy and muscle damage elevated CPK.
  - 2)hepatocellular damage.(clinicians usually assess this condition by periodical measurement of ALT levels. If the AST levels are elevated a repeat AST must be done. And if the AST levels are high as three folds that of normal statins will be discontinued.

Statins may elevate blood sugar levels mildly.(though statins shouldn't omit).

Combining statins with fibrate increases the possibility of myopathy.

Cholesterol absorption inhibitors.

- intestine absorbs the cholesterol from your diet and releases it into your bloodstream. The drug ezetimibe (Zetia) helps reduce blood cholesterol by limiting the absorption of dietary cholesterol. Ezetimibe can be used in combination with a statin drug.
- Ezetimibe is the first lipid-lowering drug that inhibits intestinal uptake of dietary and biliary cholesterol
- And the advantage this drug will not interfere with absorption of other lipid soluble nutrients.

Bile-acid-binding resins (Bile acid sequestrants)

- **cholestyramine**
- **Colestipol**

- these are bile acid binding exchange resins.

Nicotinic acid

- Nicotinic acid has a broad lipid modulating action. In can increase the HDL levels, decrease the LDL levels and triglyceride levels.
- This can be used with statins.

Diet.

- There are many internet resources regarding diet therapy and food for dyslipidaemic patients.
- As a overview there is a huge encouragement toward use of vegetables and fruits.
- Indeed a good diet plays a major role in managements of atherosclerosis.
- Role dietician is very important.

Resources and references.

- Dyslipidaemia management guidelines by European society of cardiology.
- Web portal of American association of family physicians. http://www.aafp.org/afp/1998/0501/p2192.html
- Hyperlipidaemia- http://patient.info/health/hyperlipidaemia-leaflet
- Web page myoclonic USA.-http://www.mayoclinic.org
- Atherosclerosis- http://www.heart.org/HEARTORG/Conditions/Cholesterol/WhyCholesterolMatters/Atherosclerosis_UCM_305564_Article.jsp#.WDpbdUvISs0
- Hyperlipidaemia-http://www.rightdiagnosis.com/h/hyperlipidaemia/complic.htm
- GP notebook fedrickson classification http://www.gpnotebook.co.uk/simplepage.cfm?ID=x20020617063512021840
- Primary dyslipidaemias Maersk manual http://www.merckmanuals.com/professional/endocrine-and-metabolic-disorders/lipid-disorders/dyslipidemia