Coronary Atherosclerosis without abnormal lipid profile

How to manage?

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*Atherosclerosis - An epidemic of 21st century.

*Chronic progressive disease of accumulation of atheromatous plaque within arterial wall.

*Economic development and urbanization promoted habits of poor diet and diminished physical activity, which can favor atherogenesis.
INTRODUCTION

- Definition: **Atherosclerosis** (arteriosclerotic vascular disease) is a condition in which an artery wall thickens as a result of the accumulation of fatty materials such as **cholesterol**.
- In Greek, *ather* means *gruel*, and *skleros* means *hard*.

**FOCAL LIPID ACCUMULATION**

PATHOGENESIS

- Response-to-injury hypothesis- 4 main stages to atherogenesis:
  1. Chronic endothelial injury
  2. Accumulation of lipoproteins
  3. Resultant inflammation & factor release
  4. Smooth muscle cell recruitment, proliferation and ECM production
- The process of atherosclerosis begins in childhood and has clinical manifestations in late adulthood.
- The process develops over years to decades and progression is not linear and smooth but discontinuous with periods of quiescence and rapid evolution.
More than 90% of myocardial infarctions are attributable to modifiable risk factors.

Epidemiological studies have shown that genetic predisposition account for 40 – 60% of risk for CAD: as Lt.main and proximal disease display a high heritability.

The multiplicative effect of cigarette smoking, hypertension, diabetes and high cholesterol on the risk of coronary artery disease is well known; however, the effect of serum concentrations of various lipid subsets have not been well appreciated.
The more LDL–C there in the blood the more rapidly atherosclerosis develops.

Micael Brown and Josef Goldstien Nobel award winners 1984

is that the statement till now?

Rather than population-derived indices to define normal or abnormal LDL in the untreated patient, it is more appropriate to define "normal" as "cholesterol values at which level there is no subclinical atherosclerosis" and "abnormal" as "cholesterol values at which level there is subclinical atherosclerosis," with the severity of "abnormal" depending on the degree of subclinical atherosclerosis.
The emergence of atherosclerosis imaging, using **coronary calcium** scanning and **carotid intima media thickness** as stronger predictors of cardiovascular events than risk factors of atherosclerosis, has created a paradigm shift in the primary prevention of cardiovascular disease.

- **Blood cholesterol has nothing to do with atherosclerosis**; **autopsy studies** dating back to 1936 all show the same finding: cholesterol levels do not correlate with the amount of atherosclerosis found.

- **Coronary calcification** correlate strongly with total plaque volume, obstructive coronary disease and powerful predictor of clinical outcome, nonetheless it did not correlate with any lipid fraction in the blood.

- **Cholesterol does not correlate with degree of coronary atherosclerosis on angiography** and also **peripheral atherosclerosis**.
- Absence cardiovascular risk factors (CVRFs) is traditionally considered a reliable indicator of low risk for atherosclerosis, however individuals without CVRFs still have atherosclerosis and cardiovascular events.

**Subclinical atherosclerosis** underlies most cardiovascular events, and its detection can improve risk stratification.

An elevated Lp (a) level is an independent risk factor of premature CAD and significant risk factor for premature atherosclerosis and CV events.

There is lack of available agents that is effective in reducing Lp (a) level and the best strategy to reduce it is lowering LDL level.
- Normal LDL cholesterol levels are associated with subclinical atherosclerosis in the absence of risk factors (jacc 2017).
- The low-density lipoprotein treatment goal is the level at which atherosclerosis progression is halted.
- In the absence of conventional CVRFs, the presence and extent of atherosclerosis were associated with age, male sex, LDL-C and HbA1C.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Male gender (and females after menopause)</td>
<td>Estrogen increases cholesterol removal by the liver, and the progression of atherosclerosis is less rapid in premenopausal women than in men</td>
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<tr>
<td>Family history of ischemic heart disease, stroke</td>
<td>Probably multiple genetic mechanisms.</td>
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<tr>
<td>Primary hyperlipidemia</td>
<td>Inherited disorders causing lipoprotein lipase deficiency (type I), defective LDL receptors (type IIa), abnormal apoprotein E (type III), deficiency of apoprotein C (type V), or unknown cause (types IIb and IV).</td>
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<tr>
<td>Secondary hyperlipidemia</td>
<td>Increased circulating triglycerides produced by diuretics, β-adrenergic blocking drugs, excess alcohol intake.</td>
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<tr>
<td>Cigarette smoking</td>
<td>Probably carbon monoxide-induced hypoxic injury to endothelial cells.</td>
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<tr>
<td>Hypertension</td>
<td>Increased shear stress, with damage to endothelium.</td>
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<tr>
<td>Diabetes mellitus (types 1 and 2)</td>
<td>Decreased hepatic removal of LDL from the circulation; increased glycosylation of collagen, which increases LDL binding to blood vessel walls.</td>
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<td>Obesity, particularly abdominal obesity</td>
<td>Unsettled, but obesity is associated with type 2 diabetes, hypertriglyceridemia, hypercholesterolemia, and hypertension, all of which are risk factors in their own right.</td>
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<tr>
<td>Nephrotic syndrome</td>
<td>Increased hepatic production of lipids and lipoprotein (a).</td>
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<td>Hypothyroidism</td>
<td>Decreased formation of LDL receptors in the liver.</td>
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<tr>
<td>Elevated plasma homocysteine</td>
<td>Unsettled. Probably increased homocysteine provides more H₂O₂, and other reactive oxygen molecules that foster formation of oxidized LDL.</td>
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* Key factors have emerged but do not explain all the risk, and unknown factors may account for up to 40% of the variation in risk from one person to the next.
**Recommendations:**

* HOW SHOULD INDIVIDUALS BE SCREENED FOR THE DETECTION OF DYSLIPIDEMIA: 

Global Risk Assessment

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**R1. Identify risk factors that enable personalized and optimal therapy**

<table>
<thead>
<tr>
<th>Major risk factors</th>
<th>Additional risk factors</th>
<th>Nontraditional risk factors</th>
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<tbody>
<tr>
<td>Advancing age</td>
<td>Obesity, abdominal obesity</td>
<td>Lipoprotein (a)</td>
</tr>
<tr>
<td>Total serum</td>
<td>Family history of hyperlipidemia</td>
<td>Clotting factors</td>
</tr>
<tr>
<td>cholesterol level</td>
<td>Small, dense LDL-C</td>
<td>Inflammation markers</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>Apo B</td>
<td>(hsCRP, Lp-PLA)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>LDL particle concentration</td>
<td>Homoeysteine levels</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>Fasting/postprandial hypertriglyceridemia</td>
<td>Apo E4 isoform</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>PCOS</td>
<td>Uric acid</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Dyslipidemic triad</td>
<td>TG-rich remnants</td>
</tr>
<tr>
<td>Chronic kidney disease 3</td>
<td></td>
<td></td>
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<tr>
<td>Cigarette smoking</td>
<td></td>
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<tr>
<td>Family history of ASCVD</td>
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Cardiovascular Risk

R4. The 10-year risk of a coronary event (high, intermediate, or low) should be determined by detailed assessment using one or more of the following tools:

- Framingham Risk Assessment Tool
- Multi-Ethnic Study of Atherosclerosis (MESA) 10-year ASCVD Risk with Coronary Artery Calcification Calculator
- Reynolds Risk Score, which includes highly sensitive CRP (hsCRP) and family history of premature ASCVD
- United Kingdom Prospective Diabetes Study (UKPDS) risk engine to calculate ASCVD risk in individuals with T2DM

* WHEN TO SCREEN?
Familial Hypercholesterolemia

**R9.** Individuals should be screened for familial hypercholesterolemia (FH) when there is a F/H of:
- Premature ASCVD (definite myocardial infarction [MI] or sudden death before age 55 years in father or other male first-degree relative, or before age 65 years in mother or other female first-degree relative)
- Elevated cholesterol levels (total, non-HDL and/or LDL) consistent with FH

ADULTS

- **R10.** Annually screen all adult individuals with T1DM or T2DM for dyslipidemia
- **R11.** Evaluate all adults 20 years of age or older for dyslipidemia every 5 years
- **R12.** In the absence of ASCVD risk factors, screen middle-aged individuals for dyslipidemia at least once every 1 to 2 years. More frequent lipid testing is recommended when multiple global ASCVD risk factors are present
**OLDER ADULTS**

* R14. Annually screen older adults with 0 to 1 ASCVD risk factor for dyslipidemia
* R15. Older adults should undergo lipid assessment if they have multiple ASCVD global risk factors (i.e., other than age)
* R16. Screening for this group is based on age and risk, but not gender; older women should be screened in the same way as older men

**Childhood and Adolescence**

* R17. In children at risk for FH (e.g., family history of premature cardiovascular disease or elevated cholesterol), screening should be at 3 years of age, again between ages 9 and 11, and again at age 18
* R18. Screen adolescents older than 16 years every 5 years or more frequently if they have ASCVD risk factors, have overweight or obesity, have other elements of the insulin resistance syndrome, or have a family history of premature ASCVD
**WHICH SCREENING TESTS?**

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**Fasting Lipid Profile**

* **R19.** Use a fasting lipid profile to ensure the most precise lipid assessment; this should include total cholesterol, LDL-C, TG, and non-HDL-C (Grade C; BEL 4, upgraded due to costeffectiveness).

* **R20.** Lipids, including TG, can be measured in the non-fasting state if fasting determinations are impractical.
Low-Density Lipoprotein Cholesterol: LDL-C

R21. Estimated using the Friedewald equation:

\[ \text{LDL-C} = (\text{total cholesterol} - \text{HDL-C}) - \frac{\text{TG}}{5} \]

however, valid only for values obtained during the fasting state and becomes increasingly inaccurate when TG levels are greater than 200 mg/dL, and becomes invalid when TG levels are greater than 400 mg/dL (Grade C; BEL 3).

R22. LDL-C should be directly measured in certain high-risk individuals, such as those with fasting TG levels greater than 250 mg/dL or those with diabetes or known vascular disease.

High-Density Lipoprotein Cholesterol

R23. Measurement of HDL-C should be included in screening tests for dyslipidemia.
**Non–High-Density Lipoprotein Cholesterol**

**R24.** The non-HDL-C (total cholesterol minus HDL-C) should be calculated if moderately elevated TG (200 to 500 mg/dL), diabetes, and/or established ASCVD

**R25.** If insulin resistance is suspected, the non-HDL-C should be evaluated to gain useful information regarding the individual’s total atherogenic lipoprotein burden

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**Triglycerides**

**R26.** TG levels should be part of routine lipid screening:
- moderate elevations (≥150 mg/dL) may identify individuals at risk for the insulin resistance syndrome and
- levels ≥200 mg/dL may identify individuals at substantially increased ASCVD risk
### Apolipoproteins

**R27. Apo B and/or an apo B/apo A1 ratio calculation and evaluation may be useful to assess residual risk and guide decision-making in -**
- at-risk individuals (TG ≥ 150, HDL-C < 40, prior ASCVD event)
- T2DM, and/or the insulin resistance syndrome [even at target LDL-C levels]"

**R28. Apo B measurements (reflecting the particle concentration of LDL and all other atherogenic lipoproteins) may be useful to assess the success of LDL-C-lowering therapy.**

### R 29. Secondary Causes must be ruled out : Common Causes

- Hypothyroidism
- Nephrosis
- Dysgammaglobulinemia (SLE, multiple myeloma)
- Progestin or anabolic steroid treatment
- Cholostic diseases
- Protease inhibitors for treatment of HIV infection
- Chronic renal failure
- Type 2 diabetes mellitus
- Obesity
- Excessive alcohol intake
- Hypothyroidism
- Antihypertensive medications
- Corticosteroid therapy
- Orally administered estrogens, Oral contraceptives, pregnancy
- Protease inhibitors for treatment of HIV infection.

**Affected lipids: Total cholesterol, LDL-C, TG, VLDL-C**
R30. Use highly sensitive C-reactive protein (hsCRP) to stratify ASCVD risk in individuals with-
- a borderline standard risk assessment, or
- in those with an intermediate or higher risk with an LDL-C concentration less than 130 mg/dL.

R31. Measure lipoprotein-associated phospholipase A2 (Lp-PLA2), when it is necessary to further stratify an individual's ASCVD risk, especially if hsCRP elevated.

R32. The routine measurement of homocysteine, uric acid, plasminogen activator inhibitor-1, or other inflammatory markers is not recommended.

R33. Coronary artery calcification (CAC) measurement has been shown to be of high predictive value and is useful in refining risk stratification to determine the need for more aggressive treatment strategies.

R34. Carotid intima media thickness (CIMT) may be considered to refine risk stratification to determine the need for more aggressive ASCVD preventive strategies.
TREATMENT RECOMMENDATIONS IN INDIVIDUALS WITH DYSLIPIDEMIA AND ASCVD RISK

Risk Categories and LDL-C Goals

<table>
<thead>
<tr>
<th>Risk Status</th>
<th>LDL-C Goals</th>
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<tbody>
<tr>
<td><strong>R 36.</strong> Low risk (no risk factors)</td>
<td>less than 130 mg/dL</td>
</tr>
<tr>
<td><strong>R 37.</strong> Moderate risk (2 or fewer risk factors and 10-year risk of &lt;10%)</td>
<td>less than 100 mg/dL</td>
</tr>
<tr>
<td><strong>R 38.</strong> High risk (an ASCVD equivalent including diabetes or CKD stage 3 or 4 with no other risk factors, or individuals with 2 or more risk factors and a 10-year risk of 10%-20%)</td>
<td>less than 100 mg/dL</td>
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</tbody>
</table>
### Risk Categories and LDL-C Goals

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<tr>
<td><strong>R 39. Very high risk</strong> <em>(established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease; diabetes or CKD stage 3 or 4 with 1 or more risk factors; a calculated 10-year risk greater than 20%; or heterozygous familial hypercholesterolemia [HeFH])</em>,</td>
<td>less than 70 mg/dL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Status</th>
<th>LDL-C Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R 40. Extreme risk</strong> <em>(progressive ASCVD, including unstable angina that persists after achieving an LDL-C less than 70 mg/dL, or established clinical ASCVD in individuals with diabetes, CKD stage 3 or 4, and/or HeFH, or in individuals with a history of premature ASCVD (&lt;55 years of age for males or &lt;65 years of age for females)</em>,</td>
<td>less than 55 mg/dL</td>
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Other Lipid Goals [R 42-46]

<table>
<thead>
<tr>
<th>Lipid Parameter</th>
<th>Goal (mg/dL)</th>
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<tbody>
<tr>
<td>TC</td>
<td>&lt;200</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>30 above LDL-C goal; 25 above LDL-C goal (extreme risk patients)</td>
</tr>
<tr>
<td>TG</td>
<td>&lt;150</td>
</tr>
<tr>
<td>Apo B</td>
<td>&lt;90 (patients at high risk of ASCVD, including DM)</td>
</tr>
<tr>
<td></td>
<td>&lt;80 (patients at very high risk with established ASCVD or diabetes plus ≥1 additional risk factor)</td>
</tr>
<tr>
<td></td>
<td>&lt;70 (patients at extreme risk)</td>
</tr>
</tbody>
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Treatment

**R47.** A comprehensive strategy to control lipid levels and address associated metabolic abnormalities and modifiable risk factors is recommended primarily using

- lifestyle changes
- patient education with
- pharmacotherapy as needed to achieve evidence based targets
Lifestyle interventions to reduce TC & LDL-C levels

- Reduce dietary saturated fat
- Reduce dietary trans fat
- Reduce dietary cholesterol
- Increase dietary fibres
- Utilize functional foods enriched with phytosterols
- Reduce excessive body weight
- Increase physical activity
- Utilize Soy protein products

*ESC guideline on dyslipidaemia 2015

Lifestyle interventions to increase HDL-C levels

- Reduce dietary trans fat
- Increase habitual physical activity
- Reduce excessive body weight
- Reduce dietary carbohydrate and replace them with unsaturated fat.
- Use alcohol with moderation
- Prefer carbohydrate with low glycaemic index and high fibre content
- Quit smoking
- Reduce intake of mono and disaccharides

*ESC guideline on dyslipidaemia 2015
PHARMACOLOGICAL THERAPY

- In individuals at risk for ASCVD, aggressive lipid-modifying therapy is recommended to achieve appropriate LDL-C goals.

- All patients with coronary heart disease should be given statin therapy irrespective of their serum cholesterol concentration.

Statins

**R56.** Recommended as the primary pharmacologic agent

**R57.** For clinical decision making, mild elevations in blood glucose levels and/or an increased risk of new-onset T2DM associated with intensive statin therapy do not outweigh the benefits of statin therapy for ASCVD risk reduction

**R58.** In individuals within high-risk and very high-risk categories, further lowering of LDL-C beyond established targets with statins results in additional ASCVD event reduction and may be considered
**Fibrates**

*R61*. Fibrates should be used to treat severe hypertriglyceridemia (TG >500 mg/dL)

*R62*. Fibrates may improve ASCVD outcomes in primary and secondary prevention when TG concentrations are ≥200 mg/dL and HDL-C concentrations <40 mg/dL

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**Other Drugs...**

- **Bile Acid Sequestrants**
  
  *R66*. Bile acid sequestrants may be considered for reducing LDL-C and apo B and modestly increasing HDL-C, but they may increase TG

- **Cholesterol Absorption Inhibitors**
  
  *R67*. Ezetimibe may be considered as monotherapy in reducing LDL-C and apo B, especially in statin-intolerant individuals

  *R68*. Ezetimibe can be used in combination with statins to further reduce both LDL-C and ASCVD risk
Other Drugs...

* PCSK9 Inhibitors

**R69.** Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors should be considered for use in combination with statin therapy for LDL-C lowering in individuals with FH.

**R70.** PCSK9 inhibitors should be considered in patients with clinical cardiovascular disease who are unable to reach LDL-C/non-HDL-C goals with maximally tolerated statin therapy. They should not be used as monotherapy except in statin-intolerant individuals.

Combination Therapy

**R71.** Combination therapy of lipid-lowering agents should be considered when the LDL-C/nonHDL-C level is markedly increased and monotherapy (usually with a statin) does not achieve the therapeutic goal.
**Follow-up and Monitoring**

**R75.** Reassess individuals’ lipid status 6 weeks after therapy initiation and again at 6-week intervals until the treatment goal is achieved.

**R76.** While on stable lipid therapy, individuals should be tested at 6- to 12-month intervals.

**R77.** While on stable lipid therapy, the specific interval of testing should depend on individual adherence to therapy and lipid profile consistency; if adherence is a concern or the lipid profile is unstable, the individual will probably benefit from more frequent assessment.
Follow-up and Monitoring

R78. More frequent lipid status evaluation is recommended in situations such as

* deterioration of diabetes control,
* use of a new drug known to affect lipid levels,
* progression of atherothrombotic disease,
* considerable weight gain,
* unexpected adverse change in any lipid parameter,
* development of a new ASCVD risk factor, or
* convincing new clinical trial evidence or guidelines that suggest stricter lipid goals

IS TREATMENT OF DYSLIPIDEMIA AND PREVENTION OF ASCVD COST-EFFECTIVE?
Cost Effectiveness

**R81.** Nonpharmacologic interventions, such as dietary management and smoking cessation, are the most cost-effective options available for ASCVD prevention.

**R82.** When nonpharmacologic interventions fail, pharmacologic intervention is a recommended cost-effective option for primary and secondary intervention among individuals at moderate to high risk.

**R83.** Among otherwise healthy individuals at lower risk, the cost-effectiveness of primary pharmacologic intervention varies on the basis of age and sex (with this approach being least cost-effective among women at low risk).

Cost Effectiveness

**R84.** Statins have proven cost-effective in both secondary and primary prevention of ASCVD events in individuals
- at moderate to high risk, or
- in individuals at low risk whose LDL-C levels are very high (≥190 mg/dL)

**R85.** Treatment with fibrates has been found to be cost-effective as both monotherapy and combination therapy for lowering TG and raising HDL-C.

But not in reducing cardiovascular events, except in individuals with TG concentrations greater than 200 mg/dL and HDL-C concentrations less than 40 mg/dL.
ANY QUESTION?

THANK YOU ALL