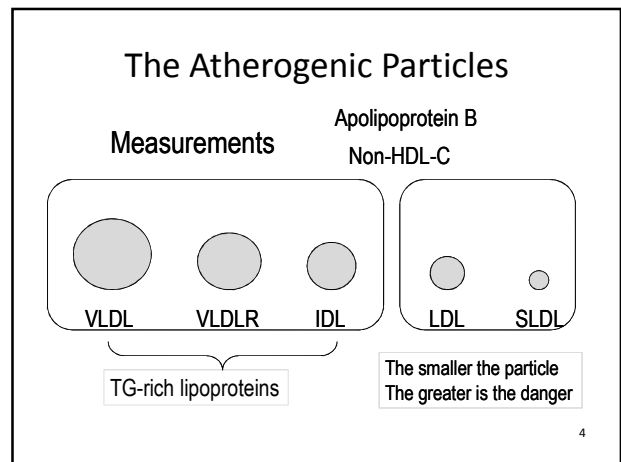


- ### The Lipids and Lipoproteins
- What are the important components (two) of lipids in the plasma ?
 1. Ester. Cholesterol (EC)
 2. Triglycerides (TG)
 - What are the other two components in lipids in their outer layer ?
 1. Free Cholesterol (FC)
 2. Phospholipids (PL)
 - What are Apoproteins ?
 1. The outer protein coat is made of Apoproteins
 - Why are they needed in the lipid molecules ?
 2. To make lipids soluble and thus help transport
- 3



- ### Non HDL Cholesterol
- Total Cholesterol – HDL = N HDL
 - LDL + (TG/5) = N HDL
 - N HDL goal is 30 mg above the LDL goal
 - Because TG should be kept at 150 (150/5 = 30)
 - Significance of N HDL
 - It includes all known atherogenic particles
 - Correlates closely with visceral adiposity, obesity
 - It is a stronger predictor of CVD than LDLc
- 5

- ### Why Apo B ÷ Apo A-1 Ratio ?
1. It incorporates both the Atherogenic and Atheroprotective molecules
 2. Apo B is the best predictor of CVD
 3. Apo A-1 is best marker of Good Cholesterol
 4. AMORIS Trial it was the best to predict CVD
 5. INTERHEART – Globally applicable – Patient pool is from 52 countries
 6. Limitation – not widely available –
 7. Unlike the popular belief, cost is Rs 400-500
- 6

Given Level of LDL

- LDL – most well documented predictor of CVD
- Apo B 100 is much better predictor of CMR (ApoB/A1)
- LDL and NHDL together – nearly as good as Apo B
- LDL is more harmful in pts with IR or DM
- Same level of LDL – no sex difference in CMR
- LDL is not a strong predictor in elderly
- Lowering LDL, ↓ CVD – primary /secondary
- TG are weak predictors, once adjusted for LDL, HDL
- DM or IR has no influence on Lp(a)
- If Lp(a) is high – more aggressive control of CMR

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Some Fascinating Facts

1. ↓ LDL therapy – isn't it enough to ↓ CAD ?
2. It can't wipe out all the CMR or CVD ? – Maasai tribes
3. CVD is multi factorial including genetic !
4. The container & the content – are both faulty ?
5. What is the ideal lowest level of LDL ? LDL-R ?
6. What is the LDL level in new born ? Other primates !
7. Atherosclerosis starts very early in childhood !
8. LDL entry, oxidation, enzymatic modification glycation, aggregation, Immune complex formation

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Prevention Strategies

1. Heart Healthy eating habits
 2. Medical Nutrition Therapy
 3. Increasing Physical Activity
 4. Therapeutic Lifestyle Change (TLC)
 5. Cessation of Smoking
- The problem is we never implement them, come what may !! Both as patients and as physicians !

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Principles of Lipid Rx.

1. LDL lowering is the primary target
2. Optimal LDL be 100 mg – may be 70 mg
3. TLC – Soluble fiber, ↓ SAFA, ↑ MUFA, PUFA
4. TLC – MNT – Pharmacotherapy concurrently
5. Statin in higher doses up to 40-80 mg
6. Ezetamibe, BAR, Niacin are add on drugs
7. N-HDL is the secondary target – Must be met

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Strategies of Lipid Rx.

1. Use higher dose of statin that keeps LDL low
2. If not tolerated – Combine Ezetamibe or BAR
3. Statin + Fibrate – Good – Be aware of myositis
4. No combination of Gemfibrozil + Statin please
5. Statin + Omega 3 fatty acids for NHDL
6. Statin + Niacin – ideal – all lipid components
7. Niacin – with Aspirin, after meal, ERN prep.

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Risk Stratification – Highest Risk

- Established CAD patients
- Non coronary atherosclerotic disease (ASCVD)
 - PAD, CKD, Stroke (CVD)
 - AAA, Symptomatic Carotid Artery Disease
- Diabetes Mellitus
- 2+ CV risk factors
- Framingham 10 yr CAD risk > 20%

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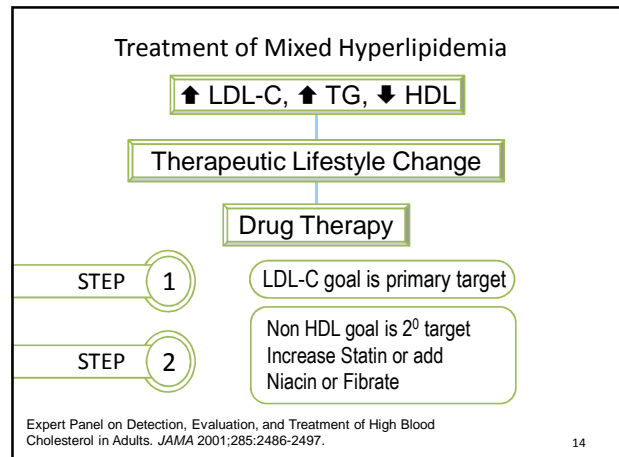
Treatment Goals – CMR

Beyond dyslipoproteinemia, smoking, HT, F H/o premature CAD

Level of Risk	LDL Cholesterol	NHDL Cholesterol	Apo B 100
Highest	< 70 mg /dl	< 100 mg /dl	< 80 mg /dl
High	< 100 mg /dl	< 130 mg /dl	< 90 mg /dl
Low	< 130 mg /dl	< 160 mg /dl	< 100 mg /dl

Highest: 1) Known CVD or 2) DM plus one or more major CV RF
 High: 1) No DM or Known CVD but two or more additional major CVD risk factors or 2) DM but no other major CVD risk factors
 Low: No DM, No CVD, ≤ 1 RF, Framing Score < 10% for 10 yrs

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- ### Statins – Side Effects
- 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
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- ### Pharmacological Options
- LDLc is more lowered than TG
 - Statins
 - Ezetamibe
 - BAR (Bile Acid sequestrant resins)
 - TG is more lowered than LDLc
 - Niacin
 - Fibrates
 - Omega-3 fatty acid ethyl esters
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- ### Fenofibrate
- Mode of Action – PPAR - α Agonists
- 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
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- ### Management of Low HDLc
- Less than 45 mg of HDLc is a low value
 - Majority of Indians (90%) have low HDL
 - Targets of therapy
 - Achieve LDL goal
 - Waist and weight reduction (in pts with MS)
 - N-HDL goal (30+ LDL goal) should be achieved
 - Consider Niacin and Fibrate
 - Increase Physical activity
 - Smoking cessation
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Causes of Low HDL

- Smoking
- Obesity (visceral fat)
- Physical inactivity
- Very high Carbohydrate diet
- Type II Diabetes
- Hyper-triglyceridemia
- β blockers, Androgenic steroids and progestins

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Statins – Beyond Lipid Lowering

1. Increase endothelial NO and improves ED
 2. Regresses atheroma and plaque burden
 3. Increase expression of (tissue) tPA-1
 4. ↓ expression of Endothelin-1 (vasoconstrictor)
 5. Stabilizes plaque – via lipid, MF, MMPs
 6. Reduce oxidative stress – CH independent
 7. ↓ hs-CRP, TNF- α , IL-6 – inflam. Markers
 8. Anti inflammatory at the site of plaque
 9. Inhibits platelet aggregation, anti thrombotic
- All those occur before the lowering of cholesterol.

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Statin – Safety Summary

- Excellent patient acceptance
- Few drug-drug interactions
- Fewer side effects
 - Most common GI – mild to moderate
 - Monitor 6-8 wks; then every 6 months
 - At high doses elevated ALT/AST in 1-2%
 - Myopathy in 0.1 to 0.2% (CK > 10 x UNL)
 - Rare cases of toxicity warranting Rx stopping
- No increase in total or non CAD mortality

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Statin Advisory - Conclusions

- Statins reduce the incidence of MACE
- Reduce PTCA, CABG
- Reduce the incidence of stroke, Amputations
- The potential of statins is not fully realized
- Under used, under dosed in many a practice
- Statins are very safe in a vast majority of pts.
- The strongest evidence base is established
- Innumerable number of studies > 200 RCTs
- In selected patients groups – caution is needed

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Newer Drugs

- Niacin + Laropiprant – to reduce flushing
- CETP inhibitors to increase HDL ? ?
- Mevinolin –mRNA inducers – ↑ LDL-R
- Squalene synthase inhibitors – Better than HMG CoA RI – in terms of Myopathy
- ACAT inhibitor – Avasimibe ? ?
- Dual PPAR α and γ agonist - Ragaglitazar

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Key Points

1. Statins reduce all forms of CVD events by 1/3
2. True for both primary and secondary prevention
3. Evidence for Statins clear cut – not for Fibrates
4. What should be the target value of LDL, NHDL ?
5. 'The Lower - The Better' is today's guideline
6. Apo B level more effective target for ↓ CVD
7. Apo B ÷ Apo A-1 ratio best summary index of CVH
8. CVD or DM is an absolute indication for Statins
9. Statins are the main stay of Rx – Be aggressive
10. Intensive LDL lowering must be the objective.

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