LIPID GUIDELINES- CONTROVERSIES TO CONSENSUS: INDIAN PERSPECTIVE

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NEW GUIDELINES

- In November 2013, ACC and AHA published a set of guidelines on the control of blood cholesterol to reduce atherosclerotic cardiovascular disease (ASCVD) risk in adults.
- The quantum shift away from the previous set of guidelines, has created controversy and confusion about the relative merits of these new ACC/AHA guidelines .

ACC/AHA VS ESC/EAS GUIDELINES

- ACC/AHA guideline committee evaluated only RCT evidence. In contrast, the ESC/EAS guidelines consider all the available evidences, not only RCTs.

- ESC/EAS guidelines provide guidance on elevated TG including the relevance of identifying and treating secondary causes.

- The ACC AHA guidelines don’t recommend any other drugs beside statins

ACC/AHA VS ESC/EAS GUIDELINES

- The ACC AHA guidelines deals with risks rather than goals.
- The ACC AHA guideline doesn't adequately address the management of the group who cannot tolerate recommended statin doses.
- But both the guidelines ESC and ACC/AHA identifies LDL as the most important risk factor and both recommend behavioural and lifestyle modifications concurrent to drug therapy.

ACC/AHA & ESC- SIMILARITIES

- Both the 2013 ACC/AHA and 2011 ESC/EAS guidelines conclude that LDL-C is unequivocally a causal factor for ASCVD.
- Both the 2013 ACC/AHA and 2011 ESC/EAS guidelines have systematically evaluated scientific evidence.
- Both the 2013 ACC/AHA and 2011 ESC/EAS guidelines encourage lifestyle modification and the engagement of the patient as a partner in disease prevention.

WHOM TO TREAT

- Both the 2013 ACC/AHA and 2011 ESC/EAS guidelines clearly identify four patient groups at the greatest risk of ASCVD.
  - Those with established ASCVD
  - Diabetes Mellitus,
  - Familial Hypercholesterolaemia
  - A high predicted CVD risk based on global risk assessment.

DEFINITION OF ASCVD VARIES

- ACC/AHA defines this as acute coronary syndromes, previous MI, stable angina, prior coronary or other revascularization, ischaemic stroke or TIA, and atherosclerotic PAD

- In contrast, the ESC/EAS include all those mentioned in the ACC/AHA guidelines, but also include any pre-clinical evidence for atherosclerotic disease on the basis of any imaging modality.

ABOUT THE RISK FACTORS

- ACC/AHA guidelines do not include chronic kidney disease (CKD), whereas the ESC/EAS guidelines consider those with CKD (as defined by a GFR ,60 mL/min/1.73 m2) as a very high-risk group.

- The ESC/EAS guidelines also recognize that there may be other factors such as elevated TG, social deprivation, central obesity, elevated Lp(a), subclinical atherosclerosis, or F/H of premature CVD which may further modify absolute risk.

A GREATER EXPENDITURE TO THE PUBLIC HEALTH BUDGET.

- ACC/AHA recommends statin treatment for primary prevention in individuals with a 10-year ASCVD risk of 7.5% or higher
- Previous guideline recommendations considered a substantially higher threshold for 10-year risk.
- The ACC/AHA 10-year threshold of 7.5% corresponds to a 2.5% risk for CVD death over 10 years in the SCORE model and are considered at moderate risk by ESC/EAS.
- Thus, the ESC/EAS guidelines allows some scope for lifestyle modifications before medication are added.
- Patients are more likely to receive medications under the new ACC/AHA guidelines.

IMPACT OF HIGH DOSE STATINS ON TOLERANCE IN A WIDE GROUP

- Lowering the threshold for statin initiation in the primary prevention setting will help young people with low short-term CVD risk but high-lifetime risk who will be initiated on statins earlier and will have a greater impact on the disease process.

- However practically all older individuals (>70 years) because of the impact of age on 10-year ASCVD risk, will now be offered moderate- to high-intensity statins. As co-morbidities and tolerability of these agents becomes more of a concern in this age group, the potential for harm is much greater.

RISK ASSESSMENT TOOLS IN PRIMARY PREVENTION

- The SCORE risk algorithm works well in Europe.
- TheACC/AHA mixed pooled cohorts equation did not work well in three North American populations overestimating risk and requires much greater scrutiny before use.
- Inaccurate in many Asians and Pacific Islanders.

MEASUREMENT OF LDL-C LEVELS

- The ESC/EAS guidelines place considerable weight to the measurement of LDL-C to determine future CVD risk

- They provide an algorithm - SCORE risk which combines clinical profile with measured LDL-C levels.

- This is of advantage as for general physicians it highlights the importance of screening for genetically elevated LDL-C levels.

LDL-C SCREENING AS PER ACC/AHA

- ACC/AHA guidelines doesn't mandate LDL-C measurement, if absolute risk is high enough to warrant statin therapy.
- Thus many cases of familial hypercholesterolaemia may remain undiagnosed.

TREAT TO TARGET-
NO LONGER CONSIDERED APPROPRIATE STRATEGIES

- This strategy has been the most widely used in the past 15 years but there are 3 problems with this approach.

  - First, current clinical trial data do not indicate what the target should be.
  - Second, the magnitude of additional ASCVD risk reduction with one target lower than another is not known .
  - Third, it does not take into account potential adverse effects from multidrug therapy that might be needed to achieve a specific goal.

*Specific LDL target of 100 or 70 were part of
ATP III 2004 update and
ACC/AHA guidelines for CHD patients in 2006

ABSENCE OF TARGET: ISSUES

- May lead to under-treatment in those with familial hypercholesterolemia with very high initial lipid levels.
- May lead to over-treatment in those with very low levels of LDL-C.
- Underestimates the role of Non-HDL cholesterol or other lipid fractions which has detrimental effects in atherogenic dyslipidemia specially among Indians.

ACC/AHA GUIDELINES: FEW CAVEATS

- **Lower is best:**
  - this approach was not taken because it does not consider the potential adverse effects of multidrug therapy with an unknown magnitude of ASCVD event reduction
- **Treat to level of ASCVD risk:**
  - A modified version of this approach was taken that considers both the ASCVD risk reduction benefits and the adverse effects of statin treatment
  - By focusing treatment on the 4 statin benefit groups, the approach is practical and simpler to implement than the past strategies
- **Lifetime risk of ASCVD:**
  - These are problematic because of the lack of data on the long-term follow-up of RCTs >15 years

- ACC/AHA guidelines treat risk alone

- ESC/ EAS guidelines treat risk, create a greater understanding of the role of LDL-C in CVD risk assessment, and use LDL-C monitoring for measuring therapeutic efficacy and patient compliance.

OTHER LIPID FRACTIONS

- ESC/EAS guidelines have given importance on the role of other lipid fractions such as TG-rich lipoproteins, remnants, and conditions associated with low HDL-C where LDL-C may not be as informative as non-HDL-C or apoB, but for which there are clear data (Class IIa, Level B).

CONTROVERSY REGARDING HIGH & MODERATE INTENSITY -STATIN DOSES

- High-intensity statin treatment is defined as those regimens which reduce LDL-C by >=50%.
- Rosuvastatin 40mg is not endorsed as RCT outcomes tested high intensity statins, even though it is Food and Drug Administration (FDA) approved.
- Moderate-intensity statin treatment (assessed in outcomes studies) is defined as regimens which reduce LDL-C by 30–50%
- Again atorvastatin 20 mg and rosuvastatin 5 are not tested in RCTs but are FDA approved doses.

RECOMMENDATION: NO RCT EVIDENCE OR CONFUSING

- 50% reduction of LDL
- Baseline LDL in those already on statin Rx
- Atorvastatin 20 mg and Rosuvastatin 5 and 40mg
- Reduce statin dose if LDL <40
- Rosuvastatin in secondary prevention

INDIAN PERSPECTIVE

CHD IN SOUTH ASIANS

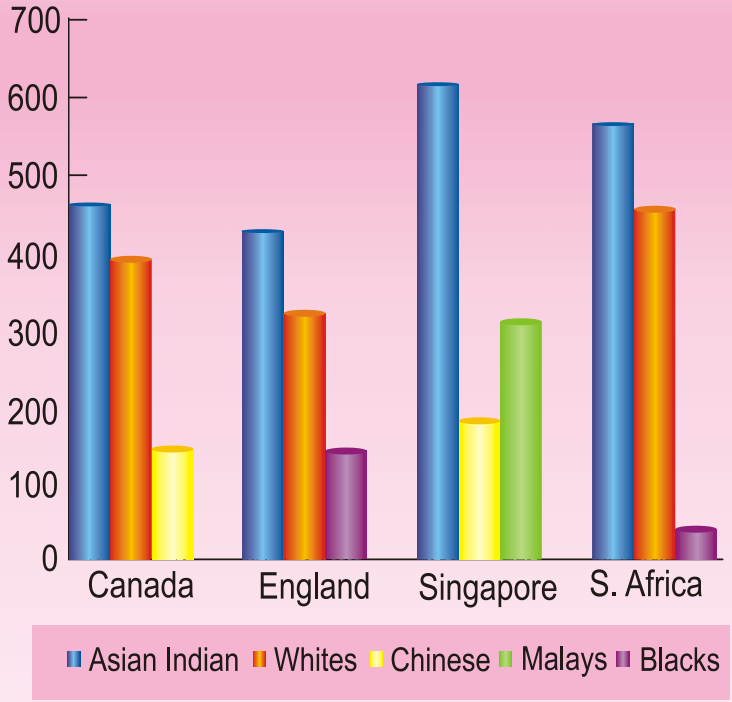
- Prone to develop CHD at a younger age, often before the age of 40 years in men.
- More likely to have an anterior location of infarction.
- More likely to have significant left main, multivessel, and diffuse coronary artery disease.
- Similar or lower prevalence of traditional risk factors than with other populations.
- Prevalence of diabetes mellitus is uniformly higher in South Asians.[7]

Can Med Assoc J. 2002; 166: 717–722.

WHY DO INDIANS NEED TO WORRY?

- **3-5 fold increase** in the risk of MI & CVD
- **Highest** CHD mortality
- CHD onset even **before 40**
- Significant left main and multivessel CAD at catheterization
- **Younger at the time of first hospitalization** for heart failure

CHD mortality rates of men in different countries: Asian Indians vs other ethnic groups. Rates are age-standardized per 100,000/year.



Enas EA *et al. Indian Heart J* 1996; 48: 727-32.

WHY IS CHD INCREASING IN INDIANS ?

1. Urbanization
2. Life Style Changes
3. Smoking
4. High Prevalence of Hypertension
5. Diabetes Mellitus
6. Dyslipidemia
7. Obesity – Truncal
8. High fat Intake
9. Lack of Physical activity
10. Stress

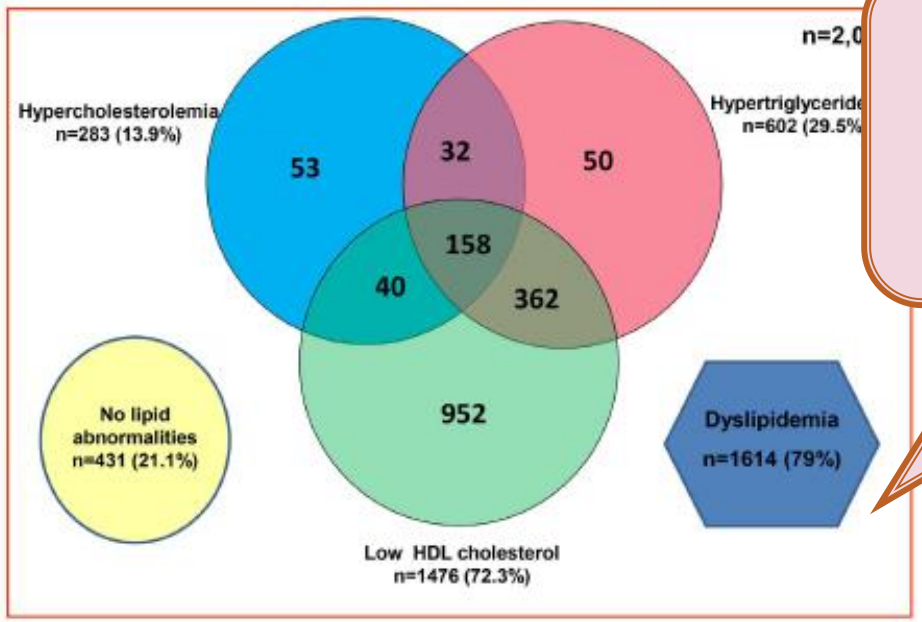
Enas EA *et al. Indian Heart J* 1996; 48: 727-32.

INDIAN DYSLIPIDEMIA

- High Triglyceride levels
- Low levels of HDL
- High levels of small dense LDL
- Moderate increase in LDL levels
- ↑ Lp(a) → 10 times more atherogenic than LDL-C
- ↑↑ Insulin resistance syndrome
- TC / HDL > 4.5 present in 42% of urban India
- Lp(a) > 30 mg/dl in 25% of Indians (CADI study)

Asian J Diabetol Jan-Mar 2002:15-18
Lipid Disorders:Implications & Management Ed. Tripathy & Das, 2002
Sethi K.K. Coronary Artery Disease in Indians, 1998

DYSLIPIDEMIA IN INDIA: LATEST DATA FROM THE ICMR-INDIAB STUDY



7.7% of adult population had 3 lipid abnormalities (high cholesterol, high TG and low HDL)

ICMR-INDIAB Study: covered population across 4 Indian states

- Of the subjects studied, 13.9% had hypercholesterolemia, 29.5% had hypertriglyceridemia, 72.3% had low HDL-C, 11.8% had high LDL-C levels and **79% had abnormalities in one of the lipid parameters.**
- **Low HDL-C was the most common lipid abnormality (72.3%)** in all the four regions studied.

PLoS One.2014 May 9;9(5):e96808.

INDIAN DYSLIPIDEMIA IS DIFFERENT FROM ITS WESTERN COUNTERPART IN TERMS OF LIPID PARAMETERS

Comparison of Indian vs. Western Dyslipidemia

Lipid	Relative Serum Concentrations
TC	Similar
LDL-C	Similar (129 Vs 124 mg/dL)
sd-LDL-C	Similar
TG	Higher (174.5 Vs 146 mg/dL)
HDL-C	Lower (40.5 Vs 46.4 mg/dL)
Lp(a)	Higher (29.3 Vs 25.9 mg/dL)

Indians living in the US - 54% of men and 68% of women had low HDL levels. Similarly, 43% of Indian males and 24% Indian females have high TG levels that exceed 150 mg/dL

20th Annual Convention of the American Association of Physicians of Indian Origin Clinical Implications: Dyslipidemia in the Asian Indian Population June 29, 2002

LIFESTYLE AND GENETIC FACTORS ALSO CONTRIBUTE TO HIGHER INCIDENCE OF DYSLIPIDEMIA IN INDIANS

- **Diet**
  - Dyslipidemic profile - seen in vegetarians*
  - Indian diets rich in carbohydrate and low in Omega-3 PUFA- exacerbates hyper-triglyceridemia.*
- **Physical Activity**
  - Asian Indians-more physically inactive: May be due to fast economic development in recent years**
- **Genetic Factors**
  - Abnormal variants of ApoC 3 and ApoE 3 genes common in India^
  - Indians have more abdominal adiposity*
  - Thrifty gene to blame too

**Misra & Vikram ,Nutrition. 2004 May;20(5):482-91*
^Misra et al, J Assoc Physicians India 2004;52:137-42
*** Talwar & Misra,J Assoc Physicians India 2002;50:1521*

BESIDES, BODY COMPOSITION OF ASIAN INDIANS MAKES THEM MORE VULNERABLE

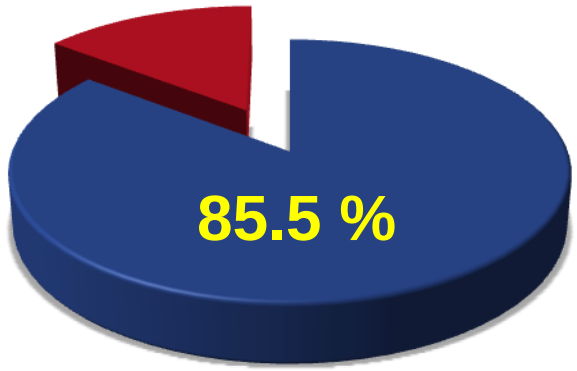
- Shorter height*
- Lower body mass index*
- Excess body fat in relation to body mass index †
- **Abdominal adiposity**
  - High waist-to-hip ratio ‡
  - Normal waist circumference* §
  - High intra-abdominal fat*
- **Truncal adiposity**
  - Thick subscapular skinfold thickness*
  - More abdominal subcutaneous fat*‖
- Less lean body mass*¶

*Misra, Nutrition. 2004 May;20(5):482-91

"9 OUT OF 10 INDIAN DIABETICS HAVE DYSLIPIDEMIA"

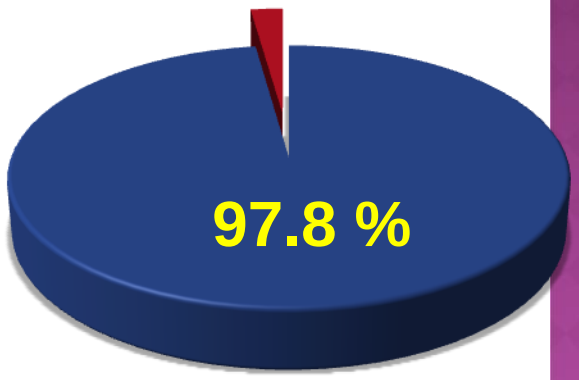
This suggests that there are >55 millions patients of diabetic dyslipidemia in India

Prevalence of Dyslipidemia (%) in Male T2 DM



Dyslipidemia

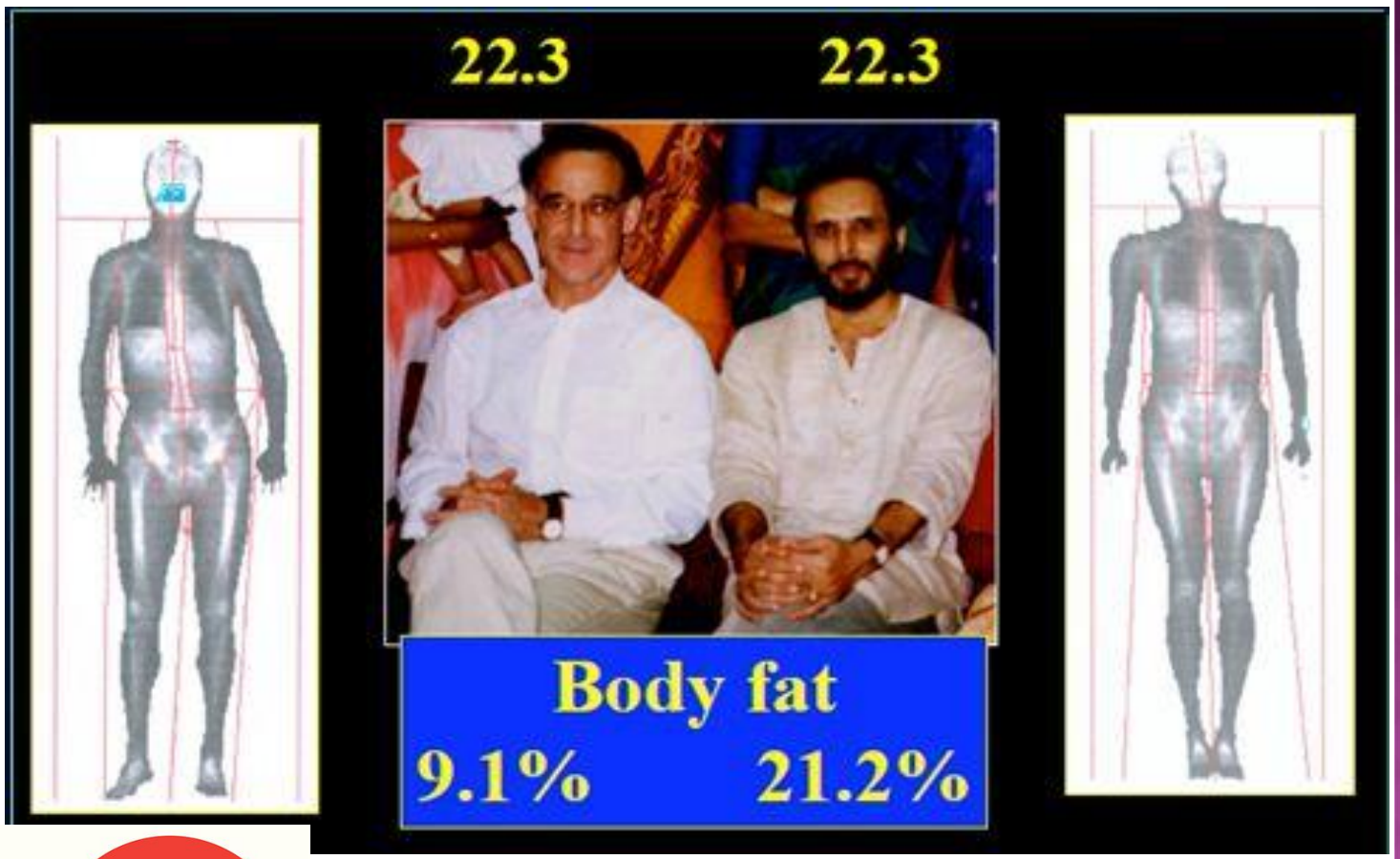
Prevalence of Dyslipidemia (%) in Female T2DM



Dyslipidemia

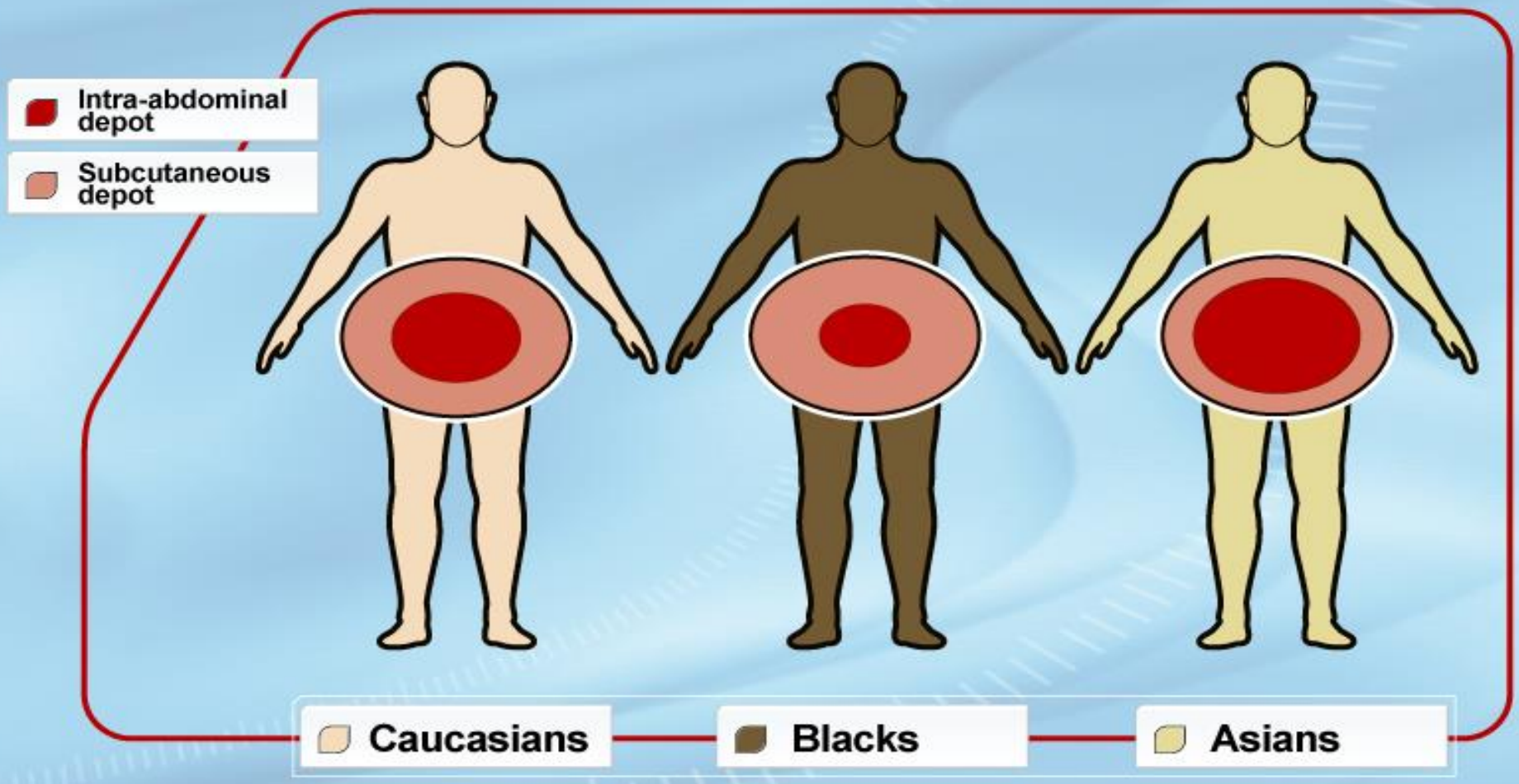
RM Parikh et al. Diabetes & Metabolic Syndrome: Clinical Research & Reviews 4 (2010) 10–12

THE INDIAN OBESITY PARADOX



The Y-Y Paradox. Lancet. 2004;363(9403):163.

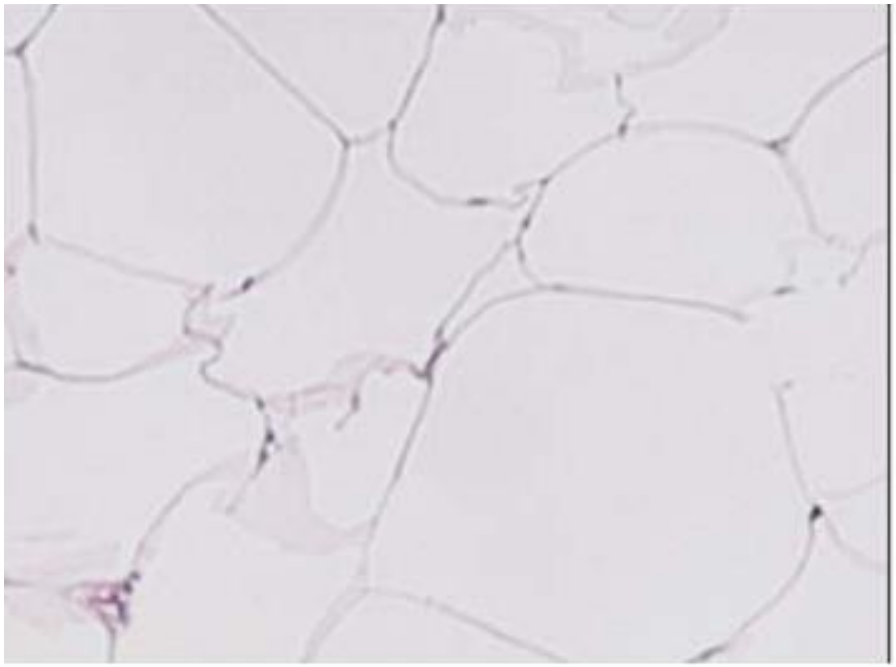
RELATIVE ACCUMULATION OF INTRA-ABDOMINAL VS. SUBCUTANEOUS DEPOT ACCORDING TO ETHNICITY



Source: International Chair on Cardiometabolic Risk
www.cardiometabolic-risk.org

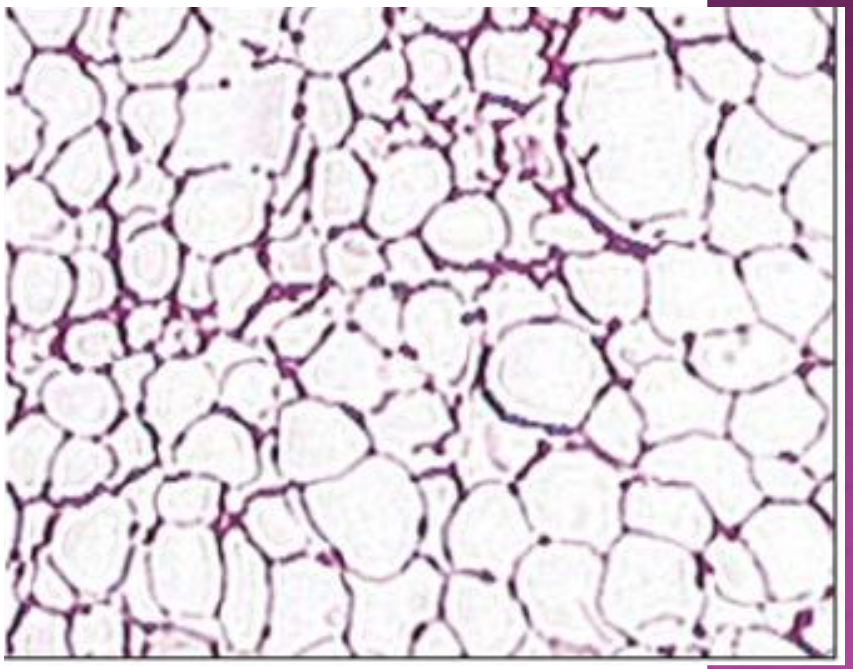
Mean Adipocyte Size

3491±1393



South Asians

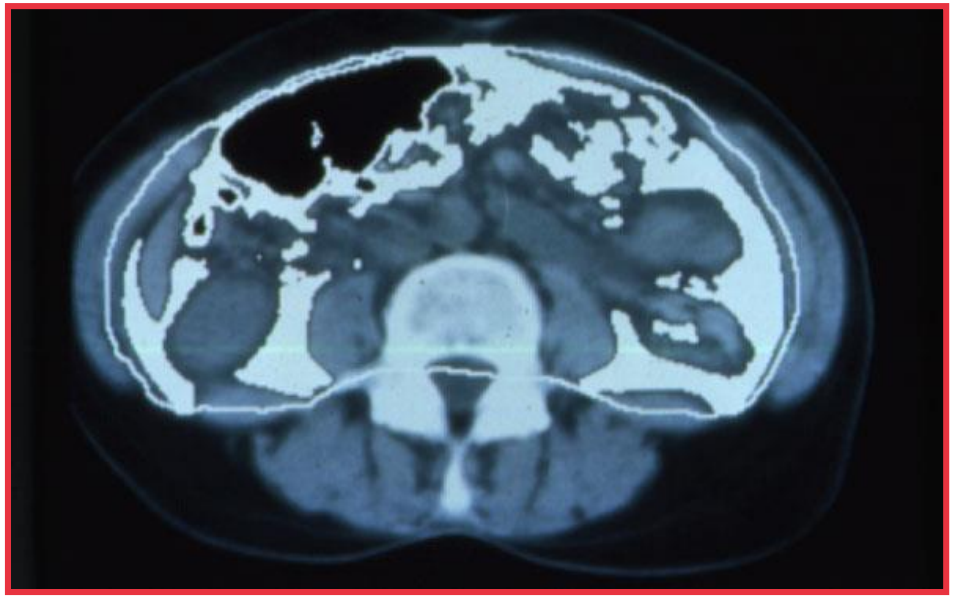
1648±648



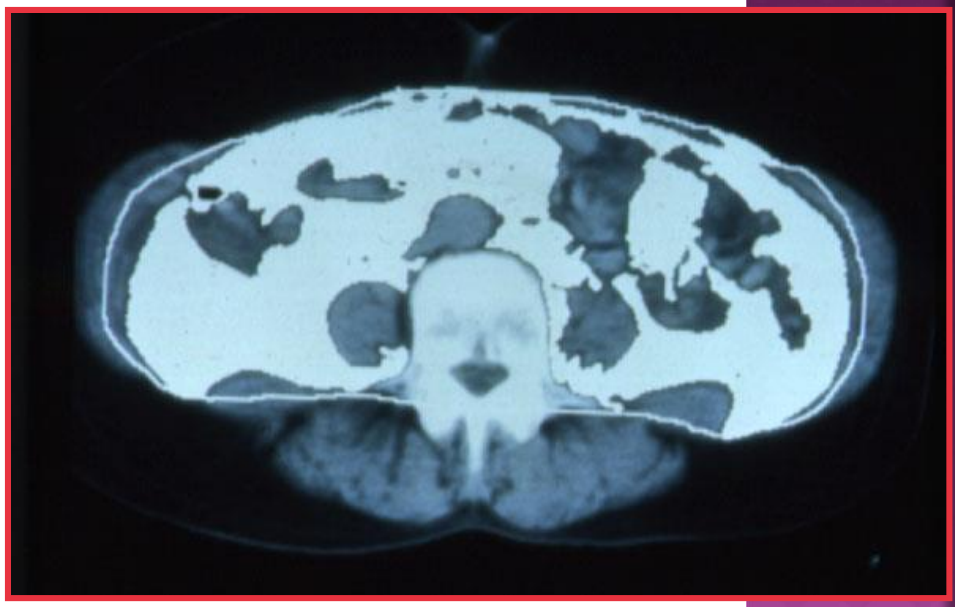
White Caucasians

Chandalia *et al.*, *PlosOne, 2007*

TREASURE IN TUMMY



Normal



Central Adiposity

APPROACH TO THE INDIAN DYSLIPIDEMIC PATIENT: THUMB RULES

- Rule out secondary dyslipidemia
- Perform risk assessment
- Encourage smoking cessation
- Control hypertension and diabetes
- Implement therapeutic lifestyle changes
- Achieve LDL-cholesterol goal with statin therapy
- Achieve other lipid (HDL, triglycerides, Non HDL) goals
- Monitor response and adherence to therapy every 4 to 6 months

20th Annual Convention of the American Association of Physicians of Indian Origin Clinical Implications: Dyslipidemia in the Asian Indian Population June 29, 2002

RISK CALCULATORS

- WHO has recently developed a series of risk prediction charts, each dedicated to a different geographic region, including South-East Asia though it has not been systematically validated in prospective studies

Singapore Med. J. 2011;52(2):116-123

WHO Bulletin. 2007

RISK CALCULATORS CONTD

- An alternate approach, is to recalibrate the FRS by multiplying the calculated FRS by a correction factor, specifically derived for a given population.

- The suggested correction factor for Indians :

  Rural men 1.0

  Rural women 0.8

  Urban men 1.81

  Urban women 1.54

WHO Bulletin. 2007

Consensus Dietary Guidelines for Indians

Recommendations

- Reduction in the intake of carbohydrates
- Preferential intake of complex carbohydrates and low glycemic index foods
- Higher intake of fiber
- Lower intake of saturated fats
- Optimal ratio of essential fatty acids
- Reduction in trans fatty acids
- Low intake of salt and restricted intake of sugar

Diabetes Technol Ther. 2011;13(6):683-94.

CONSENSUS PHYSICAL ACTIVITY GUIDELINES FOR ASIAN INDIANS

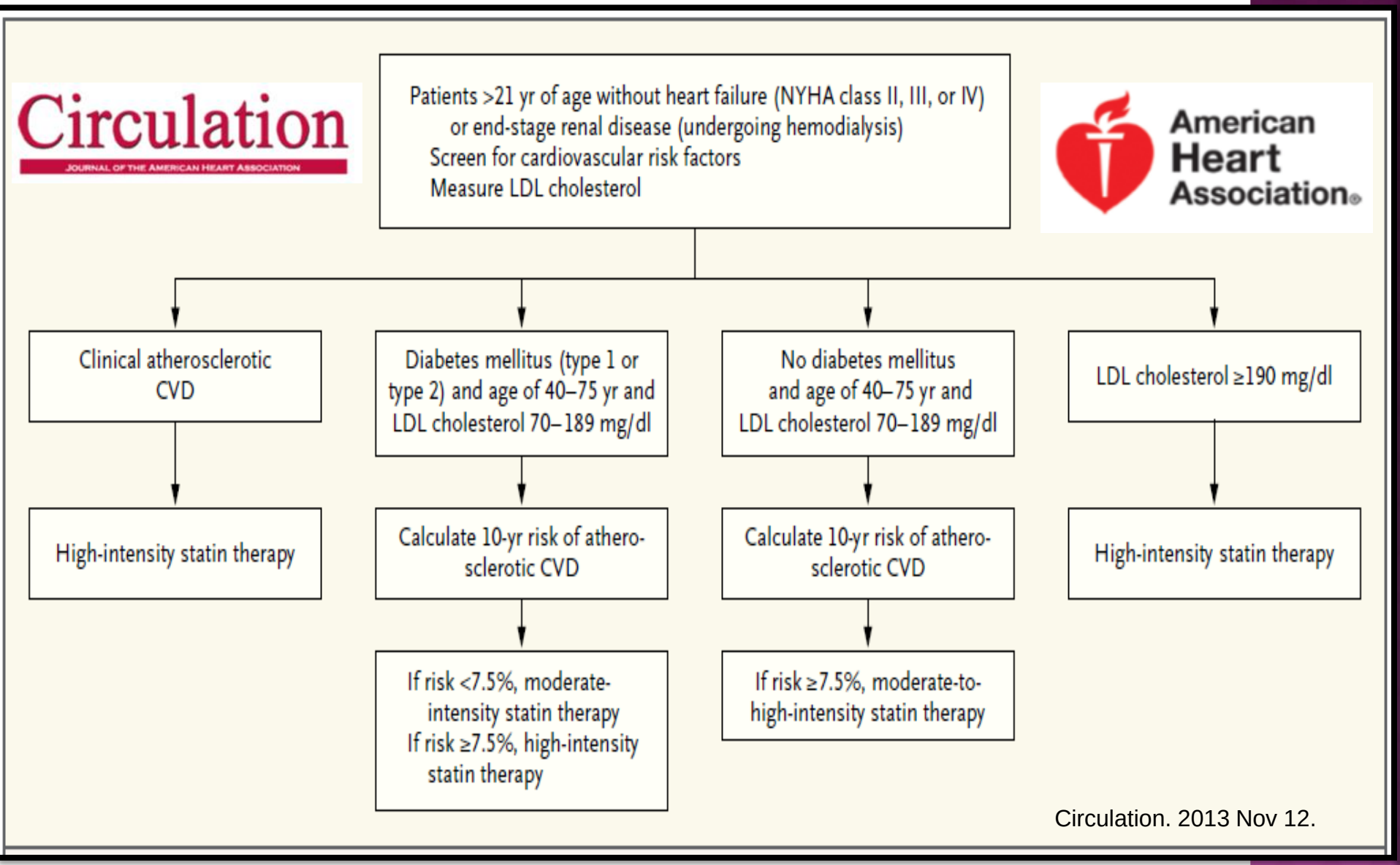
Guidelines for Physical Activity for Overweight & Obesity

Intensity	*Duration*	*Frequency*
Moderate-intensity aerobic exercise	60 min	Daily
Vigorous-intensity exercise	60 min	3 or more days/week

- A total of 60 min of physical activity every day, is recommended for Asian Indians.
- This should include at least 30 min of moderate-intensity aerobic activity, 15 min of work-related activity, and 15 min of muscle-strengthening exercises

Diabetes Technol Ther. 2012;14(1):83-98.

2013 ACC/AHA GUIDELINES



Circulation. 2013 Nov 12.

DOSE OF ATORVASTATIN

- Considering the lower body weight , 40 mg of Atorvastatin is advocated by some authorities in India as high dose therapy.

- However CURE-ACS study in Indian ACS patients indicated that atorvastatin 80 mg was more effective and also well tolerated.

J Assoc Physicians India. 2013 Feb;61(2):97-101 – CURE ACS

ALTERNATIVE TREATMENT STRATEGIES

- Atherogenic dyslipidemia in Asian Indians may be well managed by the use of fibrates along with statins.
- Fibrates along with Simvastatin have shown a favourable trend in those diabetics with hypertriglyceridemia and low HDL in ACCORD Trial.
- Fibrates and ω-3 PUFA also have anti-inflammatory properties, and may be additionally useful in Indians who have high prevalence of subclinical inflammation although there is no hard evidence.

Curr Atheroscler Rep. 2004 Nov;6(6):461-7

CONCLUSION

- South Asians are facing growing “epidemics” of obesity and dyslipidemia.
- Several factors including rapid urbanization, demographic changes, rural-to-urban migration, faulty diets, sedentary lifestyle, socio-cultural factors along with genetic predisposition have emerged as major contributory factors.
- Obesity in south Asians showed certain distinct features including preponderance of abdominal obesity, more intra-abdominal and truncal sub-cutaneous adiposity, fat deposition in liver (fatty liver) and skeletal muscles.

CONCLUSION

- One needs to individualize each patient based on clinical judgement and experience.
- Initiation of therapy should be done considering an individual's clinical as well as laboratory parameters including lipid levels.
- The high risk patients should undergo moderate to high intensity statin therapy depending on clinical perspectives.
- LDL-C should be monitored for adequate control, assessing drug compliance

CONCLUSION

- Addition of other drugs needs to be considered once optimal LDL-C lowering is not achieved though there is no strong evidence supporting their use.
- The use of fibrates and other group of drugs in addition to statins also may be appropriate if lipid fractions other than LDL-C are elevated, specialy in diabetics and those with atherogenic dyslipidemia.
- Setting a target will lead to better drug monitoring on the part of the physician and also better drug compliance on the part of the patient.