

Cardio-metabolic Risk in Diabetes

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Florida Academy of Family Physicians Foundation**

CASE

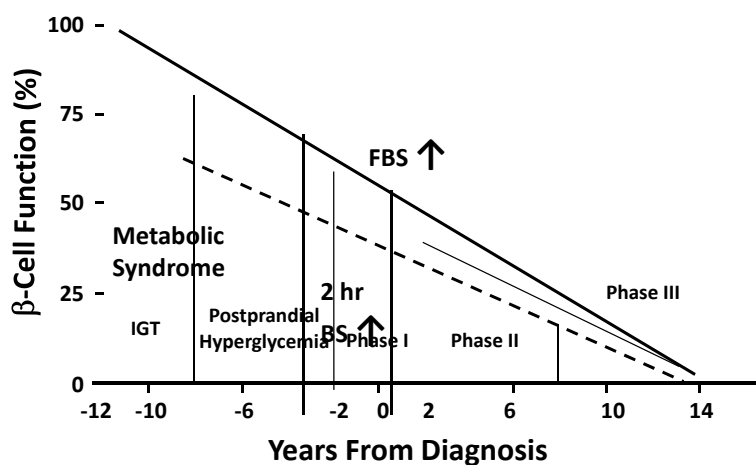
- **42 Year old man comes to your office for routine physical. No complaints**
- **Family Hx of diabetes and Father died of MI age 44**
- **BMI 28, Waist 42 in, B/P 142/90**
- **Total Chol (TC)=180, Triglycerides=250, LDL (calculated)=100 HDL=30 and Non-HDL 150**
- **FBS=132 finger stick-A1C is 6.2**

How long has he had abnormal blood sugar, hypertension and dyslipidemia?

- A. Abnormal blood sugar for 1 to 2 years
- B. Abnormal blood pressure and lipids for 8 to 10 years
- C. Increased arterial plaque and atherogenesis for 8 to 10 years
- D. A and B
- E. A B and C

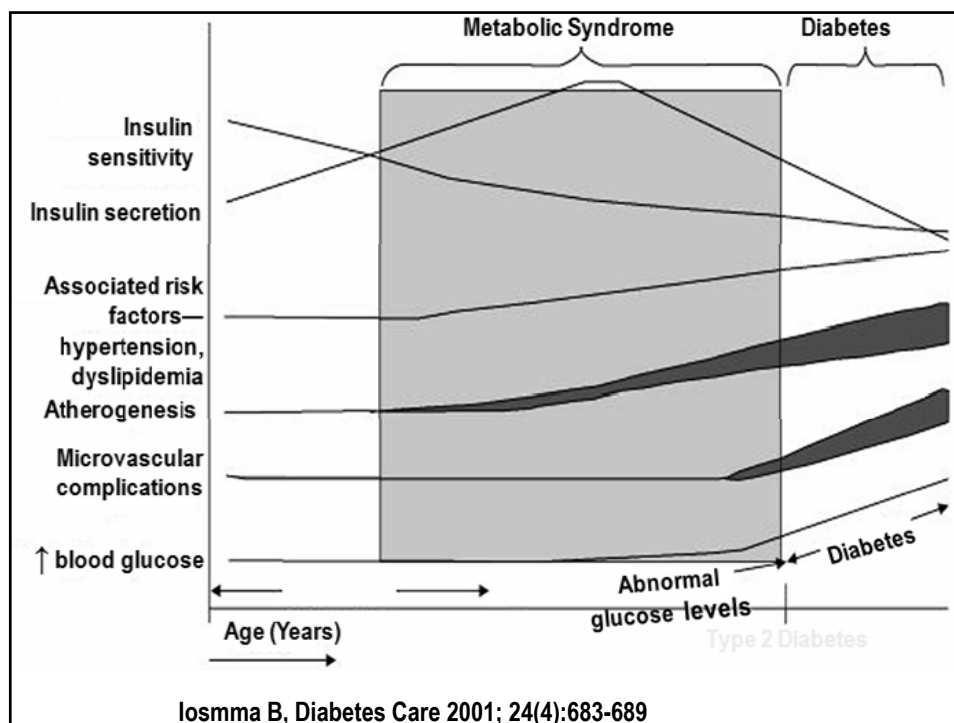
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Natural History of Type 2 Diabetes



IGT = impaired glucose tolerance; Lebovitz H (1999),
Diabetes Reviews 7:139-153

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B-Cell Function T2DM

- Characterized by decreased functional-cell mass that cannot adapt insulin secretion to compensate for increasing insulin resistance driving the development of overt T2DM
- Accumulating evidence suggests that this decline may be slowed or even reversed, particularly in the early stages of disease. Furthermore, new therapeutic classes of diabetes medications act to improve -cell function, thus potentially altering the course of the disease.
 - Donath MY, Halban PA Decreased -Beta cell mass in diabetes: *Diabetologia* 2004;47:581-589

CASE

- 42 Year old man comes to your office for routine physical. No complaints
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- Total Chol (TC)=180, Triglycerides=250, LDL (calculated)=100 HDL=30 and Non-HDL 150
- FBS=132 finger stick-A1C is 6.2
- Lets talk about his lipids

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What is the most common lipid abnormality seen with diabetes?

- A. High LDL**
- B. High HDL and high triglycerides**
- C. High total cholesterol**
- D. Low HDL and high triglycerides**

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Which of the following is true about Non-HDL Cholesterol

- A. It is an additional goal if triglycerides are >200
- B. It is calculated by subtracting HDL from total cholesterol.
- C. It is a better predictor of CHD than LDL
- D. A & B are correct
- E. A, B and C are correct

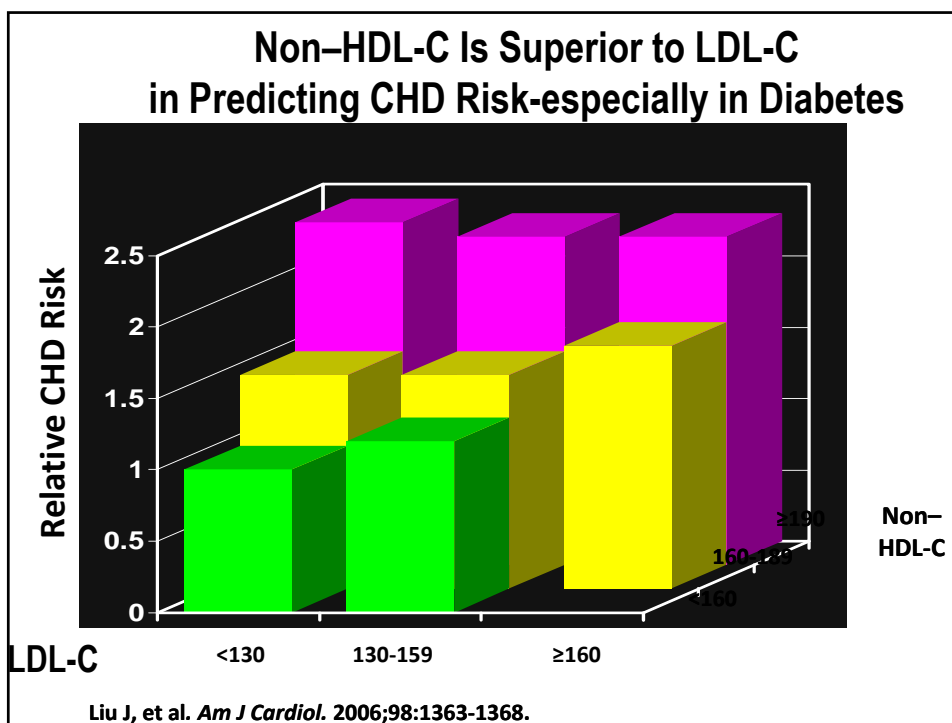
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Non-HDL Cholesterol

- Non-HDL represents all the bad ugly small dense atherogenic LDL
- Non HDL C = TC-HDL = 180-30=150
- Can not use LDL as only target when the triglycerides over 200
- Non HDL goal is LDL goal + 30 *

*Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001), JAMA 285(19):2486-2497 & 2004 addendum

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How would you treat his lipid abnormalities

- A. Just lifestyle and rely on blood sugar control to control lipids**
- B. Add a statin**
- C. Add niacin or a fibrate**
- D. All of the above**

Recommendations For Niacin

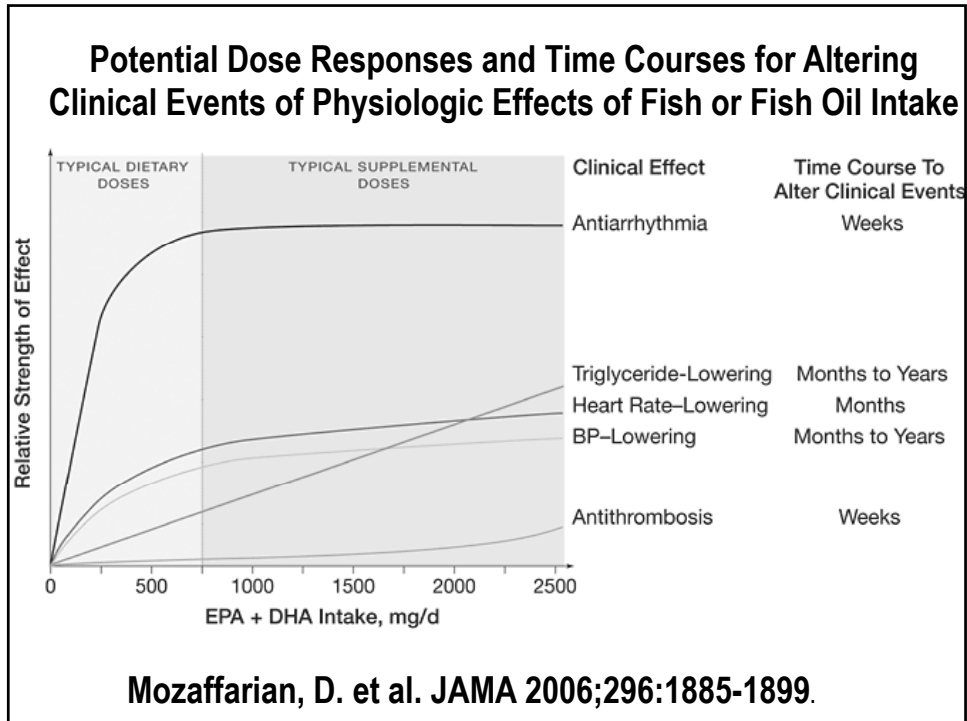
- May have 5%–10% incidence of flushing that ↓ with use. New formulation Niaspan combined with NSAID or ASA decreases chances to <5%.
- Niaspan start with 500 mg at night and increase by 500 mg a month up to 1500-2000mg may be enough
- Be aware of “creep effect” keeps improving
- Minor increases (4%–5% on average) in glucose levels often clinically insignificant.
- Niacin co-administration with a statin does not potentiate statin-related myopathy.
- Active gout is a contraindication to niacin use

National Lipid Association

Recommendations for Fibrates

- Measure serum creatinine before starting fibrates-If impaired renal function is present, consider Gemfibrozil (Lopid) or a lower starting dose of Fenofibrate
- Creatinine monitoring if taking metformin, which may need to be discontinued for creatinine elevations 1.4 mg/dL in women and 1.5 mg/dL in men,
- When combined with a statin use fenofibrate not gemfibrozil to decrease risk for myopathy and or rhabdomyolysis
- Fibrate therapy elevates homocysteine but not sure is clinically relevant
- Fibrates may increase the risk for cholelithiasis

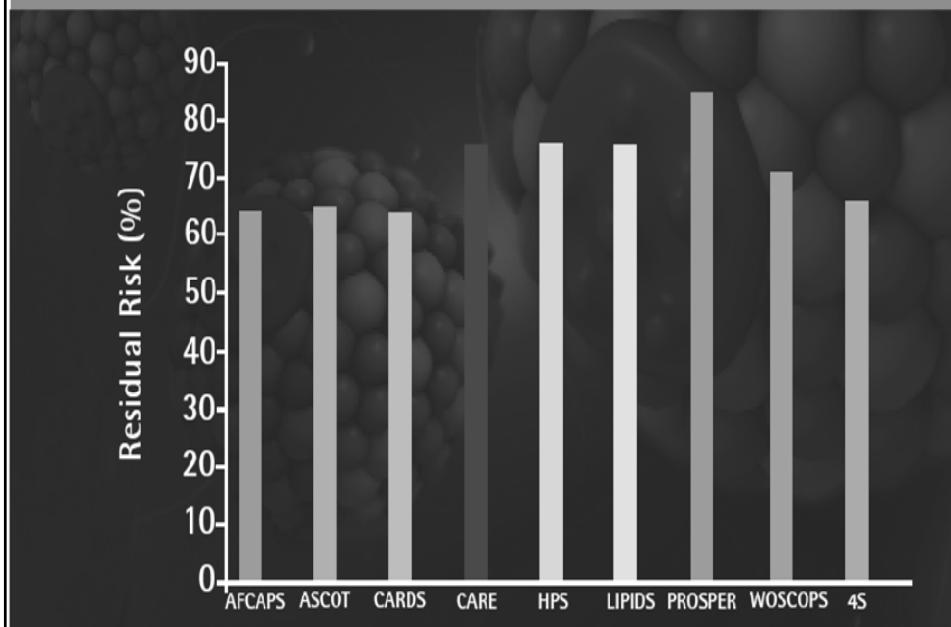
National Lipid Association



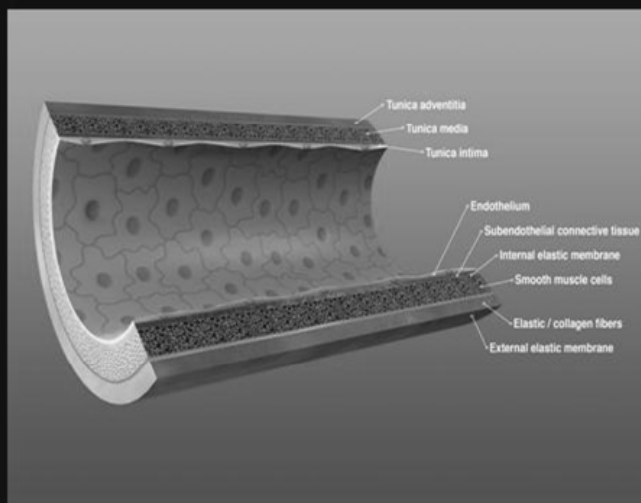
After LDL is at goal what residual risk remains?

- 20%
- 5%
- 40%
- 60%
- >60%
- None

Figure 2: Residual Risk of CVD in Statin Trials

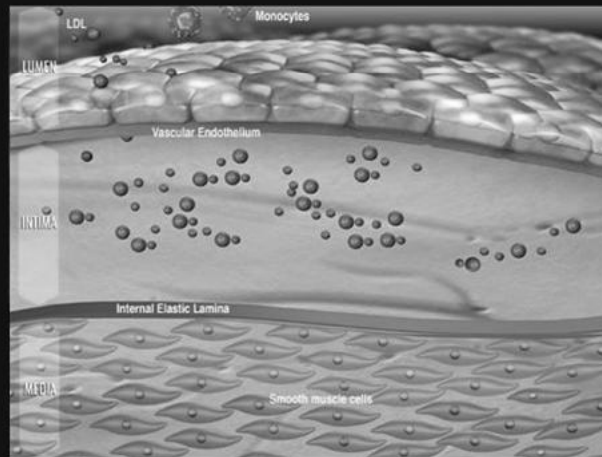


What's happening with the arterial wall in Diabetes?



Normal wall and endothelium

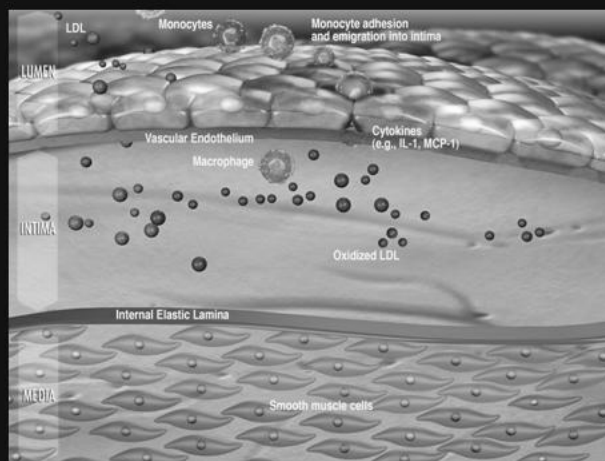
Atherosclerosis and Plaque Formation (1)



LDL = low-density lipoprotein.

Early LDL migration and Inflammation

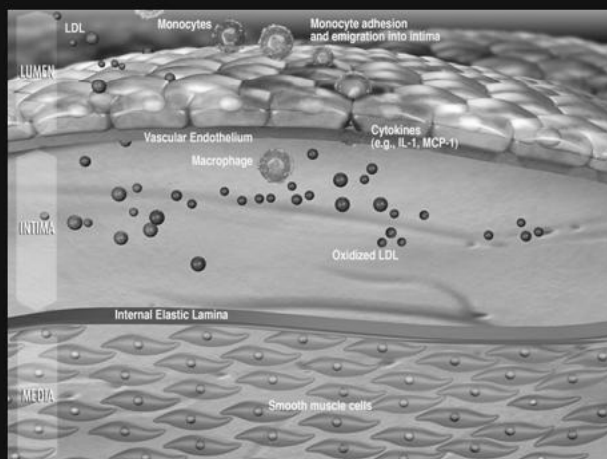
Atherosclerosis and Plaque Formation (2)



IL = interleukin; MCP = monocyte chemotactic protein.

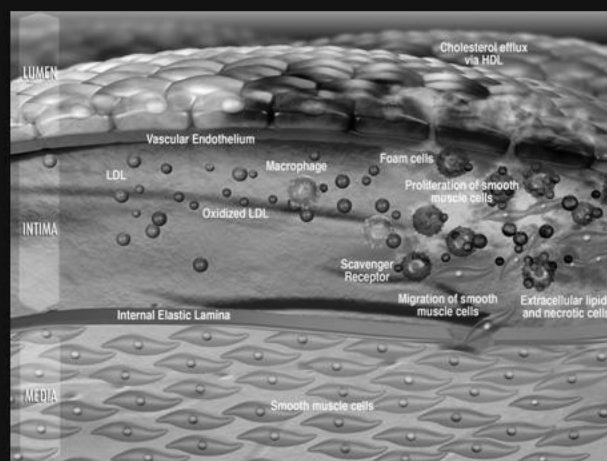
Advancing Inflammation

Atherosclerosis and Plaque Formation (2)



IL = interleukin; MCP = monocyte chemotactic protein.

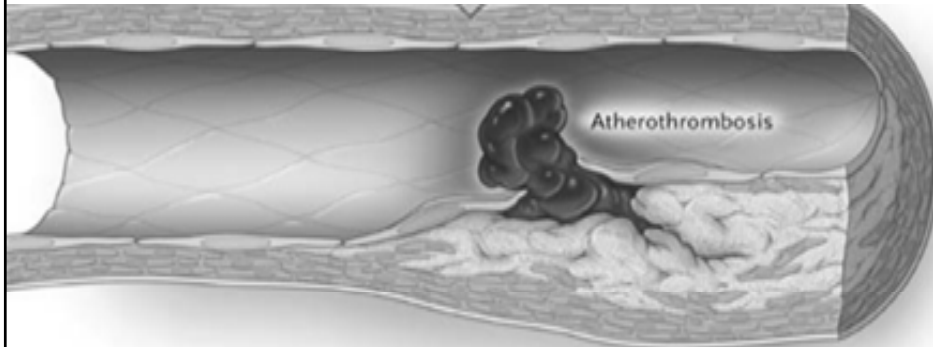
Atherosclerosis and Plaque Formation (4)



HDL = high-density lipoprotein.

Advancing inflammation and plaque formation

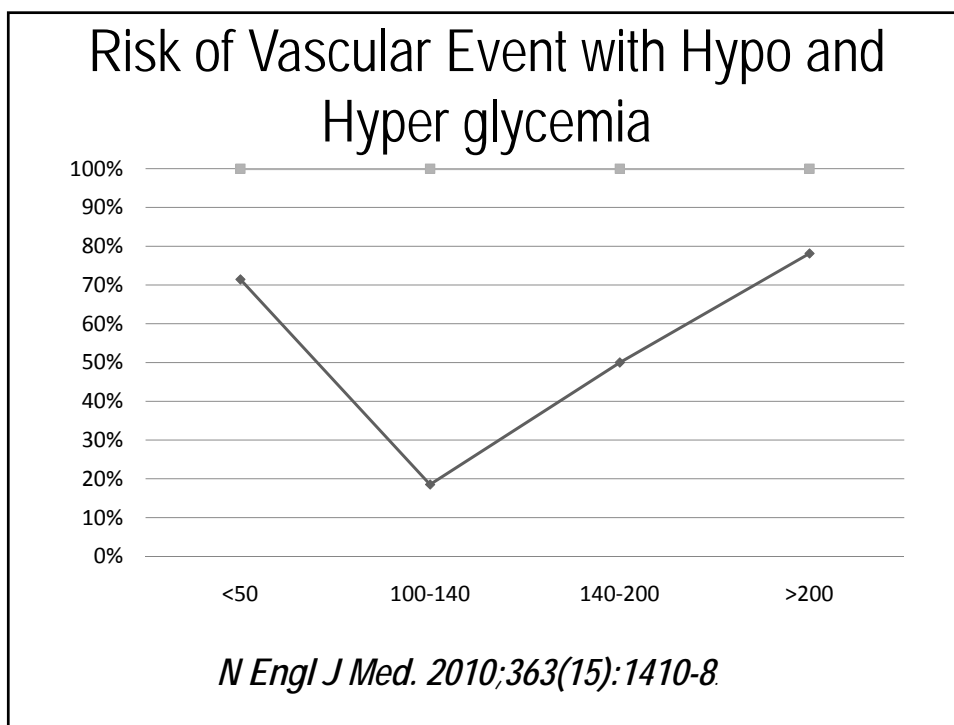
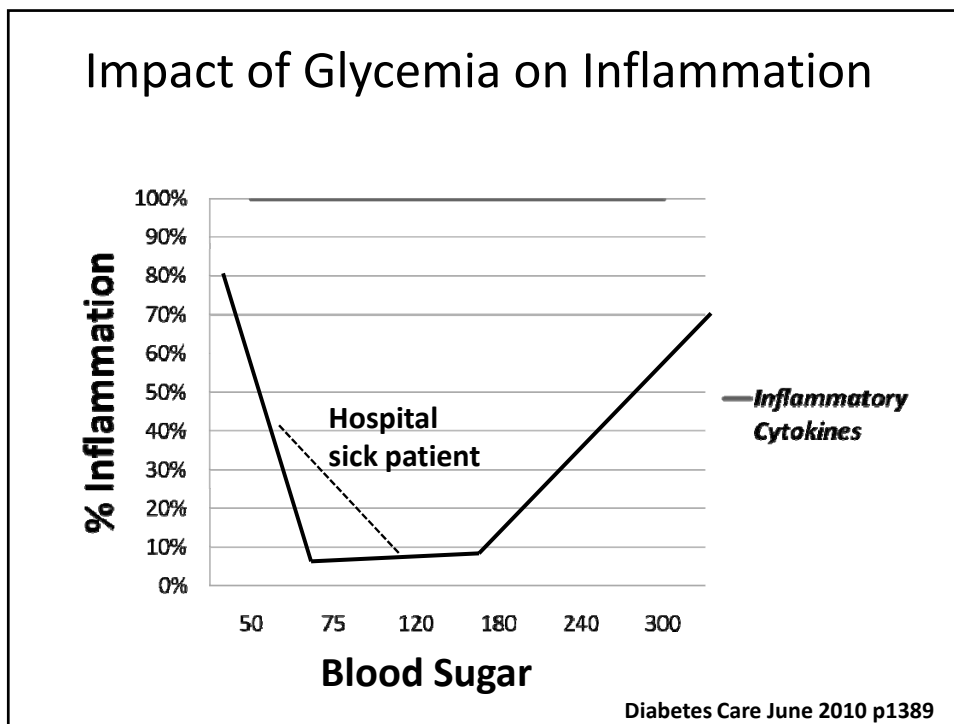
Vulnerable plaque ruptures because the Endothelium was not protected-How can we become protectors of the Endothelium?



How do we know which Diabetics are building up plaque and are at risk for Atherothrombosis?

What are the traditional risk factors or markers of endothelial dysfunction-inflammation in Diabetes?

- High LDL levels
- Low HDL levels
- Non-HDL
- Family History of CVD
- Tobacco abuse
- Lifestyle
- Hypertension
- Hyperglycemia and Hypoglycemia

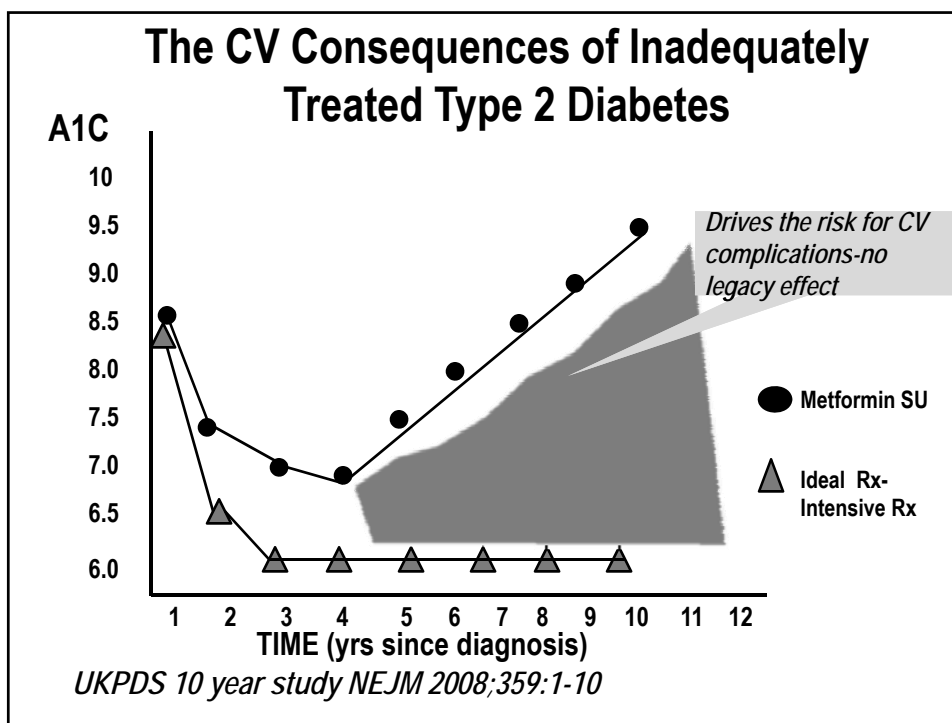


Intensive Glucose Lowering and Cardiovascular Disease Prevention in Diabetes: Reconciling the Recent Clinical Trial Data *Circulation* 2010;122;2201-2211

Study-all meta-analysis of several studies including recent trials like ACCORD	Number of Patients	Reduced CVD
Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomized controlled trials. <i>Lancet</i> . 2009;373:1765–1772	33, 040	Reduction in nonfatal MI (17%) Reduced coronary heart disease (15%)
Systematic review: glucose control and cardiovascular disease in type 2 diabetes. <i>Ann Intern Med</i> . 2009; 151:394–403.	27, 802	Reduced CVD events (10%)
Intensive glucose control and macrovascular outcomes in type 2 diabetes. <i>Diabetologia</i> . 2009;52:2288–2298.	27, 049	Reduced MI (15%)

Value of Early Aggressive Rx

- UKPDS 10 year study “Legacy Effect” those who were treated aggressively vs. those who were not had fewer macrovascular complications after 10 plus years. *UKPDS 10 year study NEJM* 2008;359:1-10
- DCCT-EDIC Study “Metabolic Memory” those who were treated aggressively vs. those who were not had fewer macrovascular complications after 10 plus years. *DCCT-EDIC NEJM* 2005;353:2643-53.



Similar Legacy effect (mortality reduction) with early use of medication for hypertension.

(Kostis et al *Hypertension* published online Oct 25, 2010)

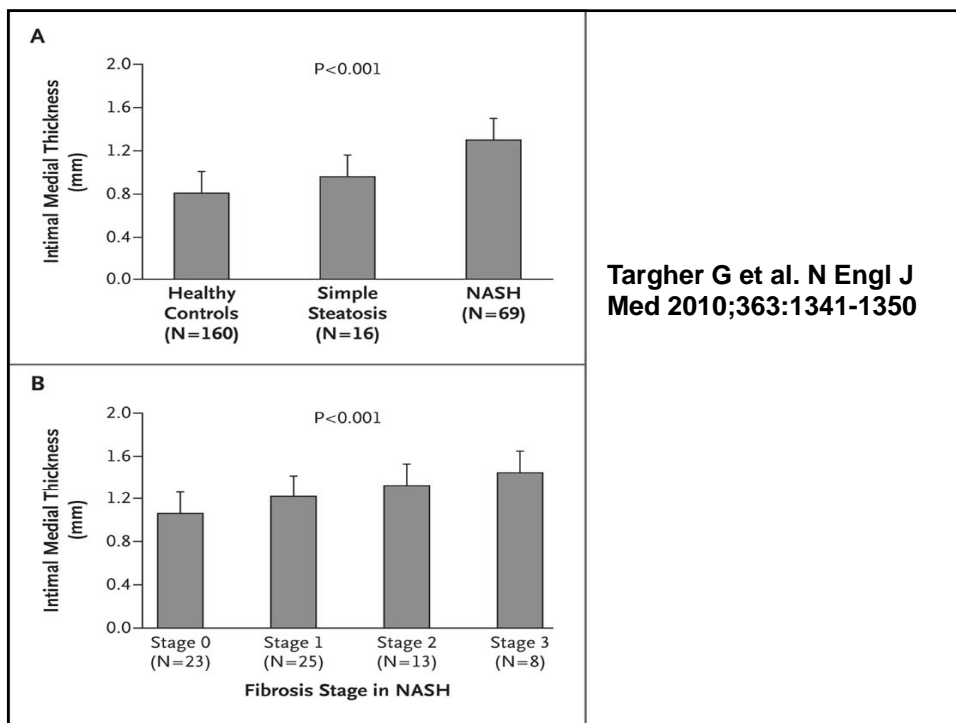
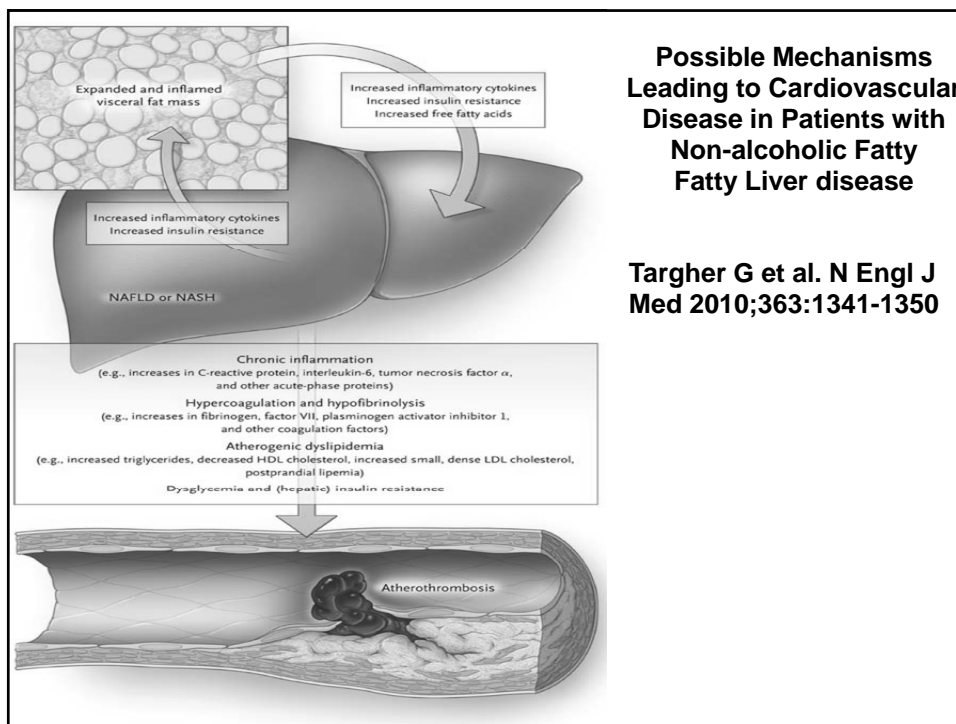
- Metanalysis 18 studies-132 854 patients; 11 988 deaths
- Overall mortality decrease persists after the end of trial phase, when most patients in both the intervention and control groups receive active therapy. These analyses imply that earlier intervention would result in better clinical outcomes.

What are the non-traditional or emerging risk factors or markers of endothelial dysfunction in Diabetes?

- Elevated urine microalbumin
- ↑↑ AST and ALT
- ↑↑ hsCRP
- ↑↑ LDL particle numbers->1000 *
- ↑↑ Small dense LDL-Pattern B vs. Pattern A *
- Apo-B, LP(a) *
- CIMT-Carotid Intima Media Thickness
- Coronary Artery Calcium scores
 - * *Advanced Lipid Tests*

Elevated Urine Microalbumin

- Several studies have shown that micro-albuminuria is associated with low-grade systemic inflammation and endothelial dysfunction.
- Even low-grade albuminuria, is an important marker of future CVD events even in individuals free of diabetes and hypertension.
 - *Stuveling EM, Bakker SJ, Hillege HL, Burgerhof JG, de Jong PE, Gans RO, de Zeeuw D. C-reactive protein modifies the relationship between blood pressure and microalbuminuria. Hypertension. 2004;43:791-796.*
 - *Clausen et al Endothelial haemostatic factors are associated with progression of urinary albumin excretion in clinically healthy subjects: a 4-year prospective study. Clin Sci (Lond). 1999;97:37- 43.*



HsCRP to assess risk?

- Jupiter study suggests it is of value. Decreased mortality with increased HsCRP.
- Recent publication-Circulation Sept 2010 on cost effectiveness of HsCRP using a theoretical model suggests traditional risk factors are just as or more cost effective. Depends on long term safety of statins.
- Other studies like advanced lipid studies (VAP) may be cost effective-\$39 or less with Medicare

Lp(a)

- CHD risk slightly increased when Lp(a) ↑ but LDL and HDL normal.
- if both LDL and Lp(a) ↑ the risk of a CV event ↑ 3X
- If the Lp(a) ↑↑ and HDL ↓↓ risk of a CV event ↑ 8X
- Approximately one third of patients at high risk for cardiovascular disease have elevated levels
- Statins do not decrease Lp(a) but Niacin does.
 - von Eckardstein A, et al. Lipoprotein (a) further increases the risk of coronary events in men with high global cardiovascular risk. *J Am Coll Cardiol.*2004;37:434-439.

Apo B as a predictor of CHD

- Although non-HDL-C and apoB were both strong predictors of CHD in this male cohort, more so than LDL-C,
- The findings support the concept that the plasma concentration of atherogenic lipoprotein particles measured by Apo B is more predictive in development of CHD than the cholesterol carried by these particles, measured by non-HDL-C.

– *Circulation. 2005;112:3375-3383*

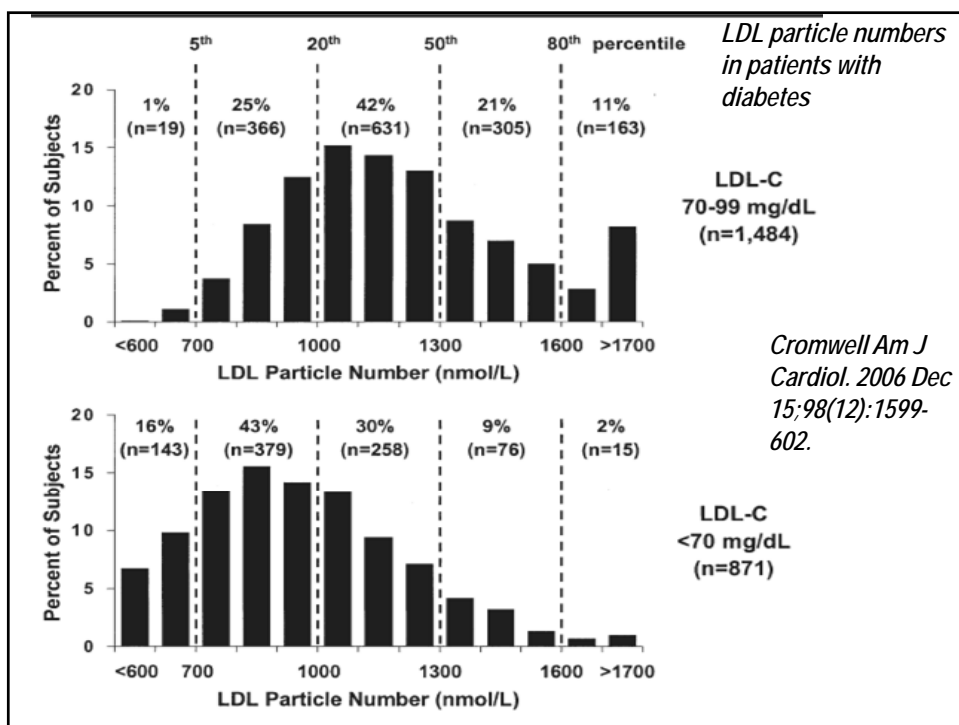
Advanced Lipid Testing Cost effectiveness?

- Expensive (except for VAP) and not for all patients
- May be of value of patient with significant family history and other traditional values that are not that significant.
- Some think should be measured in all diabetics because of residual risk after reduction of LDL.
- No data to show that reduction of LDL particles, Apo B, Lp(a) etc reduces events but does show reduction in surrogate markets.
- Keep watching for reduced prices and studies that it is of help in defining those who need increased statin dose and or add on drugs like niacin, fibrates etc.

LDL Particle Numbers in Diabetes

- 2,355 patients with type 2 diabetes in Clinical Practice
- 1,484 patients with low LDL cholesterol (70 to 99 mg/dl), only 385 (25.9%) had low levels of LDL-P whereas 468 (31.6%) had LDL-P values >1,300 nmol/L). Among the 871 patients with very low LDL cholesterol, i.e., <70 mg/dl, 349 (40.1%) had LDL-P levels >1,000 nmol/L
- Patients with type 2 diabetes mellitus and LDL cholesterol levels <100 mg/dl are heterogeneous with regard to LDL-P and, by inference, LDL-based cardiovascular risk.

– Cromwell *Am J Cardiol.* 2006 Dec 15;98(12):1599-602.



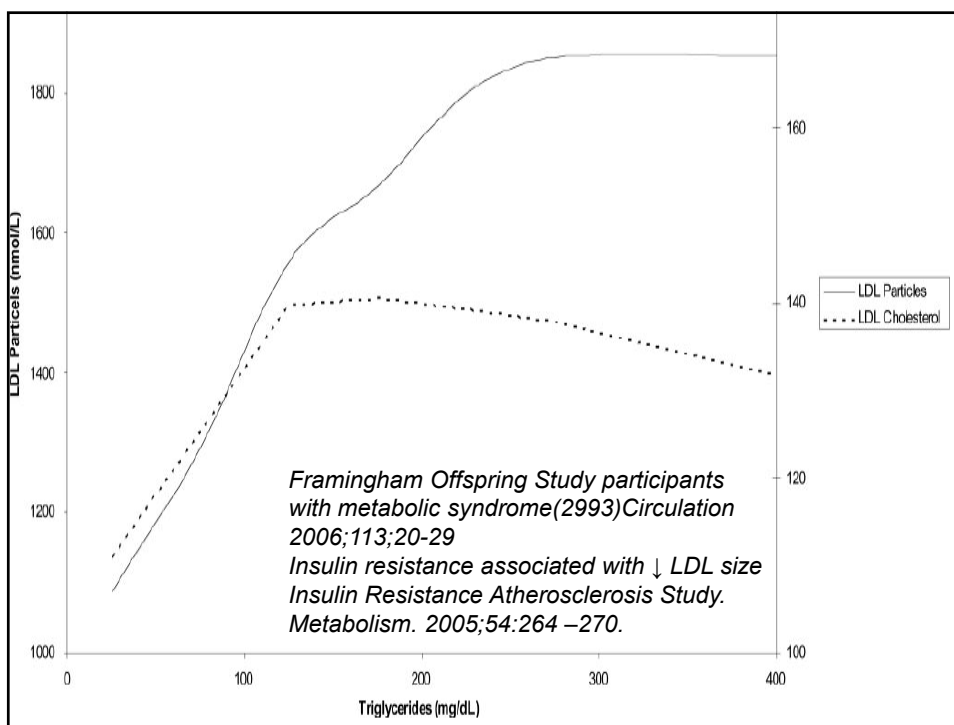
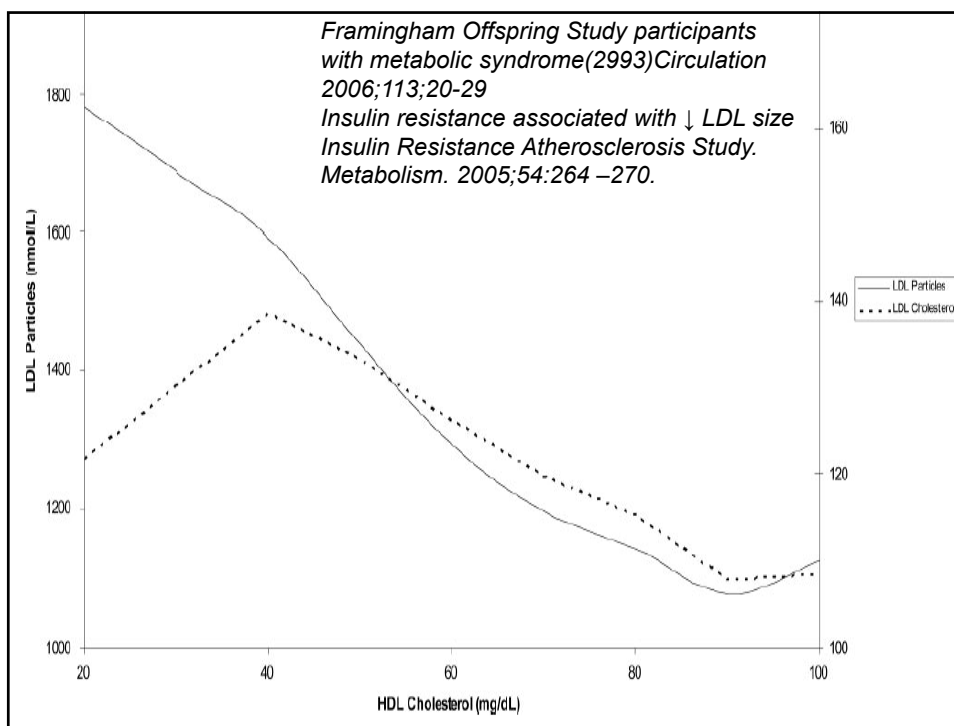
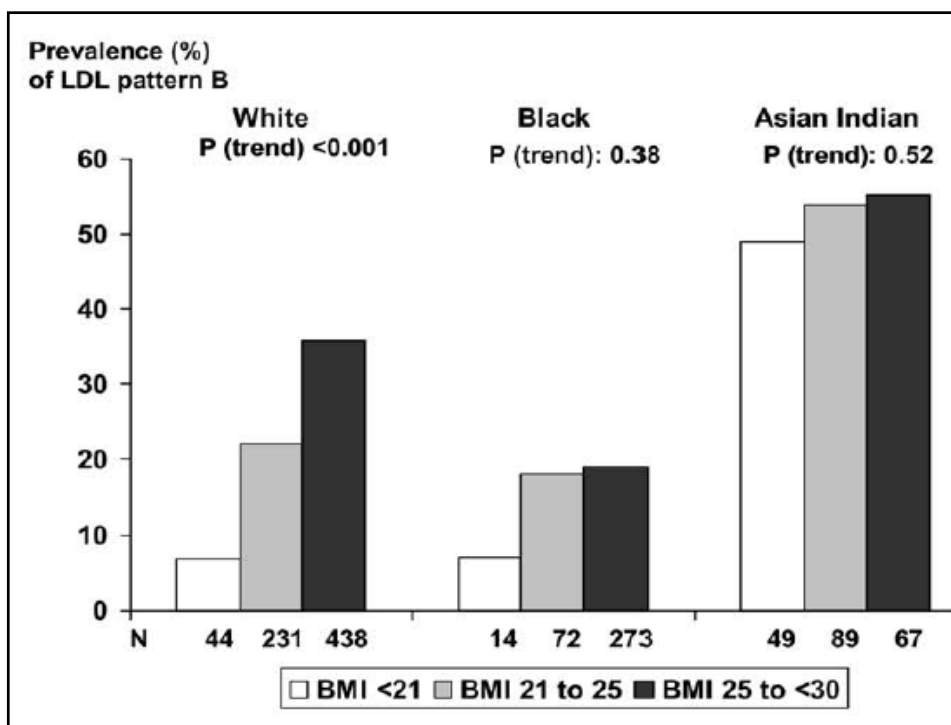
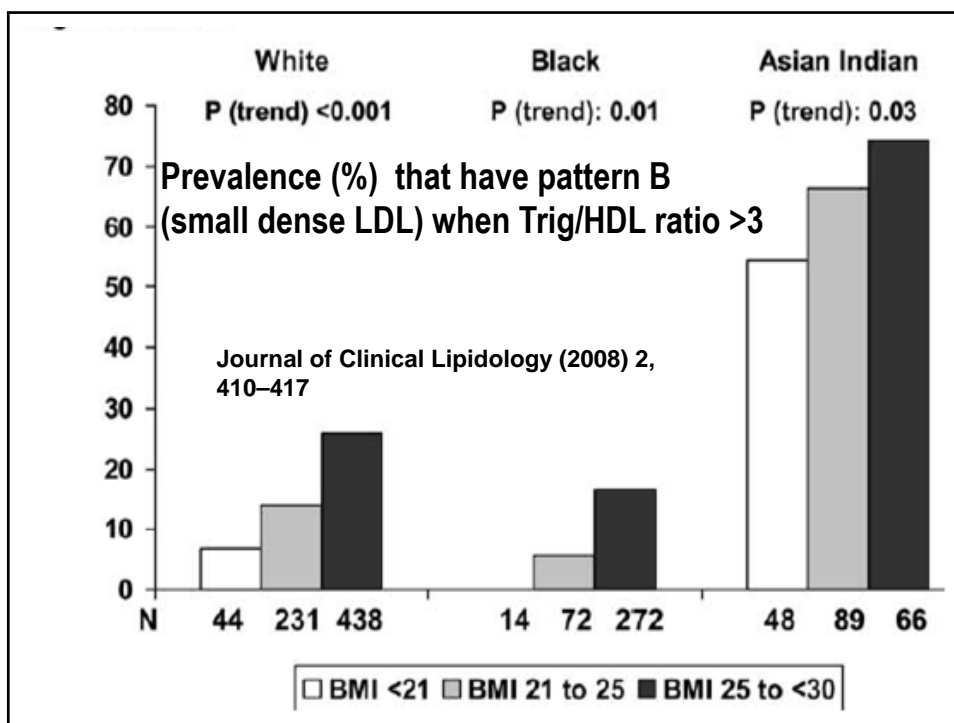


Table. Lipids and Subclasses Measured by Commercially Available Advanced Lipoprotein Tests			
LABORATORY	BERKELEY HEART LABS	LIPOSCIENCE	ATHEROTECH
METHODOLOGY USED TO PROVIDE THE UNIQUE SUBCLASS INFORMATION	GRADIENT GEL ELECTROPHORESIS	NUCLEAR MAGNETIC RESONANCE (NMR)	DENSITY GRADIENT ULTRACENTRIFUGATION "VERTICAL AUTO PROFILE"
Total cholesterol	Yes ^a	Yes ^a	Yes
LDL (method)	Yes ^a (Estimated or directly measured on request)	Yes (NMR-derived formula used)	Yes (Standard cholesterol directly measured)
LDL subclasses	IVa, IVb, IIIa, IIIb, IIa, IIb, I	Large, medium, small	4, 3, 2, 1
Lp(a)	Yes ^a	Yes ^a	Yes
IDL	No	Yes	Yes
Remnant lipoproteins	No	No	Yes
HDL	Yes	Yes	Yes
HDL subclasses	Yes	Yes	Yes
VLDL	No	No	Yes
VLDL subclasses	No	Yes	Yes
Non-HDL	No	No	Yes
Apo B	Yes ^a	No	Yes
Particle number	No	Yes	No

Karalis Advanced Lipid Testing Preventative Cardiology Fall 2007:228-234



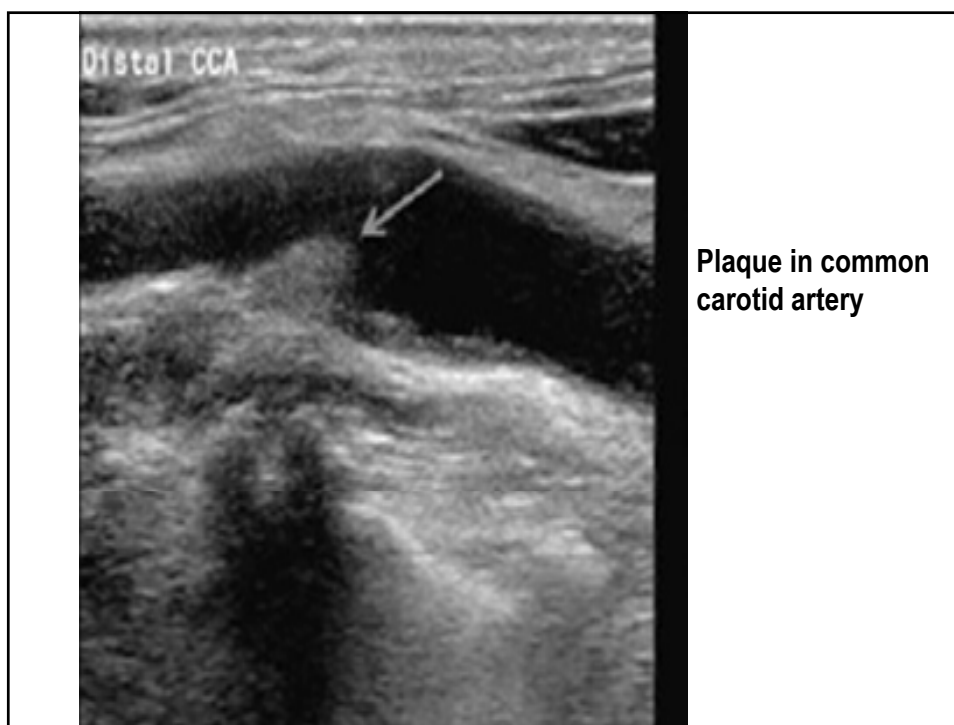
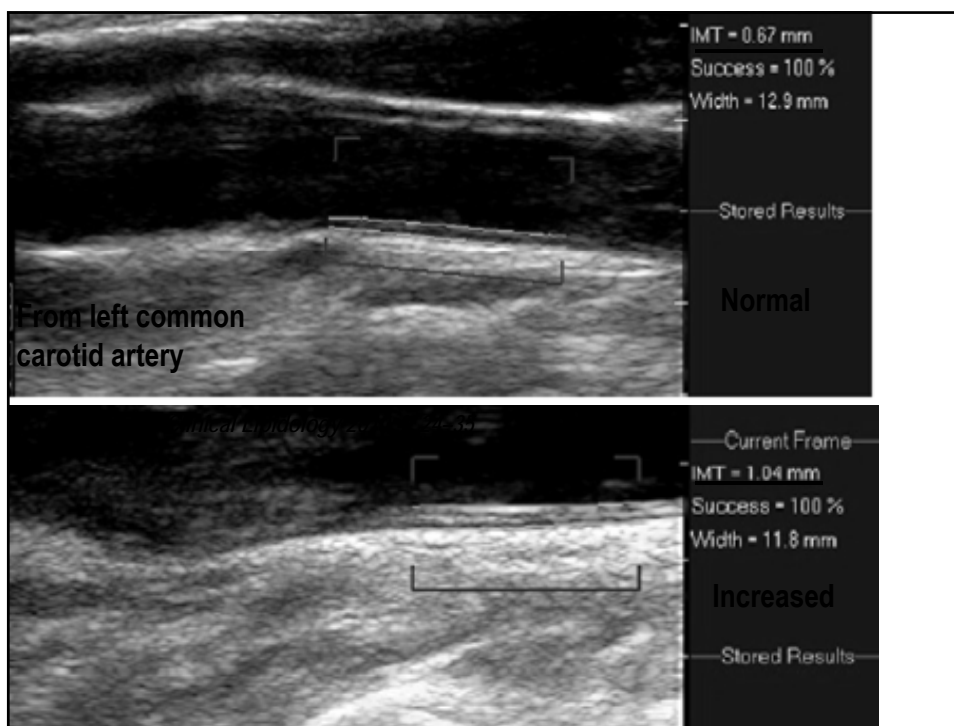


	Patient Name: PATIENT, TEST	Sex: F	Date Drawn 03/12/09
	Account: TEST CLIENT	Age: 34	Date Tested: 03/12/09
	Physician: Physician, Test	DOB: 10/01/1974	Accession: 6333743
	Fasting Status: Fasting	Client No: CLIENTACN12345	Patient ID: 3173769

Direct-Measured Cholesterol Panel	Actual	Desirable	Risk		Description
			Low	High	
Total LDL	162	<130 mg/dL	Y	Y	LDL-R + Lp(a) + IDL
LDL-R (Real LDL)	128	<100 mg/dL	Y	Y	Total LDL minus Lp(a) and IDL
Lp(a)	15	<10 mg/dL	Y	Y	More atherogenic than LDL
IDL	19	<20 mg/dL	Y	Y	More atherogenic than LDL
Total HDL	56	≥40 mg/dL	Y	Y	HDL ₂ + HDL ₃
HDL ₂	13	>15 mg/dL	Y	Y	Large Buoyant, more protective
HDL ₃	43	>30 mg/dL	Y	Y	Small Dense, less protective
Total VLDL	24	<30 mg/dL	Y	Y	VLDL ₁₊₂ + VLDL ₃
VLDL ₁₊₂	9.8	<20 mg/dL	Y	Y	Buoyant VLDL, less risk
VLDL ₃	15	<10 mg/dL	Y	Y	Dense VLDL, more risk
Total Cholesterol	243	<200 mg/dL	Y	Y	LDL + HDL + VLDL

Secondary and Emerging Risk Factors	Actual	Desirable	Risk		Description
			Low	High	
Triglycerides	141	<150 mg/dL	Y	Y	Linked to increased risk for CHD
Non-HDL Cholesterol	187	<160 mg/dL	Y	Y	LDL + VLDL
Remnant Lipoproteins	34	<30 mg/dL	Y	Y	IDL + VLDL ₃
Lp(a)	15	<10 mg/dL	Y	Y	More atherogenic than LDL
LDL Density (Pattern)	A/B	Pattern A	Y	Y	B: more risk; A/B intermediate risk; A: less risk
LDL Subclasses (mg/dL) LDL ₄ =23.7, LDL ₅ =56.6, LDL ₂ =22.3, LDL ₁ =25.4					
LDL ₄₊₅ small, dense. LDL ₂₊₃ large, buoyant					

Apolipoproteins	Actual	Desirable	Risk		Description
			Low	High	
Apo B ₁₀₀	125	<109 mg/dL	Y	Y	Sum atherogenic lipoprotein particles
Apo A1	161	>118 mg/dL	Y	Y	Sum anti-atherogenic lipoprotein particles
Apo B ₁₀₀ /A1 ratio	0.78	<0.75	Y	Y	Low ratio indicates lower risk



CMIT

- **CIMT is a suitable surrogate marker for coronary artery disease.**
- **When compared to coronary calcium scoring, CIMT of more value in the healthy young and middle-aged populations, women and African American individuals**
- **Recent findings indicate further that increased CIMT predicted CVD events in individuals without coronary calcification.**

– *Liviakis et al Carotid intima-media thickness for the practicing lipidologist
Journal of Clinical Lipidology 2010;4: 24–35*

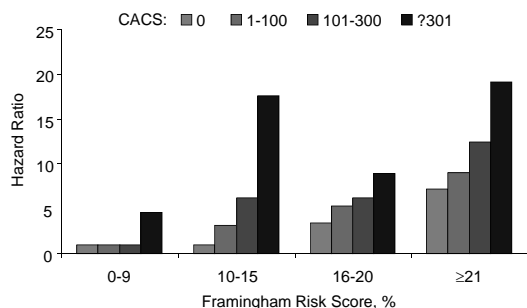
Guidelines for CIMT

- **Screen those in the intermediate risk group Framingham risk score 6% to 20% without established CHD, peripheral arterial disease, cerebrovascular disease, diabetes mellitus, or abdominal aortic aneurysm.**
- **Consider CIMT if in addition patient has 1) family history of premature CVD in a first-degree relative (men ,55 years old, women ,65 years old); 2) individuals younger than 60 years old with severe abnormalities in a single risk factor (eg, genetic dyslipidemia) who otherwise would not be candidates for pharmacologic therapy; or 3) women younger than 60 years old with a least two CVD risk factors.**
- **Guidelines discourage imaging in patients with established atherosclerotic vascular disease or if the results would not be expected to alter therapy.**
- **Serial studies of CIMT to address progression not currently recommended**

– *Liviakis et al Carotid intima-media thickness for the practicing lipidologist
Journal of Clinical Lipidology 2010;4: 24–35*

Noninvasive Screening – Coronary Artery Calcium Score (CACS)

Relationship between CACS and the baseline Framingham risk score in the prediction of coronary death or nonfatal MI*



*Hazard ratio by bivariate Cox regression analysis. Risk categories are the estimated 10-year risk for coronary death or MI based on the Framingham risk score. The CACS is measured by coronary computed tomography (CCT).

Greenland P, et al. *JAMA*. 2004;291:210-215.

Calcification Stenosis



CT angiographic image showing severe left circumflex coronary artery stenosis and 2 areas of calcification.

Coronary Artery Calcium Scores Should we obtain them?

- Depends on who you ask. Some cardiologist think they are (may do them in their office)
- American Heart Association does not believe there is good evidence to recommend them as tools for prevention-no evidence of decrease in mortality.
- American College Cardiology thinks they are based on “experience”
- Traditional risk factors more cost effective

– McCullough P, Chinnaiyan K. Annual progression of coronary calcification in trials of preventative therapies: a systematic review. *Arch Intern Med* 2009; 169:2064-2070.

– O'Malley P. A double take on serial measurement of coronary artery calcification. *Arch Intern Med* 2009; 169:2051-2052

– Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 2008;358:1336-45.

What if AST and ALT Are ↑

- **Nonalcoholic Fatty Liver Disease (NAFLD)/Nonalcoholic Steatohepatitis (NASH) is common in patients with hyperlipidemia and type II diabetes**
- **NAFLD/NASH may increase risk of CVD, so treat**
- **Liver enzymes are often normal in NAFLD/NASH; many hyperlipidemic patients with unsuspected NAFLD have likely been treated with statins without significant toxicity¹**

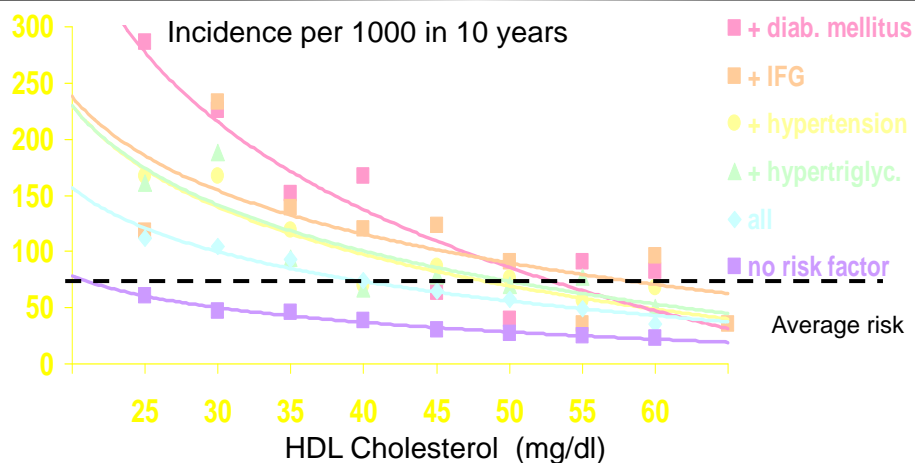
¹Chalasani N (2005), *Hepatology* 41(4):690-695; ²Rallidis LS et al. (2004), *Atherosclerosis* 174(1):193-196; ³McKenney JM et al. (2006), *Am J Cardiol* 97(8A):89C-94C

What if AST and ALT Are ↑ (Cont.)

- No supporting direct data that statins worsen hepatic histology ¹ studies indicate statins may improve liver histology in patients with NASH²
- If ALT or AST exceeds 3x UNL during statin therapy, follow the patient and repeat the measures; there is no need to D/C the statin; consider using a fractionated bilirubin to detect liver dysfunction (rather than ALT/AST)³

¹Chalasani N (2005), *Hepatology* 41(4):690-695; ²Rallidis LS et al. (2004), *Atherosclerosis* 174(1):193-196; ³McKenney JM et al. (2006), *Am J Cardiol* 97(8A):89C-94C

Incidence of Coronary Events in Men According to HDL Cholesterol and Other Risk Factors



PROCAM-Study: 4818 men aged 35-65 years; 325 coronary events in 10 years
(von Eckardstein & Assmann, Curr. Opin. Lipidol. 2000; 11: 627-637)

DEFINE: Changes in lipid parameters in the anacetrapib-treated patients

Variable	Baseline	Week 24	Week 76
LDL cholesterol (mg/dL)	81.2	44.7	48.9
HDL cholesterol (mg/dL)	40.5	101.2	102.3
Non-HDL cholesterol (mg/dL)	109.7	69.7	73.0
Apolipoprotein B (mg/dL)	88.4	70.1	69.6
Apolipoprotein A1 (mg/dL)	142.5	208.0	203.0
Total cholesterol (mg/dL)	150.3	170.8	175.2
Lipoprotein(a) (mmol/L)	26.8	14.8	16.4

Questions and Comments