Preventing Cardiovascular Disease in Women with PCOS

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Relevant Financial Relationship Disclosure Statement

- **I will not** discuss off label use and/or investigational use of any drugs/devices.
- I **have** the following relevant financial relationships to report in relationship to this presentation : Speaker's Bureau/ Consultant for Astra Zeneca , Kowa, Amarin.

Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society.

- **CONCLUSIONS**: Women with PCOS with
- Obesity
- cigarette smoking
- dyslipidemia
- hypertension
- impaired glucose tolerance
- and subclinical vascular disease
- **are at risk.**
- whereas those with metabolic syndrome and/or type 2 diabetes mellitus **are at high risk for CVD**.

Wild, RA, et al. J Clin Endocrinol Metab. 2010 May;95(5):2038-49. doi: 10.1210/jc.2009-2724. Epub 2010 Apr 7.

Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society.

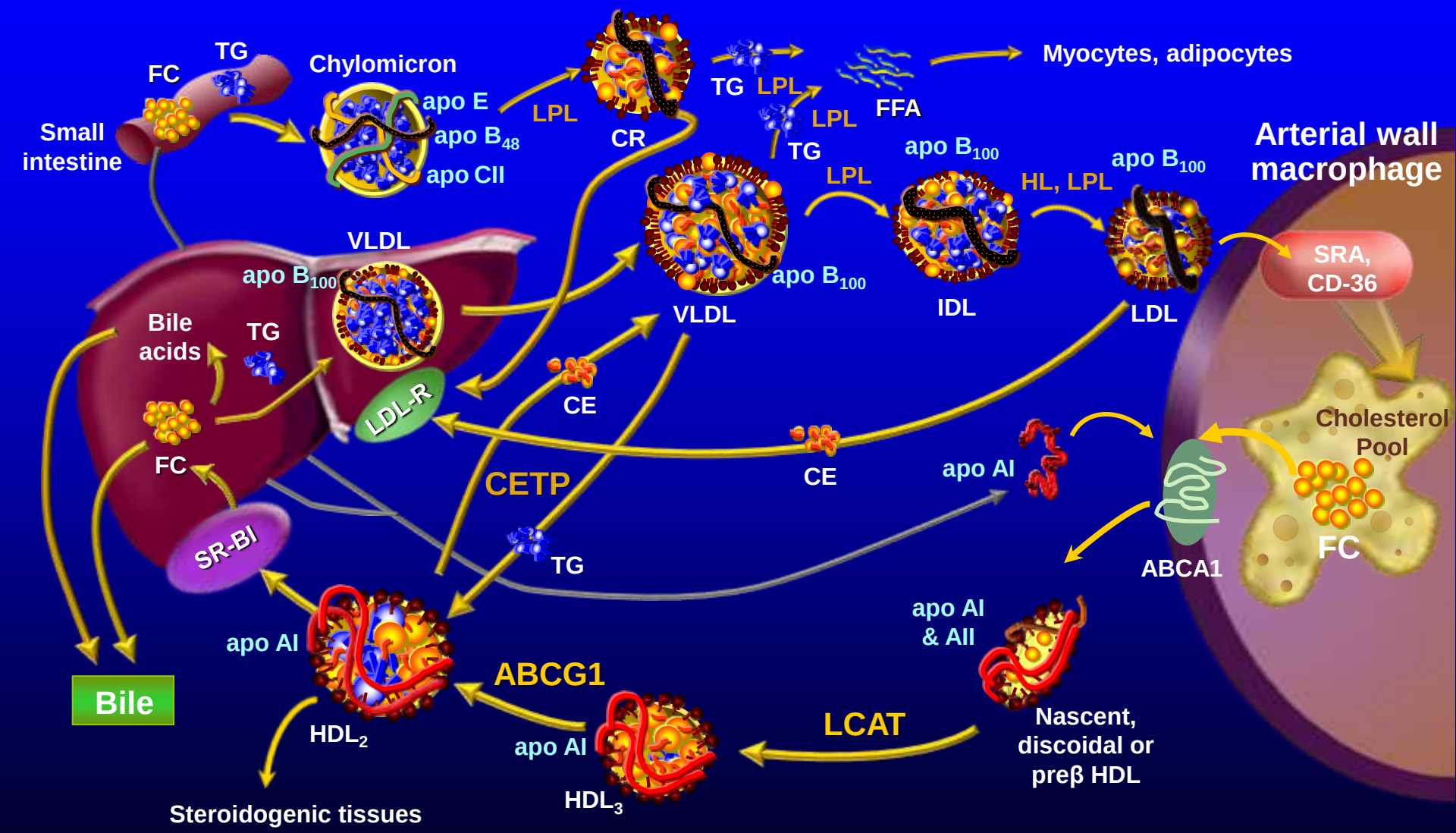
- Body mass index, waist circumference, serum lipid/glucose, and blood pressure determinations are recommended for all women with PCOS, as is oral glucose tolerance testing in those with obesity, advanced age, personal history of gestational diabetes, or family history of type 2 diabetes mellitus.
- Mood disorder assessment is suggested in all PCOS patients.
- Lifestyle management is recommended for primary CVD prevention, targeting low-density and non-high-density lipoprotein cholesterol and adding insulin-sensitizing and other drugs if dyslipidemia or other risk factors persist.

Wild, RA, et al. J Clin Endocrinol Metab. 2010 May;95(5):2038-49. doi: 10.1210/jc.2009-2724. Epub 2010 Apr 7.

Lipid and Lipoprotein Abnormalities in PCOS

- High triglycerides and low HDL-C (ratio greater than 3:1 in insulin resistant states)
- Small LDL particles are prevalent ; LDL-C may be high, but is often (misleadingly) low or normal.
- These numbers from the standard lipid panel represent serum concentrations of fats
- Underlying these abnormalities lie the pathophysiology of this (and other) insulin resistant states: hyper-production of atherogenic Beta Lipoproteins from the liver (delayed clearance also plays a roll)
- HDL particles are often “dysfunctional” in IRS states like PCOS. HDL-C tells you NOTHING about HDL function !
- Correction of this abnormal “lipoprotein trafficking” is the goal to reducing CVD risk in PCOS, NOT simply targeting the lipid abnormalities.

Lipid & Lipoprotein Metabolism



Artwork used with permission from T.Dayspring, MD. Adapted from: 1. Toth PP. *Endocrinol Metab Clin North Am*. 2009;38(1):151-170; 2. Toth PP. *Dis Mon.* 2001;47(8): 369-416; 3. Santamarina-Fojo S, et al. In: Scriver CR, et al, eds. *The Metabolic & Molecular Bases of Inherited Disease*. Vol 2. 8th ed. 2817-2833; 4. Havel RJ, et al. In: Scriver CR, et al, eds. *The Metabolic & Molecular Bases of Inherited Disease*. Vol 2. 8th ed. 2001:2705-2716. 5. Dayspring T. *J Cardiometab Syndr.* 2007;2(1):59-62.

Triglyceride Cholesterol Cholesteryl ester Phospholipids

Basic Science for Clinicians

Tabas I et al. Circulation. 2007;116:1832-1844

Subendothelial Lipoprotein Retention as the Initiating Process in Atherosclerosis

Update and Therapeutic Implications

Ira Tabas, MD, PhD; Kevin Jon Williams, MD; Jan Borén, MD, PhD

The key initiating process in

The probability that a particle's cholesterol will be delivered to an atheroma depends largely on particle number: how many LDL particles enter the artery wall, become oxidized, and are finally taken up by macrophage foam cells

Otvos JD et al J Clin Lipidol 2011;5(2):105-113

apolipoprotein B–containing lipoproteins.

(*Circulation*. 2007;116:1832-1844.)

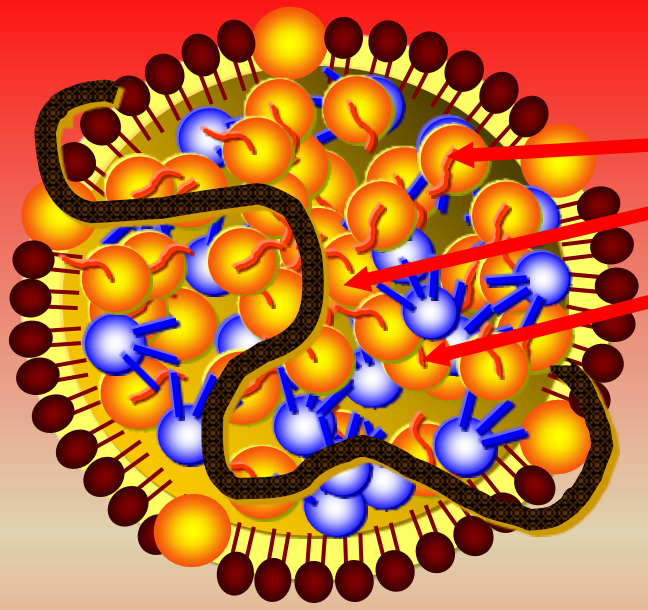
Chy ells n A-I

VLDL IDL LDL HDL

Low Density Lipoprotein Particle

LDL particle # or ApoB

(or Non-HDL-C)



Cholesterol ester content within all of the LDL particles in a deciliter (dL) of plasma.

LDL-C

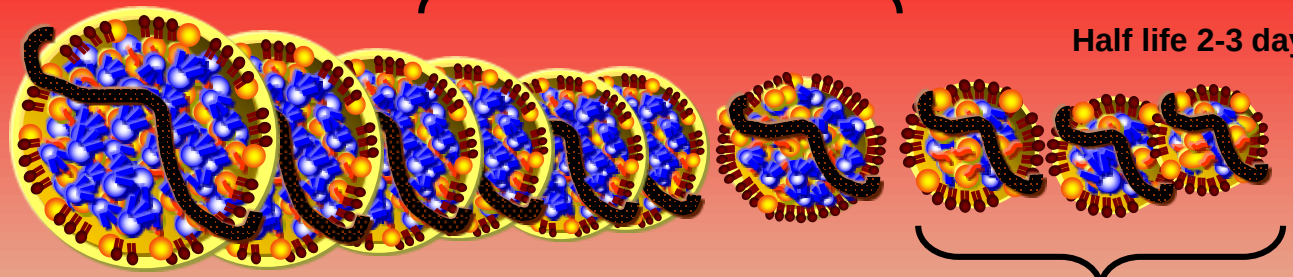
Never confuse LDL-C with LDL particle concentration = **LDL-P**

The NUMBER OF PARTICLES vs the cholesterol ester load inside the particle

Atherogenic Lipoproteins

ApoB

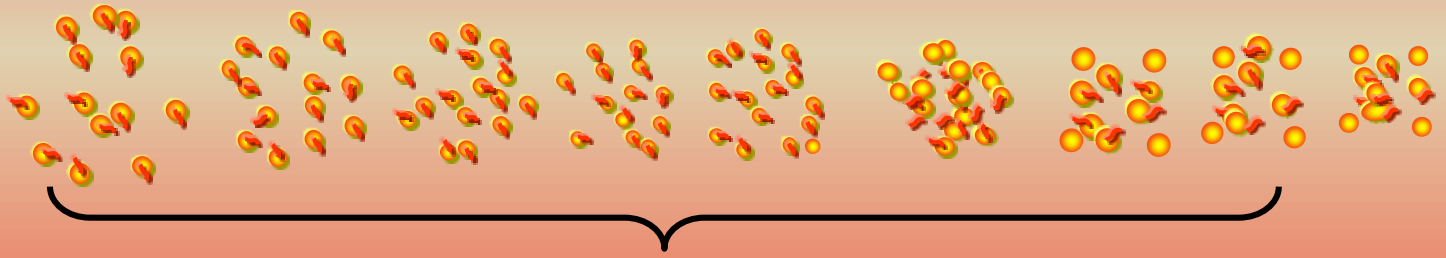
VLDL-P



Half life 2-3 days

Half life 4-6 hours

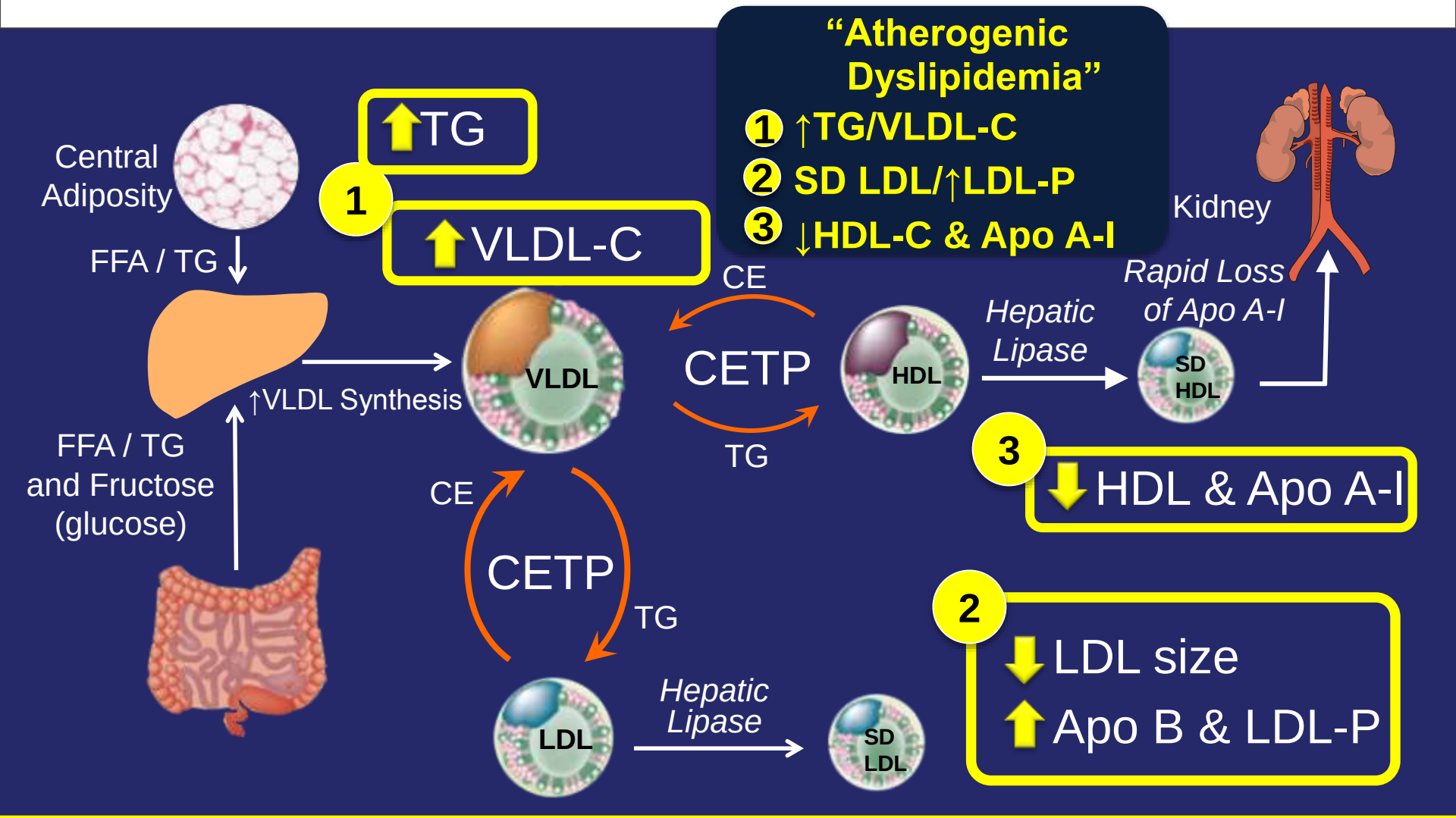
LDL-P



Non HDL-C = Total Cholesterol – HDL-Cholesterol

Since LDL-P makes up more than 90% of apoB particles,
Non HDL-C is in effect an apoB or LDL-P surrogate

Three Atherogenic Consequences of HTG



Fatty liver & ↑VLDL synthesis are key to ↑TG and consequences

CE=cholesterol ester; CETP=CE transfer protein; FFA=free fatty acid; VLDL=very-low-density lipoprotein; VLDL-C=VLDL cholesterol.

NLA Expert Panel Advice
LDL Particle Concentration (LDL-P)

Although similar outcome associations are observed for the two measures when LDL-C and LDL-P are concordant, CV risk is more strongly associated with LDL-P when these measures are discordant.

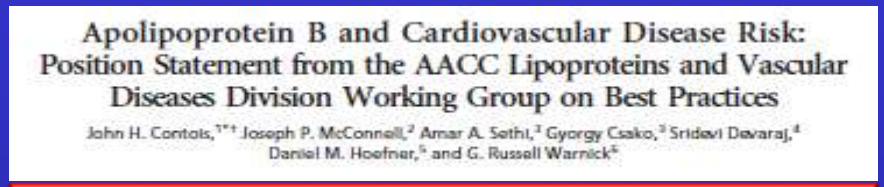
THE DISEASE FOLLOWS the PARTICLES !

Davidson MH et al. J Clin Lipidol 2011;5:338-367

US Organizations Advocating Lipoprotein Particle Concentration Use

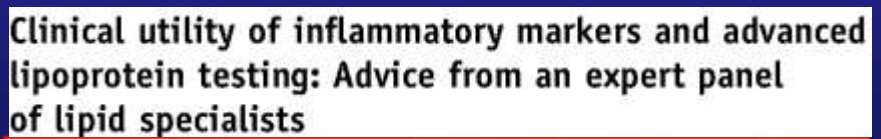
Measured apolipoprotein B or LDL-P by NMR

2008 American Diabetes Association/ American College of Cardiology Foundation Consensus statement on lipoprotein management in patients with cardiometabolic risk (Diabetes Care 2008;31:811-822) [1]



Measured apolipoprotein B or LDL-P by NMR

2009 Apolipoprotein B and Cardiovascular Disease Risk: Position Statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices (Clinical Chemistry 2009;55:3:407–419) [2, 3]



Measured Apolipoprotein B or LDL-P by NMR in all except low risk patients

2011 National Lipid Association on novel markers (J Clin Lipidol 2011;5:338-367) [4]

Measured apolipoprotein B

AACE recommends apo B to assess the success of LDL-C–lowering therapy. Endocrine Practice 2012;18 (Suppl 1) [5]

NATIONAL LIPID ASSOCIATION

NLA Recommendations for Patient-Centered Management of Dyslipidemia

Part 1 -- Final

National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1 – executive summary☆

Journal of Clinical Lipidology (2014) 8, 473–488

Terry A. Jacobson, MD*, Matthew K. Ito, PharmD, Kevin C. Maki, PhD, Carl E. Orringer, MD, Harold E. Bays, MD, Peter H. Jones, MD, James M. McKenney, PharmD, Scott M. Grundy, MD, PhD, Edward A. Gill, MD, Robert A. Wild, MD, PhD, Don P. Wilson, MD, W. Virgil Brown, MD

Guiding Principles/Conclusions

1. An elevated level of cholesterol carried by circulating Apo B-containing lipoproteins (non-HDL-C and LDL-C, termed atherogenic cholesterol) is a root cause of atherosclerosis, the key underlying process contributing to most clinical ASCVD events.
2. Reducing elevated levels of atherogenic cholesterol will lower ASCVD risk in proportion to the extent that atherogenic cholesterol is reduced. This benefit is presumed to result from atherogenic cholesterol lowering through multiple modalities, including lifestyle and drug therapies.

Guiding Principles/Conclusions

3. The intensity of risk-reduction therapy should generally be adjusted to the patient's absolute risk for an ASCVD event.
4. Atherosclerosis is a process that often begins early in life and progresses for decades before resulting in a clinical ASCVD event. Therefore, both intermediate-term and long-term/lifetime risk should be considered when assessing the potential benefits and hazards of risk-reduction therapies.
5. For patients in whom lipid-lowering drug therapy is indicated, statin treatment is the primary modality for reducing ASCVD risk.
6. Non-lipid ASCVD risk factors should also be managed appropriately, particularly high blood pressure, cigarette smoking, and diabetes mellitus.

Classifications of Cholesterol and Triglyceride Levels in mg/dL

Non-HDL-C

<130	Desirable
130-159	Above desirable
160-189	Borderline high
190-219	High
≥220	Very high

HDL-C

<40 (men)	Low
<50 (women)	Low

Trigs and HDL-C are NOT treatment goals; reduction of atherogenic lipoproteins are !

LDL-C

<100	Desirable
100-129	Above desirable
130-159	Borderline high
160-189	High
≥190	Very high

Triglycerides

<150	Normal
150-199	Borderline high
200-499	High
≥500	Very high

Targets of Therapy – Atherogenic Cholesterol

- Atherogenic cholesterol (non-HDL-C and LDL-C) levels are the primary targets of therapy. Non-HDL-C is listed first because the panel consensus was that it is a better primary target than LDL-C.
  - More predictive than LDL-C in observational studies and with regard to changes or on-treatment levels in clinical trials.
  - When non-HDL-C and LDL-C are discordant, risk is more closely aligned with non-HDL-C.
  - Elevations in apo B-containing particles, and cholesterol carried by those particles, are considered a “root cause” of atherosclerosis, and of primary importance for prevention.
  - Non-HDL-C testing is universally available, requires no additional cost, and may be measured in the non-fasting state.

Targets of Therapy – Apo B

- Apolipoprotein B (apo B) is considered a secondary, optional target for therapy.
  - Strongly associated with ASCVD event risk
  - More predictive power than LDL-C, but not consistently superior to non-HDL-C
  - May be elevated in some individuals who have obtained their non-HDL-C and LDL-C goals, thus a potential contributor to residual risk
  - Optional goals for primary and secondary/very high risk prevention are <90 and <80 mg/dL, respectively

The NLA Expert Panel acknowledges that measurement of LDL particle concentration can be useful clinically, particularly once non-HDL-C and LDL-C goals have been attained.

Steps in ASCVD Risk Assessment

1. Identify patients with ***very high risk*** conditions.*
   a. ASCVD
   b. Diabetes mellitus with ≥2 other major ASCVD risk factors or end organ damage[1]
2. Identify patients with ***high risk*** conditions
   a. Diabetes mellitus with 0-1 other major ASCVD risk factors
   b. Chronic kidney disease Stage 3 or 4[2]
   c. LDL-C ≥190 mg/dL
3. **Count** major ASCVD risk factors **(Family Hx, HDL-C < 50, age> 55, smoking, HBP)**
   a. If 0-1 and no other indicators of higher risk, assign to ***low risk*** category. Consider assigning to a higher risk category based on other risk factors, if known.
   b. If ≥3 major ASCVD risk factors are present, assign to ***high risk*** category.
4. If 2 major ASCVD risk factors, ***risk scoring*** is recommended and additional testing may be useful for some patients.
   a. If <10% 10-year hard CHD risk,[3] assign to ***moderate risk*** category.
   b. If ≥10% 10-year hard CHD risk, assign to ***high risk*** category.
   c. Assign as above, or consider assigning to ***high*** or ***very high*** **risk** category, as appropriate, if other risk indicators are present based on additional testing.

*Further risk assessment is not required in those with very high risk conditions.

Major Risk Factors for ASCVD

1. Age
   - Male ≥45 years
   - Female ≥55 years
2. Family history of early CHD
   - <55 years of age in a male first-degree relative, or
   - <65 years of age in a female first-degree relative
3. Current cigarette smoking
4. High blood pressure (≥140/≥90 mm Hg, or on blood pressure medication)
5. Low HDL-C
   - Male <40 mg/dL
   - Female <50 mg/dL

Criteria for ASCVD Risk Assessment, Treatment Goals, Levels at Which to Consider Drug Therapy

Risk Category	Criteria	Treatment Goal	Consider Drug Therapy
		Non-HDL-C mg/dL LDL-C mg/dL	
Low	▪ 0-1 major ASCVD risk factors ▪ Consider other risk indicators, if known	<130 <100	≥190 ≥160
Moderate	▪ 2 major ASCVD risk factors ▪ Consider quantitative risk scoring ▪ Consider other risk indicators	<130 <100	≥160 ≥130

High	▪ ≥3 major ASCVD risk factors
	▪ Diabetes mellitus* (Type 1 or 2)
	  ▪ 0-1 other major ASCVD risk factors, and
	  ▪ No evidence of end organ damage
	▪ Chronic kidney disease Stage 3B or 4
	▪ LDL-C ≥190 mg/dL (severe hypercholesterolemia)
	▪ Quantitative risk score reaching the high risk threshold
		<130
		<100
			≥130
			≥100

Very High	▪ ASCVD*
	▪ Diabetes mellitus* (Type 1 or 2)
	  ▪ ≥2 other major ASCVD risk factors or
	  ▪ Evidence of end organ damage
		<100
		<70
			≥100
			≥70

For patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate or high intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.

TABLE 2. PCOS risk categories and lipid target values[a]

	Risk	LDL target values, mg/dl (mmol/liter)[b]	Non-HDL target values, mg/dl (mmol/liter)[b]
PCOS	At optimal risk	≤130 (3.37)	≤160 (4.14)
PCOS with obesity, hypertension, dyslipidemia, cigarette smoking, IGT, subclinical vascular disease	At risk	≤130 (3.37)	≤160 (4.14)
PCOS with MBS	High risk	≤100 (2.59)	≤130 (3.37)
PCOS with MBS and other risk factors,[c] or with T2DM, or in presence of overt vascular and/or renal disease		≤70 (1.81)	≤100 (2.59)

[a] Values are based on at least 12-h fasting lipid determinations. Predictive utility for CVD events based on nonfasting lipoprotein lipid values has not yet been clearly validated.

[b] To convert mg/dl to mmol/liter, divide by 39.

[c] Odds of CVD increase with number of MBS components and with other risk factors, including smoking, poor diet, physical inactivity, obesity, family history of premature CVD (<55 yr of age in male relative, <65 yr of age in female relative) and subclinical vascular disease.

Risk Indicators (Other Than Major ASCVD Risk Factors) That Might Be Considered For Risk Refinement

1. A severe disturbance in a major ASCVD risk factor, such as multi-pack per day smoking, strong family history, severe hypertension or severely depressed HDL-C
2. Indicators of subclinical disease, particularly coronary artery calcium
   - ≥300 Agatston units or ≥75th percentile for age, sex and ethnicity is considered evidence of ASCVD
3. Long-term ASCVD risk ≥40%
   - Lloyd-Jones 2006 Framingham risk calculator
4. High-sensitivity C-reactive protein ≥2.0 mg/L
5. Apolipoprotein B ≥120 mg/dL or LDL particle concentration ≥1600 nmol/L
6. Lipoprotein (a) ≥50 mg/dL (protein) using an isoform insensitive assay
7. Urine albumin / creatinine ratio ≥30 mg/g

Drug Therapies – Important Considerations

- Patient-centered therapy: before initiation of pharmacotherapy, the clinician should have a discussion with the patient about treatment objectives and potential ASCVD risk reduction, as well as the potential for adverse effects, interactions with other medications and patient preferences.
- When pharmacotherapy is to be used for lowering atherogenic cholesterol, moderate or high-intensity statin therapy should be the first-line agent. Starting with a moderate dose and titrating as necessary to achieve treatment goals is a reasonable approach.
  - An alternate drug (bile acid sequestrant, cholesterol absorption inhibitor, fibrate or nicotinic acid) may be considered in those with contraindications to statin therapy

Drug Therapies – Important Considerations (continued)

- A drug targeting triglyceride reduction should be considered for first-line therapy in those with triglycerides ≥500 mg/dL.
  - Triglyceride lowering drug therapies include fibrates, high-dose omega-3 fatty acids and nicotinic acid
  - A statin may be a reasonable first-line agent if the triglyceride concentration is ≥500 mg/dL but <1000 mg/dL, if no history of pancreatitis
- When used, drug therapy should be adequate to attain levels of atherogenic cholesterol (non-HDL-C and LDL-C) that are *below* the goal cut points.
  - For patients with very high baseline levels of atherogenic cholesterol, it may not be possible to achieve goal levels, in which case an alternate goal of reductions of at least 50% for non-HDL-C and LDL-C may be considered.
- At present, no evidence suggests harm associated with LDL-C levels <40 mg/dL, so therapy may be continued in patients with LDL-C <40 mg/dL in the absence of signs of intolerance.

Drug Therapies – Important Considerations (continued)

- Combination therapy with a statin plus a second agent may be considered for patients who have not reached their treatment goals for atherogenic cholesterol levels, particularly in those at high and very high risk. Generally, the maximally tolerated statin dose should be used before add-on therapy is considered.
- For patients with statin intolerance, reducing the dose of statin, switching to a different statin, and alternate regimens such as every other day statin dosing may be considered.
- For patients who cannot tolerate a statin using the above strategies, alternate agents alone or in combination may be considered.

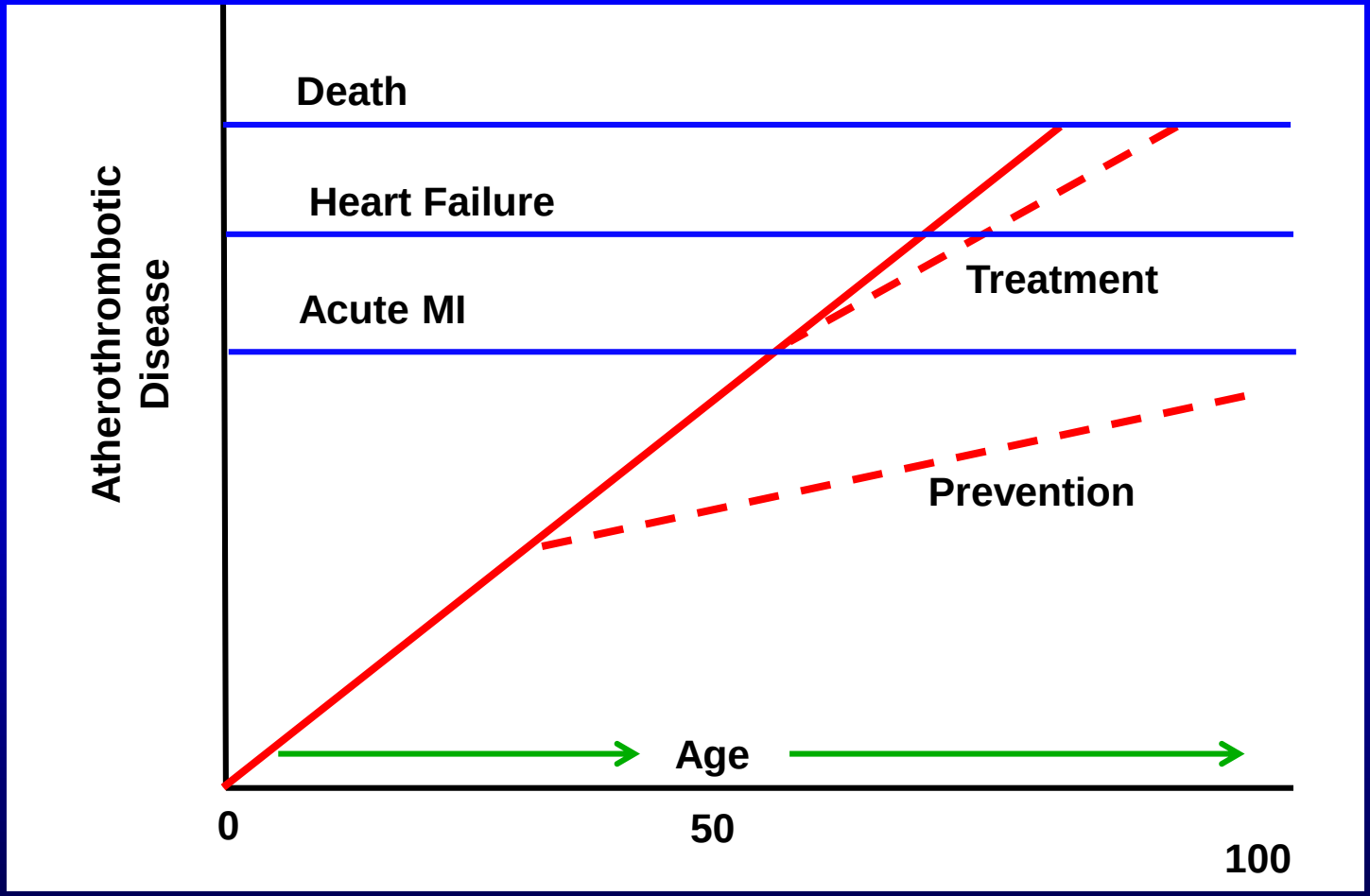
Summary

- Lifestyle Changes are the first line of therapy unless patient is high or very high risk
- Adults should be screened for cholesterol by the age of 20
- Statins are first line of therapy unless triglycerides are over 1000, other agents may be added if not to goal
- Non-HDL (130) and LDL (100) are targets of treatment unless very high risk (100/70)
- For moderate risk patients a long term and short term risk calculator should be used(Framingham 10 year/lifetime risk)

So WHAT DO WE DO NOW for PCOS ?

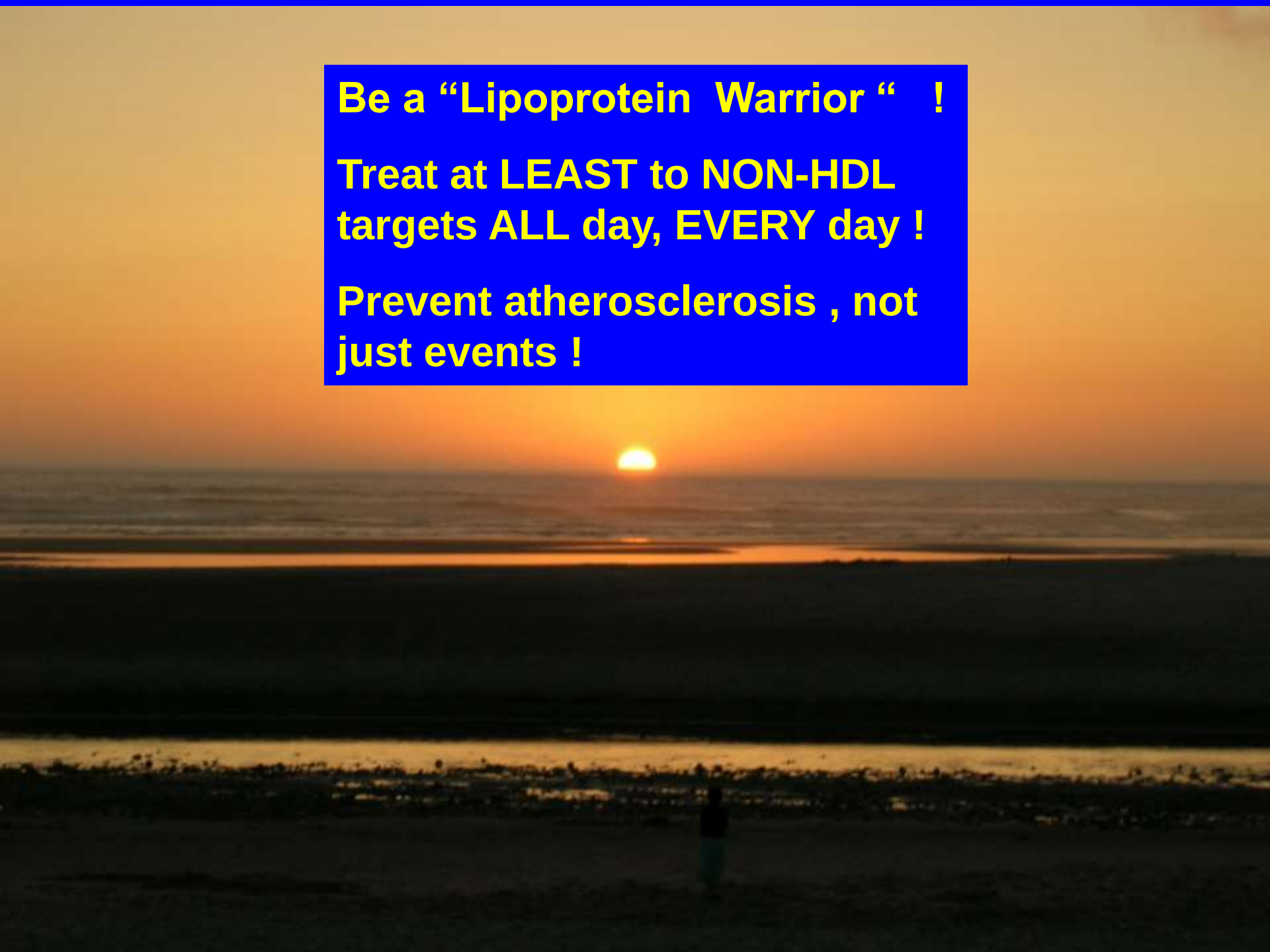
- Consider consultation with a Board Certified Clinical Lipidologist: find one a www.lipid.org or www.learnyourlipids.com
- Insulin sensitizing diet- low glycemic eating
- Exercise- “every step / every lb. lifted “ fights insulin resistance
- Assess risk using NLA guidelines and ASCVD risk calculator app
- Target atherogenic lipoproteins not individual lipids (unless trigs > 500 mg/dl) using Non HDL-C and apoB/ NMR LDL-P.
- Non HDL-C goal < 130 mg/dl (apoB < 90 mg/dl) for most women.
- Statins are first line drugs (safe and effective) but need to be wary of issues in fertile women. Metformin may or may not improve lipoproteins.
- Other meds such as BAS (colevelam) , ezetimibe, fenofibrate may be helpful.

The Message Is Clear: Prevent as Well as Treat Acute Myocardial Infarction



Natural history of atherothrombotic disease. Progression to acute myocardial infarction (AMI) may be followed by heart failure and death. Aggressive treatment after the event alters the slope of progression with delay but ultimate complications of heart failure and death. Early detection of the process can lead to preventive therapy that reduces the slope of progression and may eliminate the associated morbidity before the age of 100 years

Cohn JN *Circulation.* 2013;128:2554-2556


Be a “Lipoprotein Warrior “ !
Treat at LEAST to NON-HDL targets ALL day, EVERY day !
Prevent atherosclerosis , not just events !

Preventing Cardiovascular Disease in Women with PCOS

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