Pennsylvania Academy of Family Physicians Foundation

Pittsburgh CME Conference

November 7 - 9, 2014

Update on the New Lipid Guidelines… How Do These Affect Your Practice? ***(Patient Safety)***

Gregory S Pokrywka MD, FACP, FNLA, NCMP
Baltimore Lipid Center, Towson, MD

Disclosures:

Speaker disclosures he has a financial relationship or interest with a commercial entity that may have a direct interest in the subject matter of this session. He serves on an advisory board for AstraZeneca, Kowa, Health Diagnostics Labs, Amarin, and Amgen. He also serves on speaker's bureaus for AstraZeneca, Kowa, Health Diagnostics Labs, Amarin, and Amgen. There are no conflicts of interest with his presentation.

The speaker has attested that their presentation will be free of all commercial bias toward a specific company and its products.

The speaker indicated that the content of the presentation will not include discussion of unapproved or investigational uses of products or devices.

Clinical Lipidology Update 2014 : the New Guidelines: What to do ?

Gregory Pokrywka MD FACP FNLA NCMP

Asst. Professor of Medicine, Johns Hopkins University
Diplomate of the American Board of Clinical Lipidology
Fellow of the ACP and the National Lipid Association
North American Menopause Society Certified Menopause Practitioner
Director, Baltimore Lipid Center

www.Mysite.verizon.net/gpokmd

gpokmd@verizon.net

Twitter : @gpokmd

www.learnyourlipids.com www.lipid.org

Disclosure

- Dr. Gregory Pokrywka discloses he serves as part of the advisory boards and speaker's bureaus for AstraZeneca, Kowa, Health Diagnostics Labs, Amarin, and Amgen. No conflict of interest exists in his presentation today.

According to the 2013 AHA/ ACC Guidelines, which ONE of the following is one of the four statin benefit groups?

3

A. Individuals with clinical ASCVD
B. Individuals with primary elevations of low-density lipoprotein cholesterol (LDL-C) > 130 mg/dl.
C. Individuals 40-75 years of age with metabolic syndrome
D. Individuals without clinical ASCVD or diabetes, who are 40-75 years of age with LDL-C 70-189 mg/dl, and have an estimated 10-year ASCVD risk of 15 % or higher.

Key Differences between the 2013 AHA/ ACC Guidelines, and the NLA 2014 patient Centered Recommendations are:

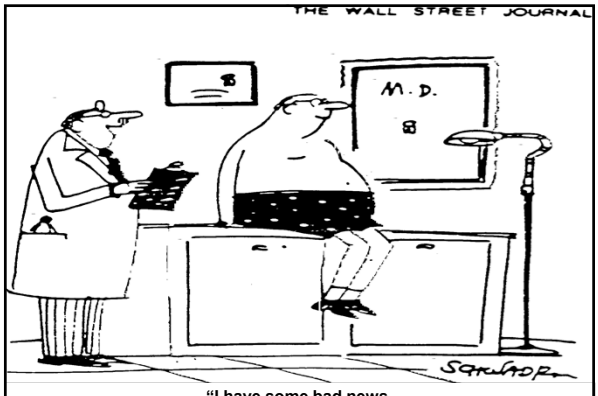
4

A. **The NLA 2014 patient Centered Recommendations have targets for LDL-C and NonHDLc-C levels.**
B. **The NLA 2014 patient Centered Recommendations consider evidence form RCTs as well as epidemiological, metabolic, mechanistic and genetic studies.**
C. **The NLA 2014 patient Centered Recommendations have a treatment goal of Non HDL-C of < 130 mg/dl for all except the very highest risk patients.**
D. **All of the above**

A drug targeted reduction of triglycerides should be considered for first line therapy in those whose triglycerides are > or = to 500 mg/dl.

5

A. True
B. False



**"I have some bad news.
While your cholesterol level has remained the same,
the guidelines have changed."**

Accumulating Evidence for Statins in Primary Prevention
Jennifer G. Robinson, MD, MPH
EDITORIAL
Editorials represent the opinions of the authors andJAMA and not those of the American Medical Association.

"Meta-analyses now provide extensive evidence that statins reduce cardiovascular events and total mortality in individuals at lower risk of cardiovascular events than has previously been appreciated, and do so with an excellent margin of safety."

Accumulating Evidence for Statins in Primary Prevention
Jennifer G. Robinson, MD, MPH

"In sum, the recent statin meta-analyses provide evidence that largely refutes the major criticisms against statins used for primary prevention. Statins are well tolerated in properly selected individuals. Statins reduce total mortality as well as atherosclerotic cardiovascular disease events in lower-risk individuals. Concerns about cost are no longer relevant with 5 of the currently available statins available as generic drugs. Indeed, recent analyses have found statins to be highly cost-effective and even cost-saving in lower-risk individuals, and can provide a large societal benefit.

The accumulated evidence should convince those with a philosophical aversion to statin therapy for primary prevention to reconsider their stance. Despite decades of exhortation for improvement, the high prevalence of poor lifestyle behaviors leading to elevated cardiovascular disease risk factors persists, with myocardial infarction and stroke remaining the leading causes of death in the United States.

Clearly, many more adults could benefit from evidence directed use of statins for primary prevention."

2013 ACC AHA Cholesterol Guidelines

Through a rigorous process, four groups of individuals were identified for whom an extensive body of RCT evidence demonstrated a reduction in atherosclerotic cardiovascular disease (ASCVD) events (including coronary heart disease [CHD], cardiovascular deaths, and fatal and nonfatal strokes) with a good margin of safety from statin therapy:

2013 ACC AHA Cholesterol Guidelines

Four Statin Benefit Groups:

- Individuals with clinical ASCVD (acute coronary syndromes, or a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin) without New York Heart Association (NYHA) class II-IV heart failure or receiving hemodialysis.
- Individuals with primary elevations of low-density lipoprotein cholesterol (LDL-C) ≥190 mg/dl.
- Individuals 40-75 years of age with diabetes, and LDL-C 70-189 mg/dl without clinical ASCVD.
- Individuals without clinical ASCVD or diabetes, who are 40-75 years of age with LDL-C 70-189 mg/dl, and have an estimated 10-year ASCVD risk of 7.5% or higher.

11

Risk Calculators

- http://my.americanheart.org/cvriskcalculator
- http://clincalc.com (android and apple apps)
- BUT, the new risk calculator has generated controversy (some studies show it may overestimate risk in many, other studies seem to validate it) and has NOT been adjudicated against clinical events !

Stone NJ, et al.
2013 ACC/AHA Blood Cholesterol Guideline

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

- New “evidence-based” practice guidelines radically changes (eliminates) cholesterol goals of therapy
- Advises initiation and maintenance of maximal statin dose
- Does not address combination therapy
- The following are no longer considered appropriate strategies: treat to target, lower is best, treat to level of ASCVD risk, and based upon lifetime risk of ASCVD

"Evidence Based Medicine" and Guidelines

- **TRUE "Evidence Based Medicine" is 'the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients."**
- Guidelines attempt to define practices that meet the needs in most circumstances and are not a replacement for clinical judgment. The ultimate decision about care of a particular patient must be made by the healthcare provider and patient in light of the circumstances presented by that patient." **Translation: You the doctor should treat each and every individual patient in the manner you deem most appropriate.**

Sackett, et al, BMJ 1996;312:71-72
Martin and Blumenthal, Ann Int Med 2014;160:354-355
Baum SJ, Journal of Clinical Lipidology(2014), doi:10.1016/j.jacl.2013.12.010

14

Feedback on New Cholesterol Guidelines

- Generally positive from the "academics" and "status/quo" types : "simpler, evidence based, treats the right people, includes CVA."
- **Generally negative from Lipidologists** : NOT a comprehensive LIPID guidelines (focus ONLY on LDLC) , "no targets, ignores non statin drugs, TOO evidence based (rigidity)", NOT endorsed by National Lipid Assn, nor AACE. Ignores Lipoprotein hypothesis, residual risk in statin patients, evidence for non-statin therapies.. Ignores expert opinion, clinical expertise.
- Generally negative from the public : "too many conflicts of interest" "too many people to be put on statins" . This second argument is easily dismissed as Jennifer Robinson (co-chief author) makes the analysis that these guidelines help put the RIGHT millions of people on statins without grossly increasing the numbers.

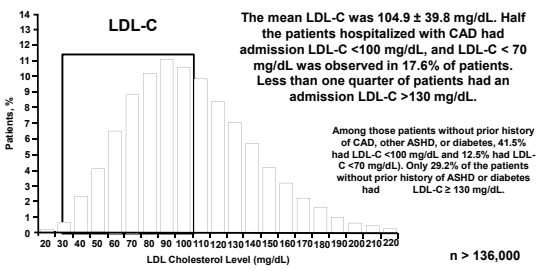
15

NLA Statement on the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

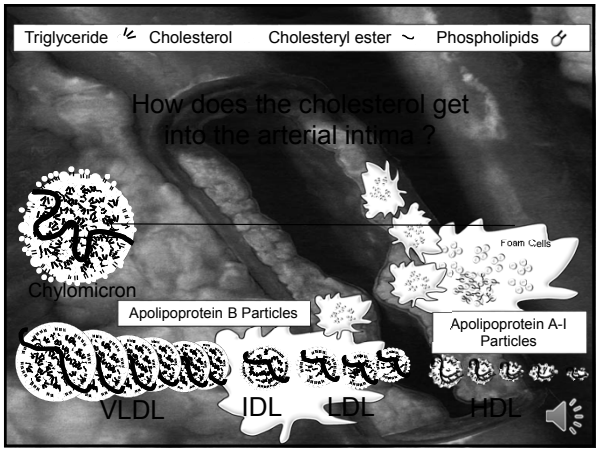
The American College of Cardiology and the American Heart Association recently modified and released the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. The National Lipid Association (NLA) was invited to participate in this process and worked initially with the NHLBI and then eventually with the AHA and ACC as the guidelines were transitioned and finalized. We provided our comments but after multiple revisions, ultimately felt that the document presented--although important and constructive--does not go far enough to address gaps in clinical care and therefore decided not to endorse them as guidelines.

- **We understand the constraints that the NHLBI panel had in limiting their review to only high quality randomized controlled trials but also believe that other important types of clinical evidence should not have been excluded. We also do not find evidence-based support for the Panel's recommendation for removing LDL-C (and Non-HDL-C) treatment targets. We question the need to remove such important and well-known clinical performance metrics that have been so widely endorsed by the clinical community. Further we find there to be an absence of discussion regarding other therapeutic options for patients on high-dose statins but which still exhibit high residual risk and/or significantly elevated LDL-C levels. There also needs to be more discussion on managing special populations such as older patients above age 75, those with familial hypercholesterolemia, those who are statin-intolerant, and younger high risk patients under age 40.**

Lipid Levels in Patients Hospitalized with Coronary Artery Disease



Sachdeva A, et al. Am Heart J 2009;157:111-7.e2



Basic Science for Clinicians

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

Subendothelial Lipoprotein Retention as the Initiating Process in Atherosclerosis

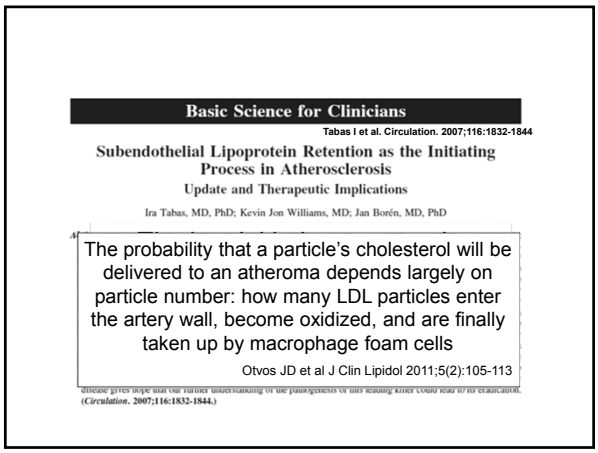
Update and Therapeutic Implications

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

Abstract—The key initiating process in atherogenesis is the subendothelial retention of apolipoprotein B–containing lipoproteins. Local biological responses to these retained lipoproteins, including a chronic and maladaptive macrophage-

The key initiating process in atherogenesis is the subendothelial retention of apolipoprotein B–containing lipoproteins.

maintain lifelong low plasma levels of apolipoprotein B lipoproteins have an ≈90% decreased risk of coronary artery disease gives hope that our further understanding of the pathogenesis of this leading killer could lead to its eradication. (*Circulation*. 2007;116:1832-1844.)



Basic Science for Clinicians

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

Subendothelial Lipoprotein Retention as the Initiating Process in Atherosclerosis

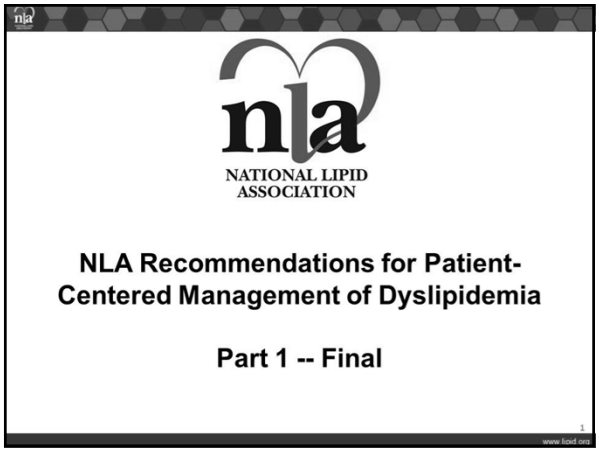
Update and Therapeutic Implications

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

The 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

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



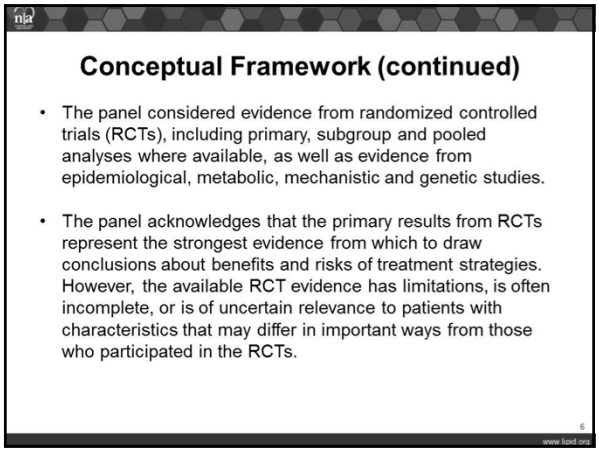
NATIONAL LIPID ASSOCIATION

NLA Recommendations for Patient-Centered Management of Dyslipidemia

Part 1 -- Final

1

www.lipid.org



Conceptual Framework (continued)

- The panel considered evidence from randomized controlled trials (RCTs), including primary, subgroup and pooled analyses where available, as well as evidence from epidemiological, metabolic, mechanistic and genetic studies.
- The panel acknowledges that the primary results from RCTs represent the strongest evidence from which to draw conclusions about benefits and risks of treatment strategies. However, the available RCT evidence has limitations, is often incomplete, or is of uncertain relevance to patients with characteristics that may differ in important ways from those who participated in the RCTs.

6

www.lipid.org

Part 2

- Part 2 of the NLA Recommendations for Patient-Centered Management of Dyslipidemia is in development and will cover the following topics:
  - Lifestyle therapies
  - Groups with special considerations
    - Children, adolescents, pregnant women, and older patients
    - Gender and ethnic differences
    - Patients with congestive heart failure (CHF)
    - Patients with human immunodeficiency virus (HIV)
    - Patients with selected chronic inflammatory states and immune disorders
    - Patients with residual risk despite statin therapy
  - Strategies to assist with patient adherence
  - Team-based collaborative care

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.

Importance of Lifestyle Therapies

- The NLA Expert Panel's consensus view is that lifestyle therapies are an important element of risk-reduction therapies, whether or not drug therapy is used.
- The application of pharmacotherapy to dyslipidemia management has been enormously successful, and may be needed in those with sufficient risk.
- Large-scale RCTs, involving, in aggregate, hundreds of thousands of participants, have shown that drug therapies (particularly statins) that lower atherogenic cholesterol levels are effective for reducing ASCVD morbidity and mortality.
- However, results from observational studies strongly suggest that lifestyle habits have an important impact on atherogenic cholesterol levels, as well as other related disturbances (i.e., obesity, hypertension, and insulin resistance).

Usefulness of Treatment Goals

- The NLA Expert Panel's consensus view is that treatment goals are useful as means to ensure that the aggressiveness of therapy to lower atherogenic cholesterol is matched to absolute risk for an event, and to facilitate effective communication between patients and clinicians while maximizing long-term adherence to the treatment plan.
- The strategy of treating patients to a specific level of LDL-C or non-HDL-C has not been tested in any of the large trials assessing ASCVD morbidity or mortality.
  - However, results from RCTs that have employed various methods for lowering atherogenic cholesterol (pharmacotherapy, diet, ileal bypass surgery) have indicated that lower on-treatment levels have been consistently associated with lower absolute risk for an ASCVD event, and generally align with results from observational studies suggesting a log-linear relationship between levels of atherogenic cholesterol and absolute ASCVD event risk.

Screening in Adults

- A fasting or non-fasting lipid profile should be measured at least every 5 years, starting at age 20; ideally fasting to allow assessment of LDL-C and triglyceride levels.
  - If non-fasting, focus on non-HDL-C (total-C minus HDL-C) and HDL-C.
- Should be accompanied by an assessment of ASCVD risk factors and risk stratification when indicated (covered later).
- If low risk, public health recommendations may be applied for those with atherogenic cholesterol levels in the desirable range (LDL-C <100 mg/dL, non-HDL-C <130 mg/dL)
  - Re-screen in 5 years, or with changes in risk factors (including weight gain), co-morbidities, new secondary causes of dyslipidemia, premature ASCVD events in first degree relatives, or other changes, based on clinical judgment
- Otherwise, institute therapies and monitoring as outlined in the subsequent slides.

Classifications of Cholesterol and Triglyceride Levels in mg/dL

Non-HDL-C		HDL-C	
<130	Desirable	<40 (men)	Low
130-159	Above desirable	<50 (women)	Low
160-189	Borderline high		
190-219	High		
≥220	Very high		

LDL-C		Triglycerides	
<100	Desirable	<150	Normal
100-129	Above desirable	150-199	Borderline high
130-159	Borderline high	200-499	High
160-189	High	≥500	Very high
≥190	Very high		

15

www.lipid.org

Treatment Goals for Non-HDL-C, LDL-C, and Apo B in mg/dL

Risk Category	Treatment Goal		
	Non-HDL-C	LDL-C	Apo B
Low	<130	<100	<90
Moderate	<130	<100	<90
High	<130	<100	<90
Very High	<100	<70	<80

16

www.lipid.org

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.
  - Non-HDL-C is more predictive of ASCVD risk 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.
  - Non-HDL-C testing is universally available, requires no additional cost, and may be obtained in the non-fasting state.

17

www.lipid.org

Targets of Therapy – Apo B

- Apolipoprotein B (Apo B) is considered an optional, secondary target for therapy. Apo B concentration is:
  - Strongly associated with ASCVD event risk;
  - More predictive of ASCVD risk than LDL-C, but not consistently superior to non-HDL-C;
  - A potential contributor to lipoprotein-related residual risk, as it may remain elevated in some individuals who have attained their non-HDL-C and/or LDL-C goals;
  - May be accurately assessed in the non-fasting state.
- Optional Apo B goals for primary and secondary/very high risk prevention are <90 and <80 mg/dL, respectively
  - Measurement is typically not necessary until goal levels of atherogenic cholesterol have been achieved.

Targets of Therapy – Apo B (continued)

- Clinicians may consider measuring LDL particle concentration as an alternative to Apo B.
  - Additional information about LDL particle concentration and Apo B may be found at www.lipid.org/practicetools/guidelines/consensus_recommendations: *Clinical Utility of Inflammatory Markers and Advanced Lipoprotein Testing: Advice form an Expert Panel of Lipid Specialists*
- 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.

Targets of Therapy – Triglycerides

- An elevated triglyceride level is not a target of therapy *per se*, except when very high (severe; ≥500 mg/dL).
- When triglycerides are between 200-499 mg/dL, the targets of therapy are non-HDL-C and LDL-C.
- When the triglyceride concentration is very high (≥500 mg/dL, and especially if ≥1000 mg/dL), reducing the concentration to <500 mg/dL to prevent pancreatitis becomes the primary goal of therapy.

HDL-C

- The level of HDL-C is an important risk indicator and used in risk factor counting and quantitative risk assessment. Low HDL-C is also a component of the metabolic syndrome.
- HDL-C is not recommended as a target of therapy *per se*, but the level is often raised as a consequence of efforts to reduce atherogenic cholesterol through lifestyle and drug therapies.

Metabolic Syndrome

- Metabolic syndrome is recognized as a multiplex risk factor for both ASCVD and type 2 diabetes mellitus.
- Increased adiposity and insulin resistance appear to be central pathophysiologic features of this cluster of interrelated metabolic and hemodynamic disturbances.
- The presence of the metabolic syndrome indicates high potential to benefit from lifestyle therapies, particularly weight loss if overweight/obese and increased physical activity.
  - Successful lifestyle intervention will reduce adiposity and insulin resistance, improving multiple physiological disturbances that may contribute to risk, including the metabolic syndrome components, as well as indicators of inflammation and thrombogenicity.

Secondary Causes of Dyslipidemia

- Some conditions and medications produce adverse changes in lipid levels and may be targets for intervention.
  - Discontinuing, reducing the dosage, or switching to an alternative medication;
  - Managing the condition (e.g., treating hypothyroidism, diabetes mellitus, obesity).

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

Other Major ASCVD Risk Factors Not Listed for Risk Factor Counting

- Non-HDL-C and LDL-C
  - Not included because these risk factors are used to assess risk category and treatment goals for atherogenic cholesterol levels
- Diabetes mellitus
  - Not listed because it is considered a *high* or *very high risk* condition for ASCVD risk assessment purposes

High or Very High Risk Patient Groups

- Quantitative risk scoring is not necessary for initial risk assessment in patients with the following conditions*:
  - Diabetes mellitus, type 1 or 2
  - Chronic kidney disease, Stage ≥3B
  - LDL-C ≥190 mg/dL - severe hypercholesterolemia phenotype, which includes FH
  - ASCVD

*Patients in these categories are all at ***high*** or ***very*** *risk* for an ASCVD event and should be treated accordingly.

Criteria for Classification of ASCVD

- Myocardial infarction or other acute coronary syndrome
- Coronary or other revascularization procedure
- Transient ischemic attack
- Ischemic stroke
- Atherosclerotic peripheral arterial disease
  - Includes ankle/brachial index <0.90
- Other documented atherosclerotic diseases such as:
  - Coronary atherosclerosis
  - Renal atherosclerosis
  - Aortic aneurysm secondary to atherosclerosis
  - Carotid plaque, ≥50% stenosis

Sequential Steps in ASCVD Risk Assessment

1. Identify patients with either ***very high risk*** **or** ***high risk*** conditions.*
   Very High Risk
   a. ASCVD
   b. Diabetes mellitus with ≥2 other major ASCVD risk factors or end organ damage[1]
   High Risk
   a. Diabetes mellitus with 0-1 other major ASCVD risk factors
   b. Chronic kidney disease Stage 3B or 4[2]
   c. LDL-C ≥190 mg/dL (severe hypercholesterolemia phenotype)
2. Count major ASCVD risk factors
   a. If 0-1 and no other major indicators of higher risk, assign to ***low risk*** category. Consider assigning to a higher risk category based on other known risk indicators, when present.
   b. If ≥3 major ASCVD risk factors are present, assign to ***high risk*** category.
3. If 2 major ASCVD risk factors, ***risk scoring*** should be considered and additional testing may be useful for some patients.
   a. If quantitative risk scoring reaches the high risk threshold,[3] assign to ***high risk*** category.
   b. Consider assigning to ***high risk*** category if other risk indicators are present based on additional testing (see later slide).
   c. If, based on above steps, no indication is present to assign to ***high risk***, assign to ***moderate risk*** category.

*Further risk assessment is not required after identifying the highest applicable risk level.

Footnotes for Steps in ASCVD Risk Assessment

[1]End organ damage indicated by increased albumin/creatinine ratio (≥30 mg/g), chronic kidney disease (CKD), or retinopathy.

[2]For patients with CKD Stage 3B (glomerular filtration rate [GFR] 30-44 mL/min/1.73 m^2) or Stage 4 (GFR 15-29 mL/min/1.73 m^2) risk calculators should not be used because they may underestimate risk. Stage 5 CKD (or on hemodialysis) is a very high risk condition, but results from randomized, controlled trials of lipid-altering therapies have not provided convincing evidence of reduced ASCVD events in such patients. Therefore, no treatment goals for lipid therapy have been defined for Stage 5 CKD.

[3]High risk threshold is defined as ≥10% using Adult Treatment Panel III Framingham Risk Score for hard CHD (MI or CHD death), ≥15% using the 2013 Pooled Cohort Equations for hard ASCVD (MI, stroke or death from CHD or stroke), or ≥45% using the Framingham long-term (to age 80) CVD (MI, CHD death or stroke) risk calculation. Clinicians may prefer to use other risk calculators, but should be aware that quantitative risk calculators vary in the clinical outcomes predicted (e.g., CHD events, ASCVD events, cardiovascular mortality); the risk factors included in their calculation; and the timeframe for their prediction (e.g., 5 years, 10 years, or long-term or lifetime). Such calculators may omit certain risk indicators that can be very important in individual patients, provide only an approximate risk estimate and require clinical judgment for interpretation.

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.

35

www.lipid.org

Risk Indicators (Other Than Major ASCVD Risk Factors) That Might Be Considered For Risk Refinement[1]

1. A severe disturbance in a major ASCVD risk factor, such as multi-pack per day smoking, or strong family history of premature CHD
2. Indicators of subclinical disease, including coronary artery calcium
   - ≥300 Agatston units[2] is considered *high risk*
3. LDL-C ≥160 and/or non-HDL-C ≥190 mg/dL
4. High-sensitivity C-reactive protein ≥2.0 mg/L[3]
5. Lipoprotein (a) ≥50 mg/dL (protein) using an isoform insensitive assay
6. Urine albumin / creatinine ratio ≥30 mg/g

36

www.lipid.org

Footnotes for Other Risk Indicators

[1]The presence of one or more of the risk indicators listed may be considered, in conjunction with major ASCVD risk factors, to reclassify an individual to a higher risk category. Except in the case of evidence of subclinical disease defining the presence of ASCVD, reclassification to a higher risk category is a matter of clinical judgment. Doing so will alter the threshold for consideration of pharmacotherapy and/or treatment goals for atherogenic cholesterol. Many other ASCVD risk markers are available, but the NLA Expert Panel consensus view is that those listed have the greatest clinical utility.

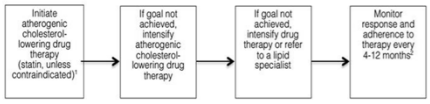
[2]Or coronary artery calcium ≥75th percentile for age, sex and ethnicity (MESA Coordinating Center. CAC Score Reference Values. Available at: http://www.mesa-nhlbi.org/CACReference.aspx.).

[3]Because of high intra-individual variability, multiple high-sensitivity C-reactive protein (hs-CRP) values should be obtained before concluding that the level is elevated; hs-CRP should not be tested in those who are ill, have an infection, or are injured. If hs-CRP level is >10 mg/L, consider other etiologies such as infection, active arthritis, or concurrent illness.

37

www.lipid.org

Progression of Atherogenic Cholesterol-Lowering Drug Therapy



[1]A moderate or high intensity statin should be first-line drug therapy for treatment of elevated levels of atherogenic cholesterol, unless contraindicated. In a patient with very high triglycerides (≥500 mg/dL), a triglyceride-lowering drug may be considered for first-line use to prevent pancreatitis. Other ASCVD risk factors should be managed appropriately in parallel.

[2]In most cases, goal levels should be achieved in approximately 6 months.

Intensity of Statin Therapy*

High Intensity Daily dose ↓ LDL-C ≥50%	Moderate Intensity Daily dose ↓ LDL-C 30 to <50%
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg
Rosuvastatin 20-40 mg	Fluvastatin 40 mg bid
	Fluvastatin XL 80 mg
	Lovastatin 40 mg
	Pitavastatin 2-4 mg
	Pravastatin 40-80 mg
	Rosuvastatin 5-10 mg
	Simvastatin 20-40 mg

*Individual responses to statin therapy should be expected to vary in clinical practice. Moderate or high intensity statin therapy is preferred unless not tolerated.

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, fibric acid or nicotinic acid) may be considered in those with contraindications or intolerance 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 fibric acids, high-dose long-chain 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.

45

Drug Therapies – Important Considerations (continued)

- Combination therapy with a statin plus a second (or third) 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.

46

Severe Hypercholesterolemia Phenotype

- FH is often, but not always, present in those with severe hypercholesterolemia.
  - Untreated severe hypercholesterolemia is associated with a marked increase in ASCVD risk, irrespective of genotype.
- Cascade screening (screening of potentially affected family members) is critically important once FH is diagnosed to identify and treat other affected family members before ASCVD events occur.
  - In FH and other forms of severe hypercholesterolemia, in the absence of a very high risk condition, the treatment goals are non-HDL-C <130 mg/dL and LDL-C <100 mg/dL, or reductions of ≥50% in atherogenic cholesterol if goal levels cannot be achieved.
  - For FH patients with multiple or poorly controlled other major ASCVD risk factors, clinicians may consider attaining even lower levels of atherogenic cholesterol.

49

Additional Classes of Medications for Severe Hypercholesterolemia

- Mipomersen: injectable antisense inhibitor of Apo B synthesis that, when given in combination with maximum tolerated doses of lipid-lowering therapy, can reduce LDL-C by an additional 25% in homozygous FH patients.
- Lomitapide: oral inhibitor of microsomal triglyceride transfer protein that can reduce LDL-C levels by up to 50% in homozygous FH patients on maximum tolerated lipid-lowering therapy and LDL apheresis.
- New classes of medications (e.g., proprotein convertase subtilisin kexin type 9 [PCSK9] inhibitors) are under investigation that, if shown to be safe and efficacious, may make attainment of goal levels of atherogenic cholesterol practical for a greater fraction of patients with severe hypercholesterolemia.

LDL Apheresis*

NLA Criteria from Expert Panel on FH	FDA-approved Indication
LDL apheresis may be considered for the following patients who, after 6 months, do not have an adequate response to maximum tolerated drug therapy: • Functional homozygous FH with LDL-C ≥300 mg/dL (or non-HDL-C ≥330 mg/dL) • Functional heterozygous FH with LDL-C ≥300 mg/dL (or non-HDL-C ≥330 mg/dL) and 0-1 risk factors • Functional heterozygous FH with LDL-C ≥200 mg/dL (or non-HDL-C ≥230 mg/dL) and high risk characteristics, such as 2 risk factors or high lipoprotein (a) ≥50 mg/dL using an isoform insensitive assay • Functional heterozygous FH with LDL-C ≥160 mg/dL (or non-HDL-C ≥190 mg/dL) and very high risk characteristics (established CHD, other cardiovascular disease, or diabetes)	LDL apheresis is considered medically necessary when patients have failed diet and maximum drug therapy from at least 2 separate classes of hypolipidemic drugs for at least 6 months in addition to any 1 of the following criteria: • Homozygous FH with LDL-C ≥500 mg/dL • Heterozygous FH with LDL-C ≥300 mg/dL • Functional heterozygous FH with LDL-C ≥200 mg/dL in patients with coronary artery disease

*The NLA criteria are more inclusive than the FDA-approved indication criteria. Clinicians should be aware of this with regard to reimbursement.

Patients with Progressive Atherosclerosis, or Recurrent Events, Despite Evidence-Based Therapy

- Very aggressive therapy to lower atherogenic cholesterol concentrations to values well below goal thresholds may be considered for such patients, although evidence to support this approach from randomized clinical trials is minimal.
- Investigation of potential causes such as elevated lipoprotein (a) or other secondary risk factors may be warranted.
- Non-lipid ASCVD risk factors should be well-controlled.

Additional Information

- Additional information from the NLA:
  - https://www.lipid.org/practicetools/guidelines/consensus_recommendations
    - Familial Hypercholesterolemia: Screening, Diagnosis and Management of Pediatric and Adult Patients
    - Clinical Utility of Inflammatory Markers and Advanced Lipoprotein Testing: Advice form an Expert Panel of Lipid Specialists
  - https://www.lipid.org/practicetools/guidelines/position_statements

So WHAT DO WE DO NOW ?

- I woud recommend using the National Lipid Assn. Patient Centered Recommendations for the management of Dyslipidemia. .
- **USE pathophysiology : Apply lipoprotein goals above and beyond lipid goals :** attempt to correct abnormal lipoprotein trafficking. AT LEAST Determine and optimize NONHDLC in ALL patients at risk.
- **Don't attempt to raise HDL-C; RECOGNIZE that the RISK of low HDL-C (esp . with coexisting Trig/ HDLC > 3) comes from an associated high ApoB (LDL-P) and treat THAT !**
- **Trigs are the primary target ONLY WHEN > 500 mg/dl**
- **USE HIGH INTENSITY STATIN TREATMENT as a base when needed, and other lipid lowering meds as adjunctive therapy , esp. in the atherogenic dyslipidemia.**

So WHAT DO WE DO NOW ?

- **Use CIMT and CAC (and coronary CT angiography) in intermediate risk patients** as tools to risk reclassify patients.
- **Biological markers** (LpPLA2, myeloperoxidase , oxidized LDL, Lp(a)) are helpful tools in understanding our patients' risks as well as motivating our patients to adjust their lifestyles and take their medications.

  Use the guidelines as a foundation to build a more dynamic and plastic way to treat patients. Don't wait for trials that may never appear. Learn from the literature and colleagues and incorporate a wide variety of data to make well considered recommendations for patients.

Baum SJ, Journal of Clinical Lipidology(2014), doi:10.1016/j.jacl.2013.12.010

Recommendations from AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices

Suggested Treatment Goals

	ApoB, mg/dL	LDL-C, mg/dL	Non-HDL-C, mg/dL	LDL-P, nmol/L	
Very High Risk		< 70	< 80		2nd percentile
High Risk	< 80	< 100	< 120	< 1100	20th percentile
Lower Risk	< 100	< 130	< 150	< 1400	50th percentile

Population cutpoints are from Framingham Offspring Study

Contois JH, et al. Clinical Chemistry 2009; 55:407-419

Why Determine LDL-P ? What About the New Guidelines?

- "Whenever there is discordance between LDL-C and LDL-P, the risk (subclinical disease, events) ALWAYS follows the particles. Period. In Every study in Every language. "
- Use of LDL-P IS compatible with the new ACC/AHA guidelines, per Neil Stone (chief author). After determining risk , and starting statin therapy, you job isn't over. These guidelines are NOT "fire and forget". One is supposed to then "assess the efficacy of LDL lowering" . The guidelines look for % LDLC lowering. One can EXTEND this to LDL-P determination as the BEST methodology of assessing the reduction of "LDL" risk.
- William Cromwell MD, LipoScience, Am Society Of Preventive Cardiology, Boca 6/2014

On-treatment CV risk: LDL-C vs LDL-P

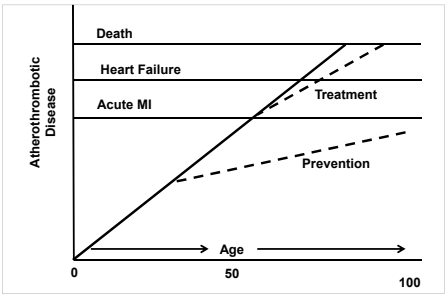
Event risk for matched LDL-P and LDL-C target cohorts over 12, 24 and 36 month follow-up periods

	12 months follow-up			24 months follow-up			36 months follow-up		
	LDL-P cohort	LDL-C cohort	p	LDL-P cohort	LDL-C cohort	p	LDL-P cohort	LDL-C cohort	p
N	2094	2094		1242	1242		705	705	
CHD Risk									
≥ 1 event, n (%)	122 (5.83)	↑156 (7.45)	0.035	126 (10.1)	↑157 (12.6)	0.050	103 (14.6)	↑134 (19.0)	0.027
Events, mean (±SD)	0.09(0.45)	0.10(0.36)	0.027	0.17 (0.61)	0.22 (0.81)	0.030	0.25 (0.80)	0.29 (0.76)	0.039
HR (95% CI)	0.78(0.61-0.98)	-	0.035	0.79(0.63-1.00)	-	0.052	0.75 (0.58-0.97)	-	0.029
Stroke Risk									
≥ 1 event, n (%)	18 (0.86)	↑28 (1.34)	0.138	23 (1.9)	↑37 (3.0)	0.067	12 (1.7)	↑27 (3.8)	0.015
Events, mean (±SD)	0.01(0.12)	0.02(0.15)	0.138	0.02 (0.61)	0.03 (0.20)	0.050	0.02 (0.16)	0.04 (0.23)	0.015
HR (95% CI)	0.64(0.36-1.16)	-	0.141	0.52(0.37-1.04)	-	0.069	0.44 (0.22-0.87)	-	0.018
CHD/Stroke Risk									
≥ 1 event, n (%)	131 (6.26)	↑170 (8.12)	0.020	136 (11.0)	↑173 (3.0)	0.025	103 (14.6)	↑134 (19.0)	0.027
Events, mean (±SD)	0.10(0.50)	0.11(0.45)	0.026	0.19 (0.70)	0.26 (0.90)	0.027	0.28 (0.86)	0.34 (0.87)	0.031
HR (95% CI)	0.76(0.61-0.96)	-	0.021	0.78(0.62-0.97)	-	0.028	0.75 (0.58-0.97)	-	0.029

P-values are from chi-square tests for categorical outcomes and t-tests for continuous outcomes.
P-values for HR are from Cox PH models

Toth PP et al. Atherosclerosis 2014;235:585-591

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 LDLC AND NONHDL targets ALL day, EVERY day!

Prevent atherosclerosis , not just events!

Don't settle for unacceptably high residual risk on statin monotherapy using lipid based guidelines!

Low Carb Diet approach to treat insulin resistance!

Clinical Lipidology Update 2014 : the New Guidelines: What to do ?

Gregory Pokrywka MD FACP FNLA NCMP

Asst. Professor of Medicine, Johns Hopkins University
Diplomate of the American Board of Clinical Lipidology
Fellow of the ACP and the National Lipid Association
North American Menopause Society Certified Menopause Practitioner
Director, Baltimore Lipid Center

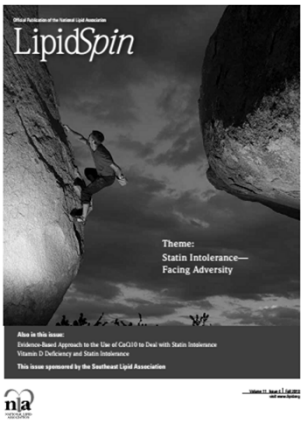
www.Mysite.verizon.net/gpokmd

gpokmd@verizon.net

Twitter : @gpokmd

www.learnyourlipids.com

www.lipid.org



Managing the Statin-Intolerant Patient: Low-Dose/Low-Frequency Treatment Regimens MARY HONKANEN, MD, ABIM, FNLA

- Listen to the patient- validate their concerns.
- Second, educate the patient on the benefits of statin therapy. A favorite "one-liner" for this purpose: "For every one high-risk person on statin who has died from an adverse muscle event, 1,188 people DIDN'T DIE because they took their statin. "
- Third, rule out other causes of myopathy and evaluate potential exacerbating factors by checking a TSH, B12, vitamin D level. A baseline CK should be established and monitored .
- Finally, initiate drug therapy by:(1) Switching to another statin, one with a different metabolism (pitavastatin is an example) or to an extended release preparation (fluvastatinXL or lovastatin XR-Altoprev).
- (2) Initiating very low doses (Ld) of long half-life statins at a low frequency (Lf),i.e. once a week to every other day (QOD), using primarily rosuvastatin (19 hours) and atorvastatin (14 hours) or pitavastatin (11 hours) QOD. Rosuva is often dosed 2.5-5 mg MWF.

NLA Lipid Spin, Fall 2013

Managing the Statin-Intolerant Patient: Low-Dose/Low-Frequency Treatment Regimens MARY HONKANEN, MD, ABIM, FNLA

- (3) Combining very low daily doses of weaker statins or alternate-day dosing of long half-life statins with ezetimibe – also used at a low-dose/low-frequency (5-10mg daily, QOD or 3 times weekly)
- (4) Combining the above (statin +/- ezetimibe) or ezetimibe alone with other non-statin lipid-lowering medications (BAS, niacin, fibrates)with an intense effort to choose a drug that has some clinical trial evidence of benefit for that individual patient, i.e. fibrate for triglycerides>200mg/dl and HDL<40mg/dl, colesevelam for diabetics with close triglyceride monitoring, niacin for LDLs not at goal and NOT for those with severeexpressions of metabolic syndrome, monitoring platelets and symptoms of ulcers and gout.
- Since most patients referred to lipid clinics have already failed multiple attempts with multiple statins, proceeding directly to options 2 and 3 above is reasonable.
- We advance the statin very gradually, as tolerated, by increasing the dose first, not the frequency. Most patients tolerate a very gradual increase in the statin dose – to a point. The art is knowing when to stop.

NLA Lipid Spin, Fall 2013

Managing the Statin-Intolerant Patient: Low-Dose/Low-Frequency Treatment Regimens MARY HONKANEN, MD, ABIM, FNLA

- While all of these results of alternate-day statin dosing, especially in combination with other lipid drugs, are quite remarkable and encouraging, these are non-approved strategies and no clinical trial evidence for cardiovascular risk reduction exists. Therefore, these strategies should be reserved for those patients who have failed recurrent attempts of conventionally dosed statins.

NLA Lipid Spin, Fall 2013

According to the 2013 AHA/ ACC Guidelines, which ONE of the following is one of the four statin benefit groups? 68

A. Individuals with clinical ASCVD
B. Individuals with primary elevations of low-density lipoprotein cholesterol (LDL-C) > 130 mg/dl.
C. Individuals 40-75 years of age with metabolic syndrome
D. Individuals without clinical ASCVD or diabetes, who are 40-75 years of age with LDL-C 70-189 mg/dl, and have an estimated 10-year ASCVD risk of 15 % or higher.

Key Differences between the 2013 AHA/ ACC Guidelines, and the NLA 2014 patient Centered Recommendations are: 69

A. The NLA 2014 patient Centered Recommendations have targets for LDL-C and NonHDLc-C levels.
B. The NLA 2014 patient Centered Recommendations consider evidence form RCTs as well as epidemiological, metabolic, mechanistic and genetic studies.
C. The NLA 2014 patient Centered Recommendations have a treatment goal of Non HDL-C of < 130 mg/dl for all except the very highest risk patients.
D. All of the above

A drug targeted reduction of triglycerides should be considered for first line therapy in those whose triglycerides are > or = to 500 mg/dl.

A. True
B. False