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Overview of Clinical Guidelines in Lipid Management

Primary Objective

- Outline current guidelines on the management and treatment of patients with dyslipidemia

National Cholesterol Education Program Adult Treatment Panels (ATP)

ATP I

- LDL-C primary target:
 - High risk >160 mg/dL or ≥ 130 mg/dL and 2 or more risk factors (RFs)–
 <130 mg/dL considered desirable
- HDL-C considered a major RF but not considered for screening purposes – concerns re: measurement accuracy and science base
- Population guide also published

ATP II

- 1993: Emphasized risk status as a guide to treatment intensity.
- Recommended HDL-C screening
- Set <100 mg/dL for LDL-C goal in those with overt disease
- Emphasized physical activity and weight reduction to enhance diet therapy

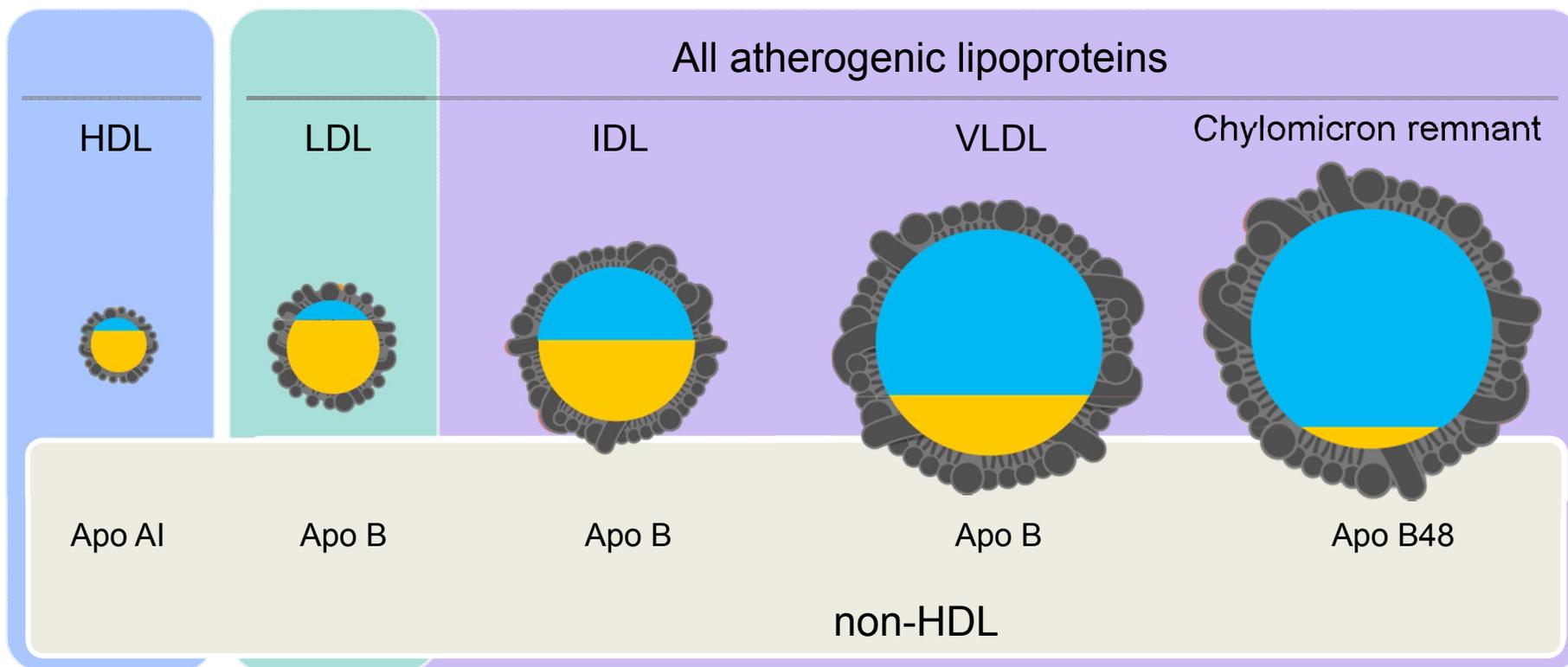
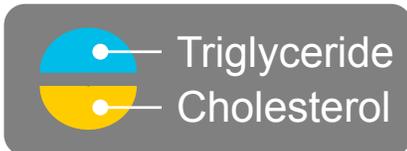
NCEP ATP III (2002): Expanded Risk Groups

<u>Exceptionally High Risk (CHD Risk Equivalent)</u>	<u>Major Risk Factors</u>	<u>“Negative” Risk Factor</u>
CHD	Cigarette smoking	HDL > 60 mg/dL
Other vascular disease	Hypertension	
Diabetes	Low HDL-C (<40 mg/dL)	
>20% Framingham Risk Score	Family history (Male <55 yr, Female <65 yr)	
	Age (Male >45 yr, Female >55 yr)	

ATP III (continued)

- Identified LDL-C <100 mg/dL optimal
- Raised definition of low HDL-C from <35 to <40 mg/dL
- Acknowledged triglycerides as an independent risk factor for CHD – set <150 mg/dL as normal – if triglycerides >500 mg/dL, triglyceride lowering should be first target to prevent pancreatitis
- Special focus on the metabolic syndrome
- Focus on treatment beyond LDL-C: triglycerides and HDL-C with an introduction of non-HDL-C as a secondary target

ATPIII: Increased Emphasis on Non-HDL Cholesterol when Triglycerides ≥ 200 mg/dL



$$\text{Non-HDL-C} = \text{Total cholesterol} - \text{HDL-C}$$

ATPIII – Treat to Target Based on Risk

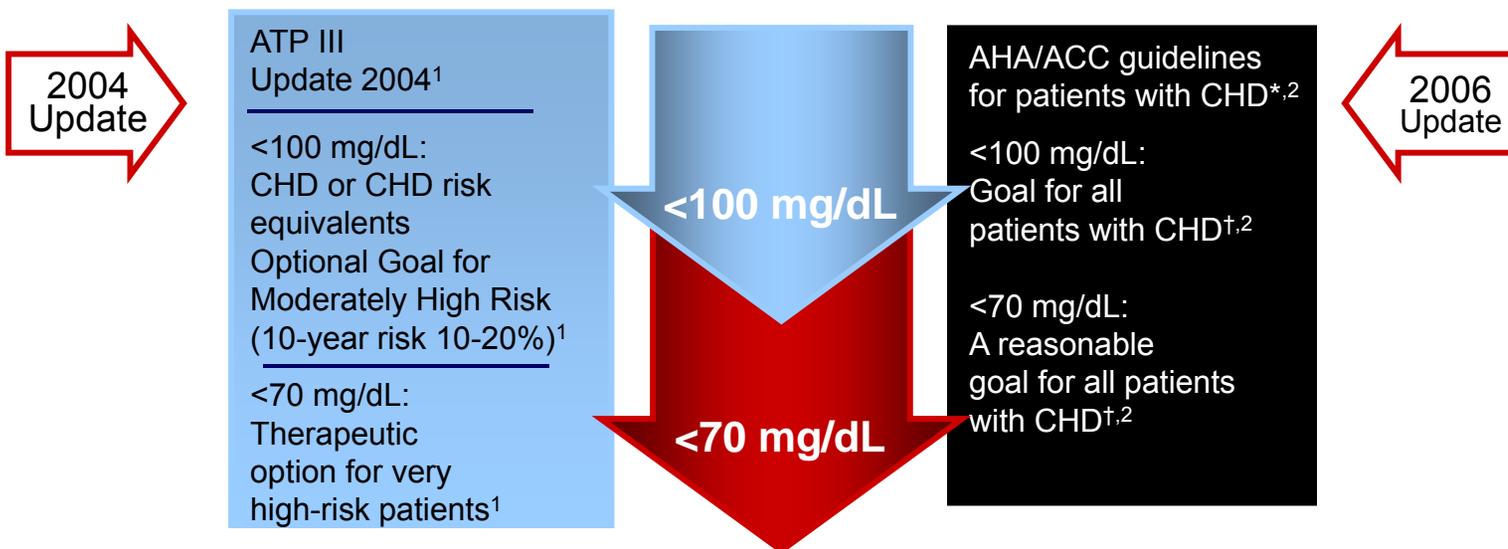
Patient Classification	LDL-C Goal (mg/dl)	non-HDL-C Goal* (mg/dL)
Low risk (0-1 risk factors)	<160	<190
Moderate Risk (At least 2 risk factors and 10 yr FRS <20%)	<130	<160
High Risk (CHD or CHD Risk Equivalent)	<100	<130

* If triglycerides > 200 mg/dl

NCEP ATP III. *Circulation*. 2002;106:3145-3421.

Updates to ATPIII: More Intensive LDL-C Goals for Higher Risk Patients

Recommended LDL-C treatment goals



- If it is not possible to attain LDL-C <70 mg/dL because of a high baseline LDL-C, it generally is possible to achieve LDL-C reductions of >50% with more intensive LDL-C lowering therapy, including drug combinations.

*And other forms of atherosclerotic disease.²

†Factors that place a patient at very high risk: established cardiovascular disease (CVD) plus: multiple major risk factors (especially diabetes); severe and poorly controlled risk factors (e.g., cigarette smoking); metabolic syndrome (triglycerides [TG] ≥200 mg/dL + non-HDL-C ≥130 mg/dL with HDL-C <40 mg/dL); and acute coronary syndromes.¹

1. Grundy SM et al. *Circulation*. 2004;110:227–239.

2. Smith SC Jr, et al. *Circulation*. 2006;113:2363–2372.

American Diabetes Association/American College of Cardiology Consensus Statement

Treatment Goals in Patients with Cardiometabolic Risk and Lipoprotein Abnormalities

	LDL-C (mg/dL)	Non-HDL-C (mg/dL)	Apo B (mg/dL)
Highest-risk patient – Known CVD – Diabetes plus ≥ 1 additional major CVD risk factor*	<70	<100	<80
High-risk patients – No diabetes or known CVD but ≥ 2 major CVD risk factors* – Diabetes but no other major CVD risk factors*	<100	<130	<90
*Major risk factors beyond dyslipidemia include smoking, hypertension, and family history or premature CHD.			

“Contemporary” Guidelines 2011-14

- ESC/EAS Guidelines -2011
- ADA Guidelines - 2013
- AACE Guidelines – 2013
- IAS Guidelines - 2013
- ACC/AHA Guidelines – 2013
- NLA Guidelines (Draft) - 2014

What Happened to ATP IV?

- ATP IV originally planned for release in 2011
 - Part of comprehensive NHLBI Cardiovascular Prevention Guidelines
 - NEW EVIDENCED BASED APPROACH
 - Postponed many times
 - Late 2013 NHLBI announces that they will not be publishing guidelines as expected but instead will compile available data and provide to ‘partner organizations’ to come up with guidelines
 - Consensus statement published by ACC/AHA November 2013

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
Endorsed by the American Association of
Cardiovascular and Pulmonary Rehabilitation,
American
Pharmacists Association, American Society for
Preventive Cardiology, Association of Black
Cardiologists, Preventive Cardiovascular Nurses
Association, and WomenHeart: The National
Coalition
for Women with Heart Disease

Recommendation 1: Continue to Focus on TLC

Lifestyle as the Foundation for ASCVD Risk Reduction Efforts

- It must be emphasized that lifestyle modification (i.e., adhering to a heart healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight) remains a critical component of health promotion and ASCVD risk reduction, both prior to and in concert with the use of cholesterol lowering drug therapies.
- Healthy diet or lifestyle modifications were recommended as background therapy for the RCTs of cholesterol-lowering drug therapy.
- See the 2013 Lifestyle Management Work Group Guideline for lifestyle recommendations for healthy adults.

Recommendation 2: Use Statins in these 4 Groups Regardless of Lipid Levels

- 1) Established Atherosclerotic Cardiovascular Disease (ASCVD)
- 2) Baseline LDL-C at least 190 mg/dl
- 3) Diabetes and age 40-75
- 4) At least 7.5% estimated 10-year ASCVD risk and age 40-75

Recommendation 3: Use Only Evidence Based Statin Doses

- Moderate-Intensity Statin (dose lowers LDL-C by 30-49%)
 - Age over 75 with ASCVD
 - Diabetes age 40-75 years
 - Primary prevention age 40-75 years with 10 year ASCVD risk \geq 7.5% (moderate or high intensity)
 - ASCVD but not a candidate for high intensity statin
- High-Intensity Statin (dose lowers LDL-C by \geq 50%)
 - Age \leq 75 years and ASCVD
 - Baseline LDL-C $>$ 190 mg/dl
 - Diabetes age 40-75 years and 10 year ASCVD risk \geq 7.5%
 - Primary prevention age 40-75 years with 10 year ASCVD risk \geq 7.5% (moderate or high intensity)

Definition of High, Moderate and Low Intensity Statin Agents and Doses

High-Intensity	Moderate-Intensity	Low-Intensity
Daily dose lowers LDL-C on average, by ~ $\geq 50\%$	Daily dose lowers LDL-C on average, by ~ 30 to $<50\%$	Daily dose lowers LDL-C on average, by $<30\%$
Atorvastatin (40)–80 mg Rosuvastatin 20 (40) mg	Atorvastatin 10 (20) mg Rosuvastatin (5) 10 mg Simvastatin 20–40 mg Pravastatin 40 (80) mg Lovastatin 40 mg <i>Fluvastatin XL 80 mg</i> Fluvastatin 40 mg bid <i>Pitavastatin 2–4 mg</i>	<i>Simvastatin 10 mg</i> Pravastatin 10–20 mg Lovastatin 20 mg <i>Fluvastatin 20–40 mg</i> <i>Pitavastatin 1 mg</i>
<p>Specific statins and doses are noted in bold that were evaluated in randomized controlled trials. Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in <i>italics</i>.</p>		

Stone NJ, et al, J Amer Coll Card 2013, doi10.1016/jacc2013.11.002

Recommendation 4: Non-statin Medications Not Generally Recommended

- “Because few trials have been performed with non-statin cholesterol-lowering drugs in the statin era, and those that have were unable to demonstrate significant additional ASCVD event reductions in the RCT populations studied, there was less evidence to support the use of non-statin drugs for ASCVD prevention”
 - May be a role in truly statin intolerant or those who achieve a less than adequate therapeutic response.

Recommendation 5: No LDL or non-HDL Goals

A New Perspective on LDL– C and/or Non-HDL– C Treatment Goals

- The Expert Panel was unable to find RCT evidence to support continued use of specific LDL–C and/or non-HDL–C treatment targets.
- The appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit.

Committee's Rationale for Doing Away with Treatment Targets

- The difficulty of giving up the treat-to-goal paradigm was deliberated extensively over a 3-year period.
- However, the RCT evidence clearly shows that ASCVD events are reduced by using the maximum tolerated statin intensity in those groups shown to benefit.
- After a comprehensive review, no RCTs were identified that titrated drug therapy to specific LDL-C or non-HDL-C goals to improve ASCVD outcomes.
- However, one RCT was identified that showed no additional ASCVD event reduction from the addition of nonstatin therapy to further treat non-HDL-C levels once an LDL-C goal was reached (AIM-HIGH).

Recommendation 6: Use New ‘Global Risk’ Assessment for Primary Prevention

- Use Pooled Cohort Equations to estimate 10-year ASCVD risk in both white and black men and women.
- By more accurately identifying higher risk individuals for statin therapy, the guideline focuses statin therapy on those most likely to benefit.
- It also indicates, based on RCT data, groups that may not benefit.
- Before initiating statin therapy, this guideline recommends a discussion by clinician and patients.

<http://my.americanheart.org/cvriskcalculator>

Committee's Rationale for Using 7.5% Global Risk Cut-off (As Opposed to Cholesterol Levels)

- The poor discrimination of RCT inclusion criteria for identifying those at increased 10-year ASCVD risk is shown by a calculation performed by the Risk Assessment Work Group using nationally representative data from NHANES.
- Use of the RCT inclusion criteria (from RCTs that found a reduction in ASCVD events to guide initiation of statin therapy) would result in:
 - Treatment of 16% of individuals with <2.5% estimated 10-year ASCVD risk
 - Treatment 45% of those with 2.5% to <5% estimated 10-year ASCVD risk (many would say inappropriately)
 - No treatment of 38% of those with >7.5% 10-year ASCVD risk would not have been identified as candidates for statin therapy.

Controversy Concerning Global Risk (Pooled Cohort) Calculator

- Estimated that new risk assessment tool identifies 32.9% of primary prevention patients as potentially eligible for statin therapy
 - ATPIII paradigm would identify 31.9% as eligible for statin therapy
 - 75% overlap
- Does not include novel risk factors or biomarkers
- May overestimate risk
 - Attempts at external validation disappointing
 - No evidence base for its use

Recommendation 7: Consider ‘Emerging Risk Factors’ In Some Patients

Role of Biomarkers and Noninvasive Tests

- Treatment decisions in selected individuals who are not included in the 4 statin benefit groups may be informed by other factors as recommended by the Risk Assessment Work Group guideline.

NLA Expert Panel: Clinical Utility of Inflammatory Markers and Advanced Lipid Testing

	CRP	LpPLA2	ApoB	LDL-P	Lp(a)	HDL or LDL subfrac
Low Risk <5% 10 year risk	Not Recommended	Not Recommended	Not Recommended	Not Recommended	Not Recommended	Not Recommended
Intermediate Risk 5-20% 10 year risk	Recommended for Routine Assessment	Consider in Selected Patients	Reasonable for Many Patients	Reasonable for Many Patients	Consider in Selected Patients	Not Recommended
High Risk >20 10 year risk	Consider in Selected Patients	Consider in Selected Patients	Consider in Selected Patients	Consider in Selected Patients	Consider in Selected Patients	Not Recommended
Family History	Reasonable for Many Patients	Consider in Selected Patients	Reasonable for Many Patients	Reasonable for Many Patients	Reasonable for Many Patients	Not Recommended
Recurrent Events	Reasonable for Many Patients	Consider in Selected Patients	Reasonable for Many Patients	Reasonable for Many Patients	Reasonable for Many Patients	Not Recommended



Not Recommended



Reasonable for Many Patients



Consider in Selected Patients



Recommended for Routine Assessment

Recommendation 8: Put Statin Safety in Context

- Incidence of adverse events in RCTs per 100 statin treated individuals
 - 0.1-0.3 excess cases DM
 - 0.01 excess cases myopathy
 - 0.01 excess cases hemorrhagic stroke
- Monitoring of Statin Safety and Efficacy
 - Measure lipid panel and LFTs at baseline
 - Check CK in patients who have or develop muscle disease or symptoms
 - Follow-up LFTs only if symptoms
 - Check repeat lipids in 4-12 weeks to assess response

Population Health Aspects of 2013 ACC/AHA Guidelines

- Will lead to more patients treated with statins
- Will likely decrease absolute risk of ASCVD across population (treating more true positives)
- Will increase number of patients taking statins who would never have had a ASCVD event (treating more false positives)
- Will increase number of patients who will not be treated due to guidelines but will develop ASCVD (treating fewer false negatives)

Probably a net benefit – but what does this mean for individualized medicine?

What does this mean for pay-for-performance and the concept of ‘control’ rates

ACC/AHA Guidelines Not the Final or Only Word

- American Diabetes Association (ADA) Guidelines
- European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) Guidelines
- American Association of Clinical Endocrinologists (AAACE) Guidelines
- International Atherosclerosis Society (IAS) Guidelines
- National Lipid Association (NLA) Recommendations (Draft)

American Diabetes Association (ADA): Lipid Goals and Treatment

- Statin therapy should be used regardless of lipid levels for patients with overt CVD or who are over the age of 40 and have at least one other CVD risk factor (A)
- LDL-C goal
 - No overt CVD: <100 mg/dl (B)
 - With overt CVD: <70 mg/dl is option (B)
- Triglyceride levels <150 mg/dl and HDL >40 mg/dl for a man and >50 mg/dl for a women are desirable (C)
- Combination therapy not generally recommended (A)

American Association of Clinical Endocrinologists (AACE) Guidelines (2013)

	Desirable Levels Moderate Risk	Desirable Levels High Risk (HTN, Fam Hx, low HDL-C, smoking, or established CVD)
LDL-C (mg/dl)	<100	<70
Non-HDL-C (mg/dl)	<130	<100
Triglycerides (mg/dl)	<150	<150
Total C/HDL-C	<3.5	<3.0
Apo B (mg/dl)	<90	<80
LDL-P (mmol/L)	<1200	<1000

Abrahamson MJ, et al, Endocrine Practice 2013;19(2):327-335

ESC/EAS Guidelines: Risk Assessment

LDL- C Baseline

Total CV Risk (%) (SCORE)	<70	70-100	100-155	155-190	>190
<1		Blue	Green	Green	Yellow
1-5		Green	Green	Yellow	Yellow
5-10		Orange	Orange	Red	Red
At least 10	Orange	Orange	Red	Red	Red

No lipid intervention

Lifestyle intervention

Lifestyle intervention, Consider drug if not controlled

Lifestyle intervention, Consider drug* *In patients with MI, statin therapy should be considered irrespective of LDL-C

Lifestyle Intervention and Immediate drug intervention

Reiner Z, et al, Europ Heart J 2011;32:1769-1818

ESC/EAS: Treatment Targets

Which Target?

- LDL-C recommended primary target
- Non-HDL-C optional secondary target in combined dyslipidemia, diabetes, metabolic syndrome or CKD
- ApoB optional secondary target
- HDL not recommended as a target

LDL-C Goal

- Very High Risk:
<70 mg/dl
- High Risk
<100 mg/dl
- Moderate Risk
<115 mg/dl

ESC/EAS: Drug Therapy

- Prescribe statin as first line drug
- In setting of statin intolerance or inability to reach LDL-C target with highest recommended or tolerated dose consider:
 - bile acid sequestrant,
 - nicotinic acid, or
 - cholesterol absorption inhibitor
- In particular high risk patients, consider lowering triglycerides with add on therapy
 - Fibrates (Recommended)
 - Nicotinic Acid
 - Omega-3 Fatty Acids

IAS: Atherogenic Cholesterol

- LDL-C = traditional primary target
 - Optimal <100 mg/dl
- Non-HDL-C = Increasingly preferred as target of therapy
 - Optimal <130 mg/dl
- Optimal levels are NOT goals of therapy
- Goals determined by clinical judgment and may be country specific

IAS: Focus on Long Term (Not 10 Year) Risk of ASCVD (Up to Age 80)

Risk Level	Lifetime Risk (Up to Age 80)	Therapy	Therapeutic Intensity
High	At least 45%	Max Lifestyle Mod + Drugs 'Indicated'	High
Moderately High	30-44%	Max Lifestyle Mod + Drugs 'Consideration'	Moderately High
Moderate	15-29%	Max Lifestyle Mod + Drugs 'Optional'	Moderate
Low	<15%	Public Health Guidelines	

No specific targets, but when drug therapies employed, optimal levels usually represent a reasonable goal of therapy
 General recommendations that may need to be revised on a country-specific basis

IAS: Drug Therapy: Primary Prevention

- Statins are first line therapy
- In those who are statin intolerant, several optional are available:
 - switching stains,
 - reducing dose,
 - every other day use, use of alternative drugs (ezetimibe, bile acid resin, nicotinic acid)
 - maximizing lifestyle interventions

IAS: Drug Therapy: Secondary Prevention

- Statin first line therapy
 - Use maximum tolerated doses
- Usually treat to optimal LDL-C (<70 mg/dl) and non-HDL-C (<100 mg/dl)
- May require combination therapy
 - Bile Acid Sequestrant or ezetimibe for LDL-C reduction
 - Nicotinic acid or fibrate for high triglycerides

Comparison of Recent Major Guidelines Up to 2013

Guideline	Treat Based On	Treat to Specific Target	First Line Therapy	Alternative or Add-On Therapies
ACC/AHA (2013)	Risk Group	No	Statin	None
ADA (2013)	Risk Group	Yes (LDL-C)	Statin	Generally Not Recommended
ESC/EAS (2011)	Risk Group and LDL-C	Yes (LDL-C +/- nonHDL-C or ApoB)	Statin	BAS, CAI, nicotinic acid, fibrate, omega 3
IAS (2013)	Risk Group	No	Statin	BAS, CAI, nicotinic acid, fibrate

BAS = Bile Acid Sequestrant
CAI = Cholesterol Absorption Inhibitor

NLA Recommendations for Patient Centered Management of Dyslipidemia (Draft 2014)

- Presented in draft form for public comment
Spring 2014
- Meant to enhance not supplant ACC/AHA
and other guidelines

NLA Recommendations (Draft 2014)

Guiding Principles

1. An elevated level of atherogenic cholesterol – cholesterol carried by apo B-containing lipoprotein particles (non-HDL-C and LDL-C) – is causally related to the development 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.

NLA Recommendations (Draft 2014)

Guiding Principles

3. Lifestyle intervention is central to efforts at ASCVD prevention
4. The intensity of risk reduction therapy should be adjusted to the patient's absolute risk for an ASCVD event.
 - Atherosclerosis is a process that often begins early in life and progresses for decades before resulting in a clinical ASCVD event.
 - 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 drug therapy is indicated, statin treatment is the primary modality for reducing ASCVD risk.
6. Other ASCVD risk factors should be managed appropriately

NLA Recommendations (Draft 2014)

Targets of Therapy

- Non-HDL-C and LDL-C are the primary targets of therapy
 - Non-HDL-C given primacy
- Triglycerides = primary target of therapy if >500 mg/dl and especially if >1000 mg/dl
- ApoB = secondary, optional target of therapy
 - Goals < 90 mg/dl for primary and <80 mg/dl for secondary prevention

NLA Recommendations (Draft 2014)

Stepwise Approach in ASCVD Risk Assessment

1. Identify Very High Risk

- ASCVD
- Diabetes with at least 2 major risk factors or end organ damage

2. Identify High Risk

- Diabetes with 0-1 major risk factors and no end organ damage
- Chronic Kidney Disease (CKD) stage 3 or 4
- LDL at least 190 mg/dl

3. Count Major Risk Factors

- 0-1 = Low Risk (unless other conditions – see next slide)
- 2 = Use risk scoring
 - <10% = Moderate Risk
 - At least 10% = High Risk
- 3 or more = High Risk

NLA Recommendations (Draft 2014)

Other Risk Indicators-Consider for 'Refinement' of Risk

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

NLA Recommendations (Draft 2014)

Initiate Therapy Based on Risk and Lipid Levels and Treat to Specific Goal

Risk Category	Criteria	Initiate Drug Therapy Non-HDL-C (LDL-C) (mg/dl)	Treatment Goal Non-HDL-C (LDL-C) (mg/dl)
Low	<ul style="list-style-type: none"> • 0-1 major RF* 	>190 (>160)	<130 (<100)
Moderate	<ul style="list-style-type: none"> • At least 2 major RF and 10-year risk <10%* 	>160 (>130)	<130 (<100)
High	<ul style="list-style-type: none"> • At least 2 major RF and 10-year risk >10% • At least 3 RF • DM with 0-1 other RFs and no end organ damage • CKD stage 3 or 4 • LDL-C >190 mg/dl 	>130 (>100)#	<130 (<100)
Very High	<ul style="list-style-type: none"> • Established ASCVD • DM with at least 2 other RFs or end organ damage 	>100 (>70)#	<100 (<70)

*Consider other risk markers

Consider moderate or high intensity statin in patient with ASCVD or DM regardless of baseline lipid levels

NLA Recommendations (Draft 2014)

Drug Therapy Considerations

- Moderate or high intensity statin is first line
 - Start with moderate dose and titrate up if needed
- Alternate drugs may be considered
 - As add-on therapy if unable to reach goal on highest tolerated dose of statin
 - Statin intolerance or contraindication
 - When triglycerides at least >500 mg/dl
- Therapy may be continued in patient with achieved LDL-C < 40 mg/dl in absence of signs of intolerance

NHLBI Expert Panel on Integrated Guidelines for CV Health and Risk Reduction in Children and Adolescents (2012)

- Lipid Screening
 - Birth-2 yrs: No lipid screening
 - Age 2-8: No routine lipid screening*
 - Age 9-11: Universal screening with non-fasting lipid panel
 - Age 12-16: No routine lipid screening*
 - Age 17-21 Universal screening with non-fasting lipid panel
- *Consider screening with fasting lipid panel in select patients with high risk characteristics (see reference for details)

NHLBI Expert Panel on Integrated Guidelines for CV Health and Risk Reduction in Children and Adolescents (2012)

Category (mg/dl)	Acceptable	Borderline	High
Total Cholesterol	<170	170-199	≥200
LDL-C	<110	110-129	≥130
Non-HDL-C	<120	120-144	≥145
ApoB	<90	90-109	≥110
Triglycerides (0-9yr)	<75	75-99	≥100
Triglycerides (10-19yr)	<90	90-129	≥130
HDL-C	>45	40-45	<40
ApoA-1	>120	115-120	<115

See reference for treatment recommendations

http://www.nhlbi.nih.gov/guidelines/cvd_ped/peds_guidelines_sum.pdf

Summary

- Guidelines continue to evolve
 - Constant struggle between simplicity and comprehensiveness
- Although the goal is to have completely evidenced based guidelines, our evidence base is incomplete
 - Expert opinion will continue to play a role
- Guidelines are just that – continue to individualize therapy
- Involve patient in decision making, especially in areas of controversy