NLA Core Curriculum in Clinical Lipidology

1.0 Classification, Measurement and Metabolism of Lipids and Lipoproteins

1.1 Lipoprotein classification and properties

- 1.1.1 Chylomicrons and remnants
- 1.1.2 Apolipoproteins
- 1.1.3 Very-low density lipoproteins and remnants
- 1.1.4 Intermediate density lipoproteins
- 1.1.5 Low density lipoproteins
- 1.1.6 Lipoprotein (a)
- 1.1.7 High-density lipoproteins
- 1.1.8 Non-HDL-C and cholesterol remnants TC- (HDL-C) - (LDL-C)

1.2 Methods of lipoprotein measurement

- 1.2.1 Traditional lipid profile, fasting or non-fasting
- 1.2.2 LDL-C calculation (Friedewald) vs. direct measurement
- 1.2.3 Apolipoprotein measurement
- 1.2.4 Nuclear magnetic resonance spectroscopy
- 1.2.5 Ion mobility testing
- 1.2.6 Vertical autoprofile testing
- 1.2.7 Electrophoretic methods
- 1.2.8 Other methods

1.3 Lipoprotein metabolism

- 1.3.1 Intestinal lipid transport and chylomicron formation, secretion and catabolism
- 1.3.2 Hepatic lipid transport and VLDL formation, secretion and catabolism
- 1.3.3 LDL receptor expression, function and catabolism (PCSK9)
- 1.3.4 HDL synthesis, maturation, catabolism, role in reverse cholesterol transport and non-ASCVD roles
- 1.3.5 Cholesterol and bile acid metabolism
- 1.3.6 Intrahepatic gene regulation via nuclear receptor factors (LXR, FXR, PPAR, SREBP)

2.0 Pathophysiology and Vascular Biology of Atherosclerosis

- 2.1. Normal arterial biology
- 2.2 Pathogenesis of atherosclerosis
- 2.3 Thrombosis
- 2.4 The role of inflammation
- 2.5 Normolipidemic arterial pathology

3.0 Pathophysiology of Genetic Dyslipidemias

3.1 Hypercholesterolemia

- 3.1.1 Familial homozygous hypercholesterolemia genotype and phenotype (FH)
- 3.1.2 Familial heterozygous hypercholesterolemia genotype, phenotype, and other (FH, Familial defective Apo B, PCSK9 (GOF)
- 3.1.3 Polygenic hypercholesterolemia
- 3.1.4 Autosomal recessive hypercholesterolemia
- 3.1.5 Sitosterolemia

3.2 Hypertriglyceridemia

- 3.2.1 Monogenic hypertriglyceridemia- familial chylomicronemia syndromes (FCS)- deficiencies in either
  LPL, APOCII, APOA5, GPIHBP1, LMF1, and GPD1)
- 3.2.2 Polygenic hypertriglyceridemia (FHTG)
- 3.2.3 Familial dysbetalipoproteinemia (Apo E II/II or other variants)

3.3 Combined or mixed hyperlipidemia

3.3.1 Familial combined hyperlipidemia (FCH)
3.3.2 Non-familial combined hyperlipidemia

3.4 Non FH xanthomatous diseases
3.5 Hypoalphalipoproteinemia syndromes (deficiencies in APOA1, apoA1milano, ABCA1 (Tangiers), ABCG1, LCAT (Fish Eye Disease)
3.6 Abetalipoproteinemia (MTP deficiency)
3.7 Hypobetalipoproteinemias
3.8 Primer on genetics for the Clinical Lipidologist- functional genomics, proteomics, metabolomics
3.9 Major lipid associated genes (GWAS studies)

3.9.1 LDL- LDLR, APOB, PCSK9, HMGCR, NPC1L1, Apo E
3.9.2 TG- APOCIII, APOA5, LPL, (ANGPTL4),
3.9.3 HDL- APOA1, ABCL1, ABCG1, LCAT, CETP

3.10 Secondary Dyslipidemias

3.10.1 Diabetes mellitus and insulin resistant states.
3.10.2 Hypothyroidism
3.10.3 Chronic kidney disease (including nephrotic syndrome)
3.10.4 Obstructive liver disease (including primary biliary cirrhosis)
3.10.5 HIV
3.10.6 Rheumatologic disorders (RA, SLE)
3.10.7 Life-style related- dyslipidemia due to diet, smoking, alcohol, obesity
3.10.8 Pregnancy
3.10.9 Drug-induced hyperlipidemia
3.10.10 Rare causes- lysosomal acid lipase deficiency (LAL)

4.0 Evidence Based Medicine and Statistics for the Clinical Lipidologist

4.1 Study design differences

4.1.1 Randomized controlled trials (RCTs)
4.1.2 Cohort trials
4.1.3 Meta-analyses
4.1.4 Hierarchy of study design

4.2 Clinical trial interpretation

4.2.1 Primary outcomes
4.2.2 Secondary outcomes
4.2.3 Post-hoc analyses
4.2.4 Subgroup analyses
4.2.5 Intention to treat analysis

4.3 Statistical and clinical significance

4.3.1 P-value and confidence intervals
4.3.2 Basic statistical tests
4.3.3 Power calculations
4.3.4 Event rates, relative risk reduction (RRR), absolute risk reduction (ARR)
4.3.5 Number needed to treat (NNT) or to harm (NNH)

4.4 Study biases and limitations

4.5 Interpreting reviews and guidelines

4.5.1 Narrative
4.5.2 Systematic
4.5.3 Meta-analysis
4.5.4 Grading of evidence – AHA/ACC level of evidence and strength of recommendation; GRADE guidelines

4.6 Clinical Decision Making

4.6.1 Patient's values, preferences, beliefs

4.6.2 Shared decision making
4.6.3 Clinical judgment

5.0 Identification and Clinical Significance of Cardiovascular Disease Risk Factors and Risk Indicators*

5.1 Global risk and risk calculators

5.1.1 Traditional risk factor counting (NCEP III, 2014 NLA)
5.1.2 2013 ACC/AHA 10 year ASCVD risk calculator (MI, CVA, CV death)
5.1.3 Framingham NCEP III 10 year CHD risk calculator (MI, CHD death)
5.1.4 Reynolds 10 year ASCVD risk score (MI, CVA, CV death, revascularization)
5.1.4 Lifetime ASCVD risk calculators- 2013 ACC/AHA Lifetime and 30 year Framingham
5.1.5 Other (for international participants only)

5.2 Advanced lipid and inflammatory biomarkers

5.2.1 High-sensitivity CRP
5.2.3 Apolipoprotein B
5.2.4 LDL particle concentration
5.2.5 Lipoprotein (a)
5.2.6 Lipoprotein PLA-2
5.2.7 HDL particle concentration
5.2.8 Lipoprotein particle size measurement
5.2.9 Other lipoprotein biomarkers

5.3 Family history premature CVD
5.4 Hypertension and effects of anti-hypertensive drugs on lipids
5.5 Smoking and effects on lipids
5.6 Microalbuminuria
5.7 Chronic kidney disease (CKD)
5.8 Metabolic syndrome
5.9 Diabetes mellitus
5.10 Inflammatory conditions (HIV, RA and other inflammatory rheumatologic conditions)
5.11 Post-transplant patients
5.12 Non-coronary atherosclerosis (PAD, stroke, TIA, carotid stenosis, aortic aneurysm, renal or other large artery atherosclerosis)
5.13 Subclincal atherosclerosis evaluation

5.13.1 Coronary artery calcium scoring
5.13.2 Carotid intima-media thickness and plaque
5.13.3 Other imaging techniques
5.13.4 Ankle-brachial index

6.0 Therapeutic Lifestyle Changes

6.1 Recommended dietary patterns for reduction of atherogenic lipoproteins and prevention and treatment of ASCVD

6.1.1 Mediterranean style diet
6.1.2 DASH
6.1.3 American Heart Association
6.1.4 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk (2013)
6.1.5 2015 Dietary Guidelines for Americans

6.2 Effect of obesity and weight loss on lipids and lipoproteins

6.2.1 Dyslipidemia associated with obesity (adiposopathic dyslipidemia) and weight gain
6.2.2 Effect of weight loss on lipids by nutritional intervention
6.2.3 Effect of weight loss on lipids by increased physical activity
6.2.4 Effect of weight loss on lipids by anti-obesity drugs
6.2.5 Effect of weight loss on lipids by bariatric surgery

6.3 Additional dietary LDL-C lowering strategies

6.3.1 Sterols and stanols
6.3.2 Soluble fiber
6.3.3 Soy protein

6.4 Food groups associated with reduced ASCVD risk independent of lipid effects

- 6.4.1 Nuts, legumes, and seeds
- 6.4.2 Fiber rich whole grains
- 6.4.3 Fish and seafood
- 6.4.4 Fruits and vegetables

6.5 Dietary strategies to address mild to moderate hypertriglyceridemia (TG ≤ 500 mg/dl) and marked hypertriglyceridemia (TG ≥ 500 mg/dl)

6.6 The role of medical nutrition therapy by registered dietitian/nutritionists to treat dyslipidemia and related ASCVD risk factors

6.7 Impact of specific dietary components on atherogenic cholesterol

- 6.7.1 Saturated fatty acids
- 6.7.2 Dietary cholesterol
- 6.7.3 Trans-fatty acids
- 6.7.4 Other

6.8 Identification of individuals susceptible to the effects of dietary cholesterol

6.9 Dietary recommendations on specific nutrients

- 6.9.1 Refined carbohydrates and added sugar
- 6.9.2 Alcohol
- 6.9.3 Sodium
- 6.9.4 Polyunsaturated vs. monounsaturated fats as replacement for saturated fats
- 6.9.5 Omega 3 fatty acids

6.10 Dietary supplements and other nutritional strategies

- 6.10.1 Probiotics and gut microbiome
- 6.10.2 Other

6.11 Physical Activity and exercise on lipid levels and ASCVD risk

- 6.11.1 Effect of aerobic and dynamic exercise on lipid levels
- 6.11.2 Effect of resistance exercise on lipid levels
- 6.11.3 Effect of modest increase in physical activity on lipid levels
- 6.11.4 Evidence-based physical activity recommendations- amount, intensity, and frequency

6.12 Counseling techniques

- 6.12.1 Behavioral change techniques (goal setting, goal review, and social support)
- 6.12.2 Motivational interviewing

6.13 Tools available to modify lifestyle behaviors to decrease ASCVD risk

7.0 Treatment of Dyslipidemia

7.1 Lipid management recommendations and guidelines (listed chronologically)

- 7.1.1 NCEP III and NCEP III Update (2004)
- 7.1.2 NLA Statin Safety Task Force (2006)
- 7.1.3 NLA Safety Task Force: The Nonstatins (2007)
- 7.1.4 EAS Consensus Statement on Lp(a) (2010)
- 7.1.5 AHA Scientific Statement on Triglycerides and CVD (2011)
- 7.1.6 NLA Expert Panel on Biomarkers: Clinical utility of inflammatory markers and advanced lipoprotein testing (2011)
- 7.1.7 NLA Expert Panel on Familial Hypercholesterolemia (2011)
- 7.1.8 ACC/AHA Guideline on the Treatment of Cholesterol (2013)
- 7.1.9 ACC/AHA Guideline on the Assessment of Cardiovascular Risk (2013)
- 7.1.10 ACC/AHA Guidelines on Lifestyle Management to Reduce Cardiovascular Risk (2013)
- 7.1.11 Chronic Kidney Disease Clinical Practice Guideline for Lipid Management (KDIGO) (2013)
- 7.1.12 EAS Consensus Statement on Familial Hypercholesterolemia (2013)
- 7.1.13 EAS Consensus Statement on Homozygous Familial Hypercholesterolemia (2014)
- 7.1.14 International Atherosclerosis Society (IAS) Lipid Management Recommendations (2014)
- 7.1.15 2014 NLA Statin Safety Update

7.1.16 2014 NLA Recommendations for Patient-Centered Management of Dyslipidemia – Part 1
7.1.17 2015 NLA Recommendations for Patient-Centered Management of Dyslipidemia – Part 2
7.1.18 2015 NLA Annual Summary of Clinical Lipidology
7.1.19 2015 ADA Lipid Guidelines
7.1.20 2015 AACE Dyslipidemia Guidelines
7.1.21 EAS Consensus Statement on Familial Hypercholesterolemia in Children (2015)
7.1.22 Other (for international participants only)

7.2 Pharmacologic treatment: statins, bile acid sequestrants, ezetimibe, fibrates, niacin, prescription omega 3 fatty acids, PCSK9 inhibitors

7.2.1 Statins

7.2.1.1 Mechanism of action, pharmacologic properties, safety, tolerability, efficacy in lipid/lipoprotein improvement
7.2.1.2 Efficacy in ASCVD risk reduction; Major outcome trials
7.2.1.3 Monitoring for and management of side effects
7.2.1.4 Statin Drug Interactions
7.2.1.5 Statin Drug Transporters- CYP-P450, OATP, p-glycoprotein.
7.2.1.6 Statin Safety-muscle, liver, new onset DM, cognition

7.2.2 Management of statin intolerance

7.2.3 Non-statins

7.2.3.1 Mechanism of action, pharmacologic properties, safety, tolerability, efficacy in lipid/lipoprotein improvement

7.2.3.2 LDL-lowering drugs-bile acid sequestrants, ezetimibe, niacin, PCSK9 inhibitors.

7.2.3.2.1 Efficacy in ASCVD risk reduction; major outcome trials
7.2.3.2.1 Monitoring for and management of side effects

7.2.3.3 TG-lowering drugs- fibrates, omega 3's, niacin, statins

7.2.3.3.1 Efficacy in ASCVD risk reduction; major outcome trials
7.2.3.3.2 Efficacy in pancreatitis
7.2.3.3.3 Monitoring for and management of side effects

7.2.4 Combination therapy: rationale, safety and efficacy

7.2.5 Residual risk

7.2.5.1 Patients on maximum statin therapy with LDL-C or Non-HDL-C not at goal
7.2.5.2 Patients with severe hypertriglyceridemia on multiple medications
7.2.5.3 Patients with recurrent CHD on maximal statin therapy at LDL-C and Non-HDL-C goal

7.3 Drugs for homozygous familial hypercholesterolemia: lomitapide, mipomersin, PCSK9 inhibitors

7.3.1 Pharmacologic properties: safety, tolerability, efficacy in lipid/lipoprotein improvement
7.3.2 Efficacy in ASCVD risk reduction; major outcome trials
7.3.3 Monitoring and management of side effects

7.4. LDL apheresis

7.4.1 Description of available apheresis systems and proper apheresis policies and procedures
7.4.2 Impact on blood lipid/lipoprotein levels
7.4.3 Impact on markers of inflammation
7.4.4 Trial data examining efficacy in ASCVD risk reduction
7.4.5 Approved indications
7.4.6 Complications

7.5 Investigational drugs- PCSK9 inhibitor (bococizumab), CETP inhibitor, apo CIII inhibitor, DGAT inhibitor, dual modulator of ATP-citrate lyase and AMP-activated protein kinase (ETC-1002), other
7.6 Medication adherence
7.7 Team-based care

8.0 Special Populations and Consultative Issues in Clinical Lipidology

8.1 Dyslipidemia management for ASCVD prevention in special populations

8.1.1 Homozygous FH

8.1.1.1 Diagnostic criteria
8.1.1.2 Physical findings
8.1.1.3 Cascade screening
8.1.1.4 Genetic testing
8.1.1.5 When to begin treatment
8.1.1.6 The role of lifestyle therapy
8.1.1.7 Drug therapy
8.1.1.8 LDL apheresis
8.1.1.9 Diagnostic testing and treatment of complications

8.1.2 Heterozygous FH

8.1.2.1 Diagnostic criteria
8.1.2.2 Physical findings
8.1.2.3 Cascade screening
8.1.2.4 Genetic testing
8.1.2.5 When to begin treatment
8.1.2.6 The role of lifestyle therapy
8.1.2.7 Drug therapy
8.1.2.8 LDL apheresis

8.1.3 Severe hypertriglyceridemia

8.1.3.1 Diagnostic criteria
8.1.3.2 Physical findings
8.1.3.3 Lifestyle therapy
8.1.3.4 Drug therapy
8.1.3.5 Clinical considerations in lipid management in treatment of the hospitalized patient with hyperchylomicronemia

8.1.4 Low HDL syndromes

8.1.4.1 Differential diagnosis and addressing, when present, secondary causes
8.1.4.2 The role of lifestyle therapy
8.1.4.3 Drug therapy

8.1.5 Elevated Lp(a)

8.1.5.1 Premature family history
8.1.5.2 Residual risk
8.1.5.3 Ethnic groups
8.1.5.4 Drug therapy

8.2 Dyslipidemia throughout the lifespan

8.2.1 Pediatric and adolescent patients

8.2.1.1 Recommendations on lipid screening and risk assessment
8.2.1.2 Dietary management
8.2.1.3 Indications for and caveats in drug therapy

8.2.2 Management of dyslipidemia in women

8.2.2.1 Lifetime risk
8.2.2.2 Primary prevention
8.2.2.3 Secondary prevention
8.2.2.4 Statin and non-statin therapy
8.2.2.5 Adverse effects of lipid lowering therapy

8.2.3 Unique issues in women's health

8.2.3.1 Reproductive years- contraception; teratogenicity of lipid medication
8.2.3.2 Pregnancy and breast feeding
8.2.3.3 Menopause transition- HRT and lipids
8.2.3.4 Polycystic ovary syndrome (PCOS)

8.2.4 Older adults (i.e.-age >75)

8.2.4.1 Caveats in risk assessment
8.2.4.2 Dietary considerations
8.2.4.3 Differences in medication dosing
8.2.4.4 Altered drug metabolism
8.2.4.5 Drug interactions
8.2.4.6 Polypharmacy
8.2.4.7 Frailty
8.2.4.8 Patient preferences

8.3 Specific Ethnic and Racial Groups

8.3.1 African Americans

8.3.1.1 Prevalence of metabolic syndrome, obesity, and insulin resistant states
8.3.1.2 Differences in lipid/lipoprotein profile (Lp(a), increased HDL, low TG)
8.3.1.3 Risk calculation
8.3.1.4 Relative impact of non-lipid risk factors on ASCVD risk

8.3.2 South Asians

8.3.2.1 Prevalence of metabolic syndrome, obesity, and insulin resistant states
8.3.2.2 Differences in lipid/lipoprotein profile (Lp(a), low HDL, HTG)
8.3.2.3 Risk calculation
8.3.2.4 Relative impact of non-lipid risk factors on ASCVD risk (hs-CRP)

8.3.3 Hispanics

8.3.3.1 Prevalence of metabolic syndrome, obesity, and insulin resistant states
8.3.3.2 Differences in lipid/lipoprotein profile (HTG, low HDL-C)
8.3.3.3 Risk calculation
8.3.3.4 Acculturation effects

8.3.4 Other high-risk ethnic groups

8.4 High-risk chronic conditions

8.4.1 Patients with rheumatoid arthritis and other chronic inflammatory states

8.4.1.1 Mechanisms of increased ASCVD risk
8.4.1.2 Special considerations in treating with statins

8.4.2 Patients with HIV/AIDS

8.4.2.1 Etiologies of increased ASCVD risk
8.4.2.2 Appropriate dosing of drug therapy and lipid therapy cautions with HIV protease inhibitors

8.4.3 Type 1 diabetes
8.4.4 Type 2 diabetes
8.4.5 Metabolic syndrome and other states of insulin resistance
8.4.6 Patients with chronic kidney disease
8.4.7 Organ transplant patients