LIPID THERAPY IN THE OLDER ADULT

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President, Southwest Chapter, National Lipid Association
Objectives

Participants should be able to:

1. Identify key primary prevention trials that included older adults
2. Describe primary prevention guidelines applying to the older adult
3. Identify key secondary prevention trials including the older adult
4. Describe secondary prevention guidelines
5. Decide appropriate steps when statin intolerance is suspected
Background

- RCT's have typically excluded very elderly subjects or group all elderly into age ≥ 65
- There are vast differences in terms of frailty/vigoroussness, comorbidities, motivation, and financial resources
- The >80 age group is rapidly growing. By 2020, more than 55 million Americans will be >65
- ASCVD prevalence increases with age: 84.7% men & 85.9% women
- In Montrose, there are 3463 adults 65 and older, 18.5% of total population
  More females than males (1977 vs 1486)
Primary Prevention Guidelines

- National Lipid Association (NLA) Recommendations for Management of Dyslipidemia – Parts 1 & 2
  
  - JCL (2015) 9, 129-169
  - JCL (2015), 9, S1-S122
  - Consensus set of recommendations developed by an expert panel
NLA Recommendations – Part 1

Primary Prevention >65

- Goals of non-HDL <130 mg/dl and LDL-C <100 mg/dl
- Lifestyle modification 3-6 month trial
- Consider moderate intensity statin
  - 1 or more major RF’s aside from age
  - Additional RF’s with >10-15% estimated 10 year risk
NLA Recommendations – Part 1 – Primary Prevention

- Pts >80 over goals
- Risk-benefit discussion
- Try to achieve at least a 30% reduction in baseline LDL-C
Lifestyle Therapies central to dyslipidemia management & CV risk reduction

- Nutrition therapy – Mediterranean-Style Diet
- Weight management – somewhat controversial in elderly, should be individualized
- Regular cardiovascular exercise/Physical activity
- Tobacco cessation
## Diseases/Disorders/Altered Metabolic States that May Elevate LDL-C and/or Triglycerides

<table>
<thead>
<tr>
<th>Cause</th>
<th>Elevate LDL-C</th>
<th>Elevate Triglycerides</th>
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<tbody>
<tr>
<td>Chronic kidney disease</td>
<td>✔️</td>
<td>✔️</td>
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<tr>
<td>Nephrotic syndrome</td>
<td>✔️</td>
<td></td>
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<tr>
<td>Obstructive liver disease</td>
<td>✔️</td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
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<td>✔️</td>
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<tr>
<td>Metabolic syndrome</td>
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<td>✔️</td>
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<tr>
<td>HIV infection</td>
<td>✔️</td>
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<tr>
<td>Autoimmune disorders</td>
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<td>✔️</td>
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<tr>
<td>Hypothyroidism</td>
<td>✔️</td>
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<tr>
<td>Pregnancy</td>
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<td></td>
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<tr>
<td>Polycystic ovary syndrome</td>
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<td></td>
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<tr>
<td>Menopause transition with declining estrogen levels</td>
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<td>✔️</td>
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# Criteria for ASCVD Risk Categories

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Criteria</th>
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</table>
| Low           | - 0-1 major ASCVD risk factors  
- Consider other risk indicators, if known |
| Moderate      | - 2 major ASCVD risk factors  
- Consider quantitative risk scoring  
- Consider other risk indicators |
| 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 |
| Very High     | - ASCVD  
- Diabetes mellitus (type 1 or 2)  
  - ≥2 other major ASCVD risk factors or  
  - Evidence of end organ damage |
2013 ACC/AHA Guidelines for Primary Prevention

- Despite lack of evidence, the Pooled Cohort Equations provide information on expected 10-year ASCVD risk for those 75-79 yrs. that may inform the treatment decision.
- Estimated 10-yr risk for pts >75 always exceeds 7.5% even when other RF's are optimal.
- Does not take life expectancy into account.
- Preference for low to moderate intensity statin.
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
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, or strong family history of premature CHD
2. Indicators of subclinical disease, including coronary artery calcium
   • ≥300 Agatston units 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
5. Lipoprotein (a) ≥50 mg/dL (protein) using an isoform insensitive assay
6. Urine albumin / creatinine ratio ≥30 mg/g
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.
## Treatment Goals for Non-HDL-C, LDL-C, and Apo B in mg/dL

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Treatment Goal</th>
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<tbody>
<tr>
<td></td>
<td>Non-HDL-C</td>
</tr>
<tr>
<td>Low</td>
<td>&lt;130</td>
</tr>
<tr>
<td>Moderate</td>
<td>&lt;130</td>
</tr>
<tr>
<td>High</td>
<td>&lt;130</td>
</tr>
<tr>
<td>Very High</td>
<td>&lt;100</td>
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</tbody>
</table>
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.
Evaluating Benefits/Risks

- Coronary Calcium Study: available at CT Dept at St. Mary for $100 (out of pocket). The absence of coronary calcium is associated with higher cumulative survival in the elderly
- ACC/AHA CV Risk Estimator
- Family history of premature onset CVD in 1st degree relatives
- Lipoprotein (a)
- Inflammatory markers: hs-CRP
- Reynolds Risk Score for women – adds family history, hs-CRP, HGB A1C
Progression of Atherogenic Cholesterol-Lowering Drug Therapy

- Initiate atherogenic cholesterol-lowering drug therapy (statin, unless contraindicated)¹
- If goal not achieved, intensify atherogenic cholesterol-lowering drug therapy
- If goal not achieved, intensify drug therapy or refer to a lipid specialist
- Monitor response and adherence to therapy every 4-12 months²

¹A 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.

²In most cases, goal levels should be achieved in approximately 6 months.
NLA Recommendations – Part 1

- Age ≥65 to ≤75 with ASCVD or DM - Moderate or High Intensity Statin
- Age >75 to <80 – Moderate to High Intensity Statin
- Age >80 – Moderate Intensity Statin
Primary Prevention Trials

- **AFCAPS/TexCAPS**: compared lovastatin to placebo in 6005 participants. 22% >65. 30% reduction in ASCVD events in elderly

- **ASCOT-LLA**: 6,570 participants. Significant benefit with atorvastatin on CHD events in pts 40-79. In pts >60, similar risk reduction in pts >60 to under 60 (34 vs 36%)

- **CARDS**: In 1,129 pts 65-75 on atorvastatin 10 mg ->38% reduced risk of CVD events

- **JUPITER**: In 5,695 pts >70+ treated with rosuvastatin -> 39% relative reduction in risk of a major ASCVD event. No sig,. Reduction in all-cause mortality.
STAREE: Statin Therapy for Reducing Events in the Elderly

- Launched in 2015 – results expected after 2020
- 18,000 pts 70+ without diabetes
- Randomized to atorvastatin 40 mg or placebo
- 2 co-primary endpoints
  - Composite all-cause mortality, dementia, disability
  - Major CV events
Considerations for Women

- More women than men die of annually from CVD
- Leading killer of women
- Women have a higher risk of stroke than men
- In statin-related trials that have included women, the lipid responses are similar
- In ASCVD primary prevention trials, there has not been adequate statistical power to draw firm conclusions by gender
- In JUPITER however, the reduction in primary endpoint (composite MI stroke, hospitalization for unstable angina, arterial revasc, ASCVD death) with rosvastatin was similar & statistically significant in both women and men
Secondary Prevention Trials

PROSPER: 5,804 UK pts 70-82 yrs, mean age 75. Pravastatin 40 mg vs placebo for 3.2 yrs. 24% CHD mortality reduction with no sig. adverse effects.

SAGE: atorvastatin 80 vs pravastatin 40 mg in 893 CAD pts 65-85. Both arms had sig. reduction in ischemia duration on serial 48 hr holters. Greater mortality reduction with atorva post-hoc. No sig. difference in adverse events.

LDS Hospital/UT: observational study of 7,220 CAD pts for 3.3 yrs. Statin therapy was associated with mortality reductions in all groups with greatest mortality benefit in the >80 group.
Secondary Prevention Trials

- NY Med. College/UT Med School: 1,410 post-MI pts with mean age 81 in longterm health facility for 3 yrs. New coronary event incidence was 46% statin vs 72% on no statin, after 3 years.

- Swedish observational study: 14,907 acute MI pts 80+ yrs. Statin-treated pts had a 37% reduction in mortality & acute MI mortality in pts surviving past 1st year.

- CTTC: meta-analysis of 5 trials of ACS or stable CAD pts. More intense statin tx 4.8% risk of vascular events vs 5.4% in pts on less intense statin therapy.
Secondary Prevention Trials including Women

- CTT Collaborators 2015 meta-analysis: similar reductions in vascular events
- Kostos et al meta-analysis: 40,275 women from 18 primary and secondary prevention RCT’s. Statistically significant benefit of statin therapy in all levels of risk in women
Statin Safety Concerns

- Dementia/Alzheimer's:
  - Li et al found no sig. association in 2,356 pts in a prospective study in pts 65+.
  - Brain autopsies of 110 statin-treated pts 65-79 found a reduced risk of typical Alzheimer’s pathology.
  - The FDA found rare post-marketing reports of cognitive impairment have not been generally serious and are reversible on discontinuation.
Statin Safety Concerns

- Liver toxicity:
  - FDA review of post-marketing data of clinically serious hepatotoxicity with statin use & found extremely low incidence of ≤2 per 1 million pt years. This prompted the FDA to remove routine LFT monitoring for asx pts from the statin package insert in 2012.
  - PROSPER reported a very low 0.03% incidence of >3 fold transaminase increase
  - SAGE reported elevated transaminases of 4.3% in pts on 80 Dg atorvastatin vs 0.2% in pts on pravastatin 40 mg. LFT’s normalized on repeat testing or D/C statin

- Myopathy:
  - PROSPER reported 1% myalgia incidence with no rhabdomyolysis cases
  - Older individuals tend to have a higher incidence of statin-associated myalgias than younger pts

- Cancer:
  - PROSPER reported an increase in cancer diagnosis however on extended follow-up to 8.6 years there was no increased cancer risk
Statin Safety Concerns

- Diabetes:
  - Modest but statistically significant increase in incidence of new Type 2 diabetes with statin vs no statin use
  - No recommendation to change clinical practice other than to monitor A1C or FBG
  - Pts with at least 1 major DM risk factor in JUPITER were at higher risk than pts without
  - The CV & mortality benefits exceeded the diabetes risk
Other Considerations

- Polypharmacy & drug-drug interactions
- Cost (Good RX app)
- Comorbidities: renal and/or liver dysfunction
- Pt adherence
- Life expectancy
Myalgia: muscle aches, pain, stiffness, discomfort (most common – 1-5% in controlled clinical trials; 11-29% in observational cohorts)

Myopathy: muscle weakness, typically proximal muscles

Myositis: muscle inflammation determined by skeletal muscle biopsy and/or MRI

Myonecrosis: muscle enzyme elevations or hyperCKemia (classified as mild, moderate, or severe)

Clinical rhabdomyolysis: severe form of myonecrosis with myoglobinuria and/or acute renal failure

Consider baseline muscle symptoms evaluation & CPK level
Statin Intolerance

- STOMP (Effects of statins on Skeletal Muscle Performance). 7,924 pts in France age 18-75 yrs.
- Proposed statin myalgia clinical index score
STOMP Study- Effect of Statins on Skeletal Muscle Function and Performance

- Evaluated 440 statin-naïve pts for muscle function and exercise tolerance on 80 mg atorvastatin or placebo
- Dechallenge and rechallenge method to establish “statin intolerance”
- There was little difference in muscle symptoms between atorvastatin and placebo
- No significant changes in muscle strength or exercise capacity with atorvastatin
Proposed Statin myalgia clinical index score

Clinical Symptoms (new or increased unexplained muscle symptoms)

<table>
<thead>
<tr>
<th>Regional distribution/pattern</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symmetric hip flexor/thigh aches</td>
<td>3</td>
</tr>
<tr>
<td>Symmetric calf aches</td>
<td>2</td>
</tr>
<tr>
<td>Symmetric upper proximal aches</td>
<td>2</td>
</tr>
<tr>
<td>Non-specific asymmetric, intermittent</td>
<td>1</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Temporal pattern</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms onset &lt;4 weeks</td>
<td>3</td>
</tr>
<tr>
<td>Symptoms onset 4-12 weeks</td>
<td>2</td>
</tr>
<tr>
<td>Symptoms onset &gt;12 weeks</td>
<td>1</td>
</tr>
</tbody>
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Dechallenge

<table>
<thead>
<tr>
<th>Improves upon withdrawal</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&lt; 2 weeks)</td>
<td>2</td>
</tr>
<tr>
<td>(2-4 weeks)</td>
<td>1</td>
</tr>
<tr>
<td>(&gt;4 weeks)</td>
<td>0</td>
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</table>

Challenge

<table>
<thead>
<tr>
<th>Same symptoms reoccur upon rechallenge</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&lt;4 weeks)</td>
<td>3</td>
</tr>
<tr>
<td>(4-12 weeks)</td>
<td>1</td>
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Statin myalgia clinical index score

- Probable: 9-11
- Possible: 7-8
- Unlikely: <7
New or Worsened Muscle Symptoms on a statin

- Administer statin muscle questionnaire
- Characterize myalgia by muscle group location & temporal relationship to statin
- Rule out hypothyroidism, Vitamin D level, assess changes in physical activity and exercise
- Check CPK level
New or Worsened Muscle Symptoms on Statin

- If symptoms are intolerable to pt, muscle weakness, or CPK >3xULN then STOP statin for 2-4 weeks

- If symptoms improve:
  - D/C any meds with potential for statin drug interaction
  - Initiate different daily statin at lowest recommended dose
  - If possible, start statin tolerated by a family member
  - If pt remains asymptomatic, increase dose gradually to highest tolerated dose
New or Worsened Muscle Symptoms on Statin

- If symptoms return, consider a non-daily dosing regimen such as atorvastatin or rosuvastatin 5-10 mg 1-2x/week (long-acting)
- If symptoms return, initiate a non-statin therapy with ezetimibe, BAS, or combination
- Consider a PCSK9-Inhibitor for high risk patient
- If symptoms return, consider referral to a Clinical Lipid Specialist
- Statins lead to reduced ubiquinone (coenzyme Q10) but studies of coenzyme Q10 supplementation have been negative
New or Worsened Muscle Symptoms on Statin

- If NO symptom improvement:
  - Check Vitamin D level and consider inflammatory or metabolic myopathies
  - If CPK remains >3x ULN refer to a neuromuscular specialist for a skeletal muscle biopsy
Genetic testing for statin intolerance

Variant of SLCO1B1 gene (or OAT1B1)

Influx transporter that moves drugs into cells
Summary

- Statins should not be withheld based on age alone. Age is a powerful independent risk factor.
- Absolute risk reduction from statin therapy in trials is similar or greater in the elderly than in younger pts.
- Adverse effects of statins are greatly outweighed by the benefits.
- The cost of generic statins is now very low.
- Treatment should be individualized with active pt involvement in a shared decision-making approach.
- A stepwise approach is indicated in the pt with a statin intolerance.
Questions
Upcoming NLA Conferences:

- Portland Feb. 22-24, 2019
- Miami May 16-19, 2019
- Minneapolis Sept. 13-15, 2019

www.lipid.org

  Clinician Lifestyle Modification Toolbox
  Position Statements