Lipid Management to Reduce ASCVD Risk in the Elderly: Reviewing the evidence and implementing NLA recommendations

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Disclosures

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  - KOWA
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  - Amgen
The elderly are complex and heterogeneous, therefore lipid management can be equally complex

1. Who are the elderly?
2. Risk assessment
4. The literature
   1. Primary prevention
   2. Secondary prevention
5. Statin therapy issues
6. Recommendations for lipid management
7. Summary of recommendations for lipid management from the 2015 NLA Expert Panel on older patients

The Elderly

- Most developed countries accept the chronological age of 65 years as the definition of “elderly” per the WHO
- AHA and American Stroke Association statistics indicate that about 80% of people who die from CVD are ≥65 years of age

Mozaffarian, D, Benjamin, et al American Heart Association Statistics Committee and Stroke Statistics 2015 Update Circulation2015;131:e29-e322
The Elderly and Vascular Disease

- In those 60–79 years of age
  - 69.1% (men) and 67.9% (women) have CVD, heart failure, stroke or hypertension, and some have a combination of these
- In those ≥80 years of age, 84.7% (men) 85.9% (women) CHD accounts for ~47.7% and stroke 16.4% of deaths
- The average age of first heart attack is 65.0 years in men and 71.8 years in women,
- Nearly 70% of first strokes are in patients ≥65 years of age

ASCVD risk assessment in older patients

- All current scoring systems that assess ASCVD risk reflect the progressive increase in absolute risk that occurs with advancing age
  - likely reflecting an age-related increase in atherosclerotic plaque burden.
  - However, population norms often do not apply to individual patients.
  - Application of average risk scores for age to specific patients may lead to miscalculation of risk and inappropriate consideration of drug therapy
ASCVD risk assessment in older patients

- The ACC/AHA Pooled Cohort Risk Equation was applied for ASCVD risk assessment to 4854 Rotterdam Study participants with a mean age of 65 years.
  - Using $\geq 7.5\%$ 10-year risk as the threshold for consideration of initiation of moderate or high intensity statin therapy, 96.4% of men and 65.8% of women were potential candidates for such therapy.
  - In this population the average predicted vs observed cumulative incidence of ASCVD events was 21.5% vs. 12.7% for men and 11.6% vs. 7.9% in women, reflecting poor calibration of risk in this European sample.

Risk Assessment

- 1999 AHA Scientific Statement on ASCVD Risk Assessment suggested that when risk scoring is used to adjust the intensity of risk factor management in elderly patients, RR estimates, which eliminate the age factor and focus on the major risk factors, might be more useful than absolute risk estimates.
- This approach allows providers to risk stratify and compare patients of the same age and select those at highest RR for the most aggressive treatment strategies.
- Results from some studies suggest that serum lipids partially lose their predictive power for relative ASCVD risk prediction in the elderly. A variety of reasons exist for this, including the increased number of co-morbidities among patients of advanced age.
In a study of Rotterdam study participants, 2028 patients underwent electron beam tomographic imaging of the epicardial coronary arteries and CAC scores were reported using Agatston's method.

During a mean follow-up of 9.2 years there were 135 hard coronary events. Subjects were classified into:

- low (<10%)
- intermediate (10–20%)
- high (>20%) 10-year coronary risk
- using a Framingham refitted risk model

The model was extended by CAC and reclassification percentages were calculated. Reclassification into high or low risk categories was greatest in those classified as intermediate risk.

A total of 52% of men and women were reclassified into either higher or lower risk categories based upon their CAC score.

Empirically derived CAC cutoffs at, which subjects were reclassified into either high or low risk categories were 615 and 50 Agatston units, respectively.

EBCT Continued

- Although measurement of CAC provides a more accurate means of CHD risk assessment than the use of traditional risk factor-based algorithms:
  - cost of the test
  - lack of widespread availability
  - absence of studies linking results with outcomes
  - is a limiting factor in its implementation in older patients.
- Nevertheless, when such testing is available it may be a valuable addition to CHD risk assessment, particularly in older patients.

Value of statin therapy in older patients

- There appears to be a weaker correlation of cholesterol with ASCVD in older vs younger individuals which may include:
  - Pts with higher cholesterol and more susceptible to CVD may have died before reaching old age, reducing number of patients with higher cholesterol among the population of older adults, and thus resulting in lower mean lipid levels among older survivors
  - Although lifelong dyslipidemia contributes to the development, promotion, and progression of atherosclerosis, clinical ASCVD event in older individuals may be more often related to non-lipid ASCVD risk factors that trigger instability, rupture, and/or thrombosis
Statin Safety in Older Adults

- Older individuals have increased risk of other chronic diseases, weight loss, and malnutrition, which may result in lower cholesterol levels.
- Older individuals are at increased risk of hemorrhagic stroke, which is often reported to have an inverse association with cholesterol levels.

Biases in reporting side effects

- Although there have been no definite signals in RCTs to suggest a higher incidence of side effects in older vs younger populations treated with statins, the use of RCTs for this purpose has limitations.
- **Observational studies often report a higher incidence of side effects than RCTs. Patients entering RCTs and experiencing side effects during run-in periods, or exhibiting conditions that predispose to side effects are often excluded.**
- Other issues including definition of adverse events, selective reporting of outcomes, and publication bias may affect the reported incidence of side effects.

Myalgia

- Generally reported that older individuals have a higher incidence of statin-associated myalgia than younger patients.
- Unclear whether related to:
  - decreasing muscle mass that occurs during aging
  - polypharmacy common among older patients that increases the risk for drug-drug interaction
  - loss in the function of drug metabolizing enzymes
  - or combination of these factors
- Results from a study based on the Understanding Statin Use in America and Gaps in Education Internet survey showed:
  - more muscle side effects in older patients
  - older patients were more likely to discontinue a statin due to muscle side effects

Diabetes

NLA Task Force on Statin Safety – 2014 Update, clinical trial data, including meta-analyses, suggest a modest, but statistically significant increase in the incidence of new-onset type 2 diabetes with statin vs no statin use and with use of higher vs. lower intensity statin use.

However, because of the well-established benefits for ASCVD risk reduction with statin use, there have been no recommendations to change clinical practice with regard to statin use other than recommending the measurement of glycated hemoglobin or fasting glucose in patients at elevated risk for diabetes.
Diabetes

- In JUPITER, which included patients with a median (interquartile range) age of 66.0 (60.0–71.0) years, patients with at least 1 major diabetes risk factor were at higher risk for developing diabetes than patients without a major diabetes risk factor.
- However, the cardiovascular and mortality benefits exceeded the diabetes hazard in all patients, including those at high risk for developing diabetes.
- Because the incidence of diabetes increases with age, periodic glucose monitoring, and when appropriate, glycated hemoglobin measurement, should be performed when administering statins to older patients.

Cognitive Dysfunction

- There have been case reports of patients noting cognitive dysfunction during the course of statin therapy.
- The NLA Task Force on Statin Safety – 2014 Update defined cognitive dysfunction as impairment in any of 4 domains, including:
  - Executive function, memory, language and visuo-spatial ability.
  - Mild cognitive impairment was defined as a state of cognitive dysfunction between normal cognition and dementia involving 2 domains and is sufficiently severe to interfere with activities of daily living associated with progressive loss of independence.
Cognitive Dysfunction

- Clinically, it is especially important to differentiate a potential medication side effect causing cognitive impairment from other causes of dementia in older patients, including:
  - Alzheimer's disease
  - frontoparietal dementia
  - Parkinson's disease
  - Lewy body dementia
  - infectious processes
  - inflammatory
  - vascular or metabolic disorders
  - depression

The following perspective on statins and cognition was put forth by the NLA Task Force on Statin Safety:

1) a baseline cognitive assessment does not need to be performed prior to initiation of statin therapy
2) statins as a class are not associated with adverse effects on cognition
3) in patients who report cognitive symptoms after beginning a statin, cognitive testing should be performed, other potential contributors should be ruled out, and the risk of stopping the statin should be assessed

4. The provider may consider stopping the statin to assess the reversibility of symptoms, lowering the dose, or switching to an alternative statin.

5. If the statin is switched, consideration may be given to starting a statin that is less likely to penetrate the brain, including pravastatin or rosuvastatin.

Polypharmacy and drug-drug interactions

- Polypharmacy, defined as the concurrent use of 5 or more medications, is common in older patients, and is likely contributed to by changes in absorption, bioavailability, and volume of distribution.
  - Multiple pathways of altered metabolism have been described in statin drug-drug interactions; the CYP3A4 and CYP2C9 pathways are most commonly implicated.
  - In addition, single-nucleotide polymorphisms in organic anion transporter 1B1 may be an additional cause of statin-related drug interactions.

Polypharmacy and drug-drug interactions

- Reduced muscle mass in older patients may also predispose to muscle-related side effects.

- It has been suggested that older patients on polypharmacy regimens be:
  - regularly evaluated for drug-drug-interactions
  - medication reconciliation be carefully performed at each clinic visit.

Recommendations for lipid management in older patients in other major guideline documents

- The 2013 ACC/AHA Guideline for the Treatment of Blood Cholesterol includes different treatment regimens for individuals >75 years of age compared to those who are younger.
  - In those with CHD, moderate intensity statin therapy is recommended for secondary prevention in those >75 years of age vs. high intensity in those who are younger.
- In primary prevention, the ACC/AHA guidelines recommend the use of the Pooled Cohort Risk Equations to inform statin treatment decisions and the use of provider-patient discussion in which the pros and cons of statin therapy are discussed.
- No specific recommendation is made for the intensity of statin therapy in primary prevention for those >75 years of age.
The International Atherosclerosis Society Guidelines

- Recommend for persons >65 years of age - use of short-term (10-year) Framingham risk scoring (recalibrated for country) to estimate CHD risk, and then elevation of the estimated value by 1/3 to estimate total ASCVD risk.
- The guideline suggests that statin therapy should be used in those whose risk is estimated to be moderately-high or high, but that decisions about the use of drug therapy should be made while considering the pros and cons of polypharmacy, drug-drug interactions, and cost.


The European Atherosclerosis Society/European Society of Cardiology Guidelines

- Advocate for elderly patients that statin therapy generally be given for secondary prevention in the same manner as in younger patients (class 1, level of evidence B).
- However, because of co-morbidities and altered pharmacokinetics, therapy should be started at a low dosage and the dosage should be titrated to achieve target lipid levels that are the same as for younger patients (class 1, level of evidence C).
- They also recommend statin therapy for primary prevention in those with 1 or more additional risk factors, aside from age (class IIb, level of evidence B).

Summary of recommendations for lipid management from the 2015 NLA Expert Panel on older patients

Clinical Practice decisions

- The decision to initiate statin therapy in patients ≥75 years of age is based on all forms of evidence, including generalization from applicable clinical trials, via a “patient-centered” approach, and includes:
  - Benefit vs. risk assessment
  - Comorbidities
  - Life expectancy
  - Quality of life considerations
  - Patient preferences
  - Tolerability of the statin
  - Clinical judgment
  - Knowledge that continued statin therapy beyond age 75 years provides benefit in reducing ASCVD risk
Recommendations for older patients
PRIMARY PREVENTION 65-79

- Primary prevention strategies in patients 65-79 years of age should be managed in accordance with the NLA Recommendations for the Patient-Centered Management of Dyslipidemia-Part 1
  
  **STRENGTH** A
  **QUALITY** HIGH

Patients age $\geq 65$ to $< 80$ years of age with ASCVD or diabetes mellitus

- Moderate or high intensity statin therapy should be considered after a careful consideration of the risk-benefit ratio.
  
  **STRENGTH** A
  **QUALITY** HIGH
Secondary prevention in patients ≥80 years of age

• **Moderate intensity statin** therapy should be considered based upon a provider-patient discussion of the risks and benefits of such therapy:
  - consideration of drug-drug interactions
  - polypharmacy,
  - concomitant medical conditions including frailty
  - cost considerations
  - patient preference

  **STRENGTH** B
  **QUALITY** Moderate

Statin Eligible Primary Prevention Patients

• Older, primary prevention patients who are statin-eligible should undergo a patient-centered discussion with their provider about the risks and benefits of statin therapy so that they can make a more informed decision about taking statins over the long term

  **Strength** E
  **QUALITY** LOW
Primary Prevention Patients unable to achieve atherogenic cholesterol goals after 3 – 6 month trial on lifestyle modification

- provider should discuss the pros and cons of drug therapy
- If feasible, prescribe **moderate intensity** statin therapy, particularly for patients with one or more ASCVD risk factor aside from age, with risk exceeding the high risk threshold using the Pooled Risk Equation or ATP III Framingham Risk Calculator

  Strength E  Quality Moderate

Coronary Artery Calcium Scoring

- CAC scoring may be useful to further assess risk in older patients for whom questions remain about whether to prescribe drug therapy

  Strength  E  Quality  Low
Statin Intolerance

- If statin intolerance is an issue, consideration should be given to the use of alternate statin regimens such as:
  - low intensity statin therapy or
  - non-daily moderate intensity statin therapy
  - low dose statin combination therapy with ezetimibe bile acid sequestrants, or niacin
  - non-statin monotherapy (i.e., ezetimibe or bile acid sequestrants, PCSK9 Inhibitors) or their combination, with a goal of at least a 30% reduction in LDL-C

Strength: B
Quality: Moderate

Summary and Take Home Message

- The elderly are a diverse group of the population
- Chances of cardiovascular events increase with age
- Diverse assessment techniques may be necessary for a thorough evaluation
- Multiple guidelines exist both nationally and internationally
- The NLA in the Part 1 & 2 recommendations has synthesized current literature and best practices to provide a hands on tool for the provider who treats the elderly population
Thank you for your kind attention

We will now open the floor to questions & discussion