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ELDER CARE

A Resource for Interprofessional Providers

Statin Therapy for Cardiovascular Risk Reduction in Older Adults

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While older adults face the largest risk for and burden of cardiovascular disease and events, they have been underrepresented in major clinical trials examining lipid-lowering therapy. Perhaps because of the resulting uncertainties about the safety and benefit of lipid-lowering therapy in older adults, statins have long been underused in this age group, even though older adults may derive the most benefit in terms of cardiovascular risk reduction.

Aside from the SAGE and PROSPER trials which included patients aged 65-85 and 70-82 years, respectively, the majority of our data on statin use in older adults is derived from subset analysis of larger trials. There are currently no completed studies that include patients >85 years of age, though in December 2014, the STAREE trial was launched which is examining the use of atorvastatin 40 mg in healthy adults >70 years of age.

Choosing Initial Statin Therapy

The 2013 recommendations from the Expert Panel of the American College of Cardiology (ACC) and the American Heart Association (AHA) provide a new framework for choosing initial statin therapy.

The panel recommended that high-intensity statin therapy (atorvastatin 40-80 mg or rosuvastatin 20-40 mg) should be given to patients ≤ 75 years of age who have a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, peripheral vascular disease, stroke, or transient ischemic attack. The panel also recommended that high-intensity statins should be used if the low-density lipoproteins (LDL) level is ≥ 190 mg/dL or if the 10-year risk of an atherosclerotic cardiovascular disease (ASCVD) event is $\geq 7.5\%$ (see 10-year risk calculator in References/Resources; the age limit for use of the calculator is considered to be 79 years).

For patients >75 years, the evidence for using high-intensity statins to reduce ASCVD events is less strong. Thus, a decision to use statins should be individualized by considering risk factors such as high LDL (>160 mg/dL), family history of early ASCVD, high C-reactive protein levels (>2 mg/L), peripheral vascular disease (as shown by

an ankle-brachial index <0.9), drug-drug interactions, and patient preference.

Statin Therapy for Patients with Diabetes

The panel recommended that diabetics aged 40-75 with a 10-year ASCVD risk $\geq 7.5\%$ should receive high-intensity statins, while an ASCVD risk of <7.5% warrants a moderate-intensity statin with either lower doses of atorvastatin (10-20 mg) or rosuvastatin (5-10 mg), or therapy with simvastatin (20-40 mg), pravastatin (40-80 mg), lovastatin (40 mg), or fluvastatin (40 mg twice daily). There are limited data to guide therapy in diabetics older than 75 and decisions should be individualized.

There have been reports of increased rates of diabetes with statin use. But, the incidence is low (0.3 cases of diabetes/100 users of high-intensity statins) and considered negligible in comparison to the reduction of ASCVD events.

Monitoring Patients on Statin Therapy

Baseline alanine aminotransferase (ALT) levels should be obtained before statin therapy and does not need to be repeated unless there are symptoms suggesting hepatotoxicity (e.g., nausea, appetite loss, jaundice).

Routine monitoring of creatine kinase (CK) is not recommended either, but can be considered if muscle symptoms develop. A baseline CK is reasonable in those with a history of statin intolerance or muscle disease, or taking other medications that increase risk of myopathy.

While there are mixed results in regards to the effects of statins on muscle strength, gait speed, and fall risk, consider monitoring these in patients, particularly in frail, older adults.

As there are no longer specific LDL or high-density lipoprotein (HDL) goals, re-checking the lipid profile should only be considered for monitoring high triglyceride levels, if the LDL is >190 mg/dL, or if there is a concern for non-adherence. It is unclear what the acceptable lower limit of LDL is, but a dose reduction should be considered if two consecutive LDL readings are <40 mg/dL.

TIPS ABOUT DRUG THERAPY FOR HYPERLIPIDEMIA IN OLDER ADULTS

- There is considerable underuse of statins in older adults who have the highest ASCVD risk.
- If there is a concern for myopathy, consider rosuvastatin 20-40 mg if a high intensity statin is needed; or pravastatin 40-80 mg or fluvastatin 40 mg bid if a moderate-intensity statin is appropriate.

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Statin Myopathy

While statin-associated myalgias (muscle symptoms without CK elevation) occur in 5 to 10% of patients, statin myopathy (muscle symptoms with CK elevations) is quite rare, even in older adults. Overall, the myopathy safety profile of statins is considered acceptable for older adults.

In choosing an agent when there is a concern about myopathy, the PRIMO study found that rates of muscle symptoms were lowest with fluvastatin (5.1%) and pravastatin (10.9%) and highest with atorvastatin (14.9%) and simvastatin (18.2%).

As atorvastatin and rosuvastatin have longer half-lives (15 and 20 hours, respectively), alternate-day dosing with either drug or weekly dosing with rosuvastatin may also be considered to reduce myopathic symptoms while still lowering LDLs. Whether reduction in ASCVD risk still occurs with these dosing regimens, however, is not yet known.

Patients on statins metabolized through the CYP3A4 system may have increased statin levels when also taking other drugs that inhibit CYP3A4 (see table). This increases the risk of myopathy. In this situation, pravastatin (renally excreted) and fluvastatin and rosuvastatin (metabolized by CYP2C9) may be safer options.

For patients with muscle pain, also consider other conditions that may be the cause, such as hypothyroidism, renal or hepatic dysfunction, steroid-induced or primary myopathy, and polymyalgia rheumatica.

Cognitive Changes

The Food and Drug Administration issued a warning in 2012 regarding potential adverse cognitive effects of statins, such as forgetfulness and confusion. Reports of these effects are very rare, and other evidence suggests that statins may improve cognition. However consider a statin

Commonly Used CYP3A4 Inhibitors	
Amiodarone	Fibrates
Azole Antifungals	Grapefruit Juice
Calcium Channel Blockers	Macrolide Antibiotics
Cimetidine	Omeprazole
Cyclosporine	Protease Inhibitors

References and Resources

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

ASCVD risk calculator: <http://tools.acc.org/ASCVD-Risk-Estimator/>

Joy TR, Hegele RA. Narrative review: statin-related myopathy. *Ann Intern Med.* 2009;150:858-68.

Szadkowska I, Stanczyk A, Aronow WS, et al. Statin therapy in the elderly: a review. *Arch Gerontol Geriatr.* 2010;50(1):114-8.

Pedro-Botet, Juan et al. Statins for primary cardiovascular prevention in the elderly. *J Geriatr Cardiol.* 2015; 12:431-438.

Giugliano R, Sabatine M. Are PCSK9 inhibitors the next breakthrough in the cardiovascular field? *J Am Coll Cardiol.* 2015; 65:2638-2651

discontinuation trial if a temporal association is seen between statin initiation and cognitive changes. There are also anecdotal reports of statin-induced mood changes.

Non-Statin Therapies

The ACC/AHA Expert Panel did not find any randomized controlled trials supporting the use of drugs to achieve specific LDL or HDL levels as recommended in prior guidelines or the addition of non-statin medications to a statin regimen. It is, however, reasonable to consider a non-statin for patients who are completely statin intolerant, or in higher-risk patients such as those with clinical ASCVD, LDL >190 mg/dL, or diabetics aged 40-75.

If non-statins are used, fenofibrate may be considered in addition to a low-moderate intensity statin to lower triglyceride levels to <500 mg/dL. Gemfibrozil is not recommended because the rate of rhabdomyolysis is 15 times higher with gemfibrozil-statin therapy vs fenofibrate-statin therapy.

Ezetimibe achieves a LDL reduction of 15-42%, but there is no evidence for ASCVD reduction when used as monotherapy. Ezetimibe 10 mg combined with simvastatin 40 mg has, however, been shown to improve outcomes for patients (mean age 64 years) who had been hospitalized for acute coronary syndrome within the past 10 days.

Currently, phase-3 trials are underway to examine the ASCVD risk reduction and safety of evolocumab and alirocumab, monoclonal antibodies against proprotein convertase subtilisin/kexin type-9 (PCSK9). Preliminary trials showed significant LDL reductions and these agents may soon be available to selected high-risk patients, such as those with familial hypercholesterolemia and those who have mixed dyslipidemia or are statin intolerant.

Terminally Ill Patients

A recent study examined the safety of discontinuing statin therapy in patients with a life expectancy of 1 month to 1 year. More than half (58%) of the patients had a history of ASCVD. The 60-day survival rate was similar to those who continued their statin and there was an improved quality of life in the statin-discontinuation group. Thus, in the setting of concern for pill-burden in terminally ill patients, statins can likely be safely discontinued without concern for increasing the risk of a major ASCVD event.

Interprofessional care improves the outcomes of older adults with complex health problems

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