Long-Term Care Updates

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Statin deprescribing in older adults

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Introduction

Cardiovascular disease (CVD) is a primary public health problem and a major cause of morbidity and mortality worldwide.[1] In the United States, one person dies every 33 seconds from CVD, accounting for 1 of every 5 deaths.[2] Coronary atherosclerotic heart disease is the largest contributor to CVDs and is closely associated with environmental, genetic and other risk factors including dyslipidemia.[1] Development of atherosclerosis, plaque buildup in arteries, is caused by a high concentration of low density lipoprotein cholesterol (LDL-C) in the blood. Lowering LDL-C can work to reverse or retard atherosclerosis, thus preventing cardiovascular disease in both symptomatic and asymptomatic individuals.[3]

HMG Co-A reductase inhibitors, commonly known as statins, have been the mainstay therapy for CVD prevention over the last 30 years.[1] Statin medications primarily work via inhibition of HMG-CoA reductase, the rate-limiting enzyme in the cholesterol biosynthesis pathway in the liver.[4] Two different lipoproteins in the body are made of fat and protein and serve as vehicles for cholesterol to travel through the body. High-density lipoproteins (HDL) serve as the "good cholesterol" and work to carry cholesterol away from the arteries and back to the liver where they are flushed from the body. Low-density lipoproteins (LDL) serve as the "bad cholesterol" and work to carry cholesterol formed in the liver to different arteries in the body contributing to fatty plaque build ups.[5] Pharmacologic studies have demonstrated that statins can reduce LDL-C levels and increase HDL-C levels.[6]

Novel Drug Approvals (December 2024)

Brand	Generic	Indication	Mechanism of Action	Dosage Form
Alhemo	Concizumab-mtci	Hemophilia	Tissue factor pathway inhibitor (TFPI)	Subcutaneous injection
Alyftrek	Deutivacaftor; tezacaftor; vanzacaftor	Cystic fibrosis	CFTR potentiator (deutivacaftor); CFTR modulators (tezacaftor, vanzacaftor)	Oral tablets
Bizengri	Zenocutuzumab-zbco	NSCLC, pancreatic adenocarcinoma	Bispecific HER2- and HER3-directed antibody	Intravenous injection
Crenessity	Crinecerfont	Congenital adrenal hyperplasia	Corticotropin-releasing factor type 1 receptor antagonist	Oral capsules, oral solution
Ensacove	Ensartinib	NSCLC	Kinase inhibitor	Oral capsules
Nemluvio	Nemolizumab-ilto	Prurigo nodularis	Interleukin-31 antagonist	Subcutaneous injection
Tevimbra	Tislelizumab-jsgr	Esophageal squamous cell carcinoma	PD-1 blocking antibody	Intravenous injection
Tryngolza	Olezarsen	Familial chylomicronemia syndrome	APOC-III-directed antisense oligonucleotide	Subcutaneous injection
Unloxcyt	Cosibelimab-ipdl	Metastatic or locally advanced cutaneous squamous cell carcinoma	PD-L1 blocking antibody	Intravenous injection

While extremely beneficial in most patient populations, no study has been conducted to evaluate the impact of statins on cardiovascular outcomes among older adults without preexisting coronary artery disease. However, it is estimated that over 40% of adults aged 75 years and older are taking these medications.[7] Despite the widespread use of statins to lower cholesterol and reduce cardiovascular morbidity and mortality, the potential for statin-related adverse events remains particularly high. Statin therapy may be associated with a variety of musculoskeletal disorders including myopathy, myalgias, muscle weakness and arthropathies. These disorders become particularly problematic in older individuals as it may contribute to overall physical deconditioning and frailty. Additionally, statins have also been associated with cognitive dysfunction, which may contribute to reduced functional status, increased risk of falls and overall disability. The combination of several risk factors puts this population at an increased risk of overall mortality.[8]

The decision to discontinue statin therapy remains an ongoing problem as there are both benefits and harms of this medication therapy. Medication-related problems are extremely common in the older adult population who take a disproportionately high share of medications.[9] Deprescribing is an essential part of good prescribing and is a process that requires attention, time, and in many cases special skills and knowledge.

Primary vs Secondary Use of Statins

Atherosclerotic cardiovascular disease (ASCVD) is caused by plaque buildup in arterial walls and refers to the following conditions:

- Coronary heart disease such as myocardial infarction, angina, and coronary artery stenosis >50%
- Cerebrovascular disease such as transient ischemic attack, ischemic stroke, and carotid artery stenosis >50%
- Symptomatic peripheral artery disease, such as claudication
- Aortic atherosclerotic disease such as abdominal aortic aneurysm and descending thoracic aneurysm

Primary prevention refers to the efforts to prevent or delay the onset of clinical ASCVD whereas secondary prevention refers to the effort to treat know, clinically significant ASCVD and to prevent or delay the onset of disease manifestations.[10] Statins are a mainstay of therapy in both primary and secondary prevention of ASCVD.

Standard of Care/Clinical Guidelines

2018 American College of Cardiology/ American Heart Association Guideline on the Management of Blood Cholesterol[11]

CoR	LoE	Recommendation
IIa	B-R	In patients older than 75 years of age with clinical ASCVD, it is reasonable to initiate moderate- or high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug-drug interactions, as well as patient frailty and patient preferences.
IIa	C-LD	In patients older than 75 years of age who are tolerating high-intensity statin therapy, it is reasonable to continue high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug-drug interactions as well as patient frailty and patient preferences.
IIa	B-NR	In adults older than 75 years of age with diabetes mellitus and who are already on statin therapy, it is reasonable to continue statin therapy.
IIb	C-LD	In adults older than 75 years with diabetes mellitus, it may be reasonable to initiate statin therapy after a clinician-patient discussion of potential benefits and risks.
IIb	B-R	In adults 75 years of age or older with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), initiating a moderate-intensity statin may be reasonable.
IIb	B-R	In adults 75 years of age or older, it may be reasonable to stop statin therapy when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statin therapy.
IIb	B-R	In adults 76 to 80 years of age with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), it may be reasonable to measure CAC to reclassify those with a coronary artery calcium (CAC) score of zero to avoid statin therapy.

*CoR, Class of Recommendation; LoE, Level of Evidence

2019 American College of Cardiology/ American Heart Association Guideline on the Primary Prevention of Cardiovascular Disease[12]

For patients >75 years of age, assessment of risk status and a clinician patient risk discussion are needed to decide whether to continue or initiate statin treatment. For a detailed discussion of statin safety and management of statin-associated side effects, refer to the 2018 Cholesterol Clinical Practice Guidelines.

2019 European Society of Cardiology and European Atherosclerosis Society Guidelines for the Management of Dyslipidemias[13]

Class/Level of Recommendation	Recommendation
I-A	Treatment with statins is recommended for older people (aged >65 years) with ASCVD in the same way as for younger patients.
IIb-B	Initiation of statin treatment for primary prevention in older people aged >75 years may be considered if at high-risk or above.

U.S. Preventative Task Force: Statin Use for the Primary Prevention of Cardiovascular Disease in Adults[14]

GoR	Recommendation
B	The USPSTF recommends that clinicians prescribe a statin for the primary prevention of CVD for adults aged 40 to 75 years who have 1 or more CVD risk factors (i.e., dyslipidemia, diabetes, hypertension, or smoking) and an estimated 10-year risk of a cardiovascular event of 10% or greater.
C	The USPSTF recommends that clinicians selectively offer a statin for the primary prevention of CVD for adults aged 40 to 75 years who have 1 or more CVD risk factors (i.e, dyslipidemia, diabetes, hypertension, or smoking) and an estimated 10-year risk of a cardiovascular event of 7.5% to less than 10%. The likelihood of benefit is smaller in this group than in persons with a 10-year risk of 10% or greater.
I	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of initiating a statin for the primary prevention of CVD events and mortality in adults 76 years or older.

*GoR, Grade of Recommendation

Choosing Wisely Campaign[15]

Advises not to start lipid-lowering medications in patients with limited life expectancy.

Clinical Evidence[16]

Peixoto, et al., conducted a systematic review to evaluate and summarize the benefits and harms of discontinuation versus continuation of statins for cardiovascular disease prevention. These analyses included randomized controlled trials (RCT), cohort studies, case-control studies, and quasi-randomized studies that compared discontinuation of statins to statin continuation. Eligible studies included participants aged ≥18 years in any setting. The primary outcome measures were all-cause mortality, CV mortality and major adverse cardiovascular events (MACE) (composite and their individual components: MI, transient ischemic attack, stroke, and revascularization). Secondary outcomes of interest included: adverse effects, quality of life, and pill burden. A Grading of Recommendations, Assessment, Development and Evaluations (GRADE) assessment was performed to judge the certainty of evidence according to the outcome. A subgroup of persons ≥75 years of age was also examined. In total, 37 reports from 36 studies were eligible which included 35 non-randomized studies (n=1,708,684): 28 retrospective cohort studies, 6 prospective cohort studies, one case-control study; and 1 RCT (n=381) were included. In 4 out of 37 reports, the population was exclusively primary prevention compared to 12 out of the 37 for exclusively secondary prevention compared to 7 out of the 37 reports looking at a mix of primary and secondary prevention. The remaining 14 reports investigated specific populations and clinical situations. There were five reports from four studies in the aged ≥75 years subgroup.

Primary Outcomes:

	All-cause mortality	*CV mortality*	*MACE-composite*	*MACE- MI*	*MACE-stroke*
Overall Population	**HR 1.96 95% CI 1.52 to 2.44**	**HR 1.63 95% CI 1.27 to 2.10**	**HR 2.31 95% CI 2.13 to 1.39**	**HR 1.40 95% CI 1.25 to 1.58**	**HR 1.37 95% CI 1.24 to 1.53**
Primary Prevention	-	-	**HR 1.34 95% CI 1.23 to 1.45**	**HR 1.43 95% CI 1.29 to 1.58**	**HR 1.30 95% CI 1.16 to 1.46**
Secondary Prevention	**HR 2.16 95% CI 1.57 to 2.97**	HR 2.41 95% CI 0.96 to 6.04	**HR 1.40 95% CI 1.10 to 1.78**	**HR 1.46 95% CI 1.04 to 2.05**	**HR 1.45 95% CI 1.20 to 1.75**
Mixed Prevention	**HR 1.61 95% CI 1.40 to 1.85**	HR 1.41 95% CI 0.96 to 2.08	**HR 1.27 95% CI 1.13-1.43**	-	-

*bolded values = statistically significant

It was found that statin discontinuation was associated with higher risk of all-cause mortality compared to continuation in 22 out of the 23 non-randomized studies that reported this outcome. A meta-analysis of nine studies showed that discontinuation was associated with a higher risk of mortality compared to continuation in the overall population, secondary prevention population and mixed prevention populations. A meta-analysis was not conducted for primary prevention as only one of the exclusively primary prevention studies reported all-cause mortality which showed a higher crude 5-year rate (16.0 per 1000 person years for discontinuation compared to 2.6 per 1000 person years for continuation. Statin discontinuation was also found to be associated with a higher risk of cardiovascular mortality in all nine reports that evaluated this outcome. A meta-analysis of five reports showed that discontinuation was associated with higher risk of CV mortality compared to continuation in the overall population but not statistically significant in the secondary or mixed prevention population. CV mortality was only reported in one primary prevention study and was associated with a higher rate of CV mortality in the statin discontinuation group. Twelve reports investigated the effect of statin discontinuation on a composite outcome of MACE. A meta-analysis of eight studies showed that discontinuation with associated with higher risk of MACE in the overall population, primary prevention population, secondary prevention population and the mixed prevention population. All analyses reported looking at the primary outcomes had high degrees of heterogeneity. Lastly, statin discontinuation was associated with increased risk of incidence MI in 12 out of 14 reports and increased risk of stroke in five out of seven studies. Lastly, four reports evaluated revascularization with only one showing statistically significant reduced risk of harm associated with statin discontinuation compared to continuation (HR 0.73, 95% CI -5 to -2). While the analysis suggests an association between statin discontinuation and the risk of *all cause mortality, CV mortality and MACE*, researchers did not evaluate whether statin discontinuation was associated with improved QoL or reduced muscle pain (among other statin-related side effects)).

One RCT that examined statin discontinuation versus continuation in people with a limited life expectancy (between 1 month and 1 year) found there was no significant difference in all-cause mortality at 60 days and no difference in time to CV events over 1 year. The mean drug cost savings per day were $3.37 USD per day for statin discontinued and mean quality of life scores at 20 weeks were higher in the discontinuation group compared with the continuation group (95% CI 0.02 to 0.50).

Meta-analysis results for the age ≥75 years subgroup found that statin discontinuation was associated with a numerically higher rate of all-cause mortality (HR 1.49, 95% CI 0.65 to 3.38, two studies, I^2 = 54%) and MACE (HR 1.26, 95% CI 1.18 to 1.35, four reports, I^2 = 44%) compared to continuation. Additionally, statin discontinuation was associated with a higher risk of MI (HR 1.33, 95% CI 1.21 to 1.47, three reports, I^2 = 0%) and stroke (HR 1.32, 95% CI 1.22 to 1.43, three reports, I^2 = 0%) compared with continuation.

Ongoing Trials

There are currently two on-going trials that are examining statin discontinuation in primary prevention in older adults. The Statins in the Elderly (SITE) trial is investigating the quality-adjusted life years gain and mortality at three years following statin discontinuation versus continuation in patient who were originally prescribed statin therapy for primary prevention.[17] This trial will be conducted as an open-label comparative multi-center randomized trial. This trial will be conducted in two parallel groups in outpatient primary care offices. Participants will meet inclusion criteria if they are ≥75 years of age and being treated with statins as primary prevention for CV events. After randomization of the participants, participants will withdraw treatment of statin medication if they were assigned to the statin-cessation group or continue their statin at the usual dose if they are in the statin-continuation group. The cost-effectiveness of each group will be estimated through the incremental cost per quality-adjusted life years gained as 36 months. In total, the SITE trial is estimated to include 2430 participants.[18]

The Statins in Multimorbid Older Adults without Cardiovascular Disease (STREAM) trial is investigating the impact of statin discontinuation versus continuation on all-cause death and major non-fatal cardiovascular events.[19] This trial will be conducted as a multi-center, randomized non-inferiority trial. Participants will meet inclusion criteria if they are ≥70 years of age, have ≥2 coexistent chronic conditions, and take their statin medication ≥80% of the time before enrollment into the study. Participants will be randomly assigned in a 1:1 ratio to either discontinue or continue statin therapy. Participants will then participate in yearly follow-ups for a mean of 24 months (minimum follow-up period 12 months, maximum follow-up period 48 months). In total, the STREAM trial is expected to include 1800 participants.[20]

Conclusion

Evidence from on RCT suggested that statin discontinuation probably did not have any effect on mortality at 60 days or CV events at 1 year. Data from the non-randomized studies suggested that statin discontinuation might be associated with a relative increase in the risk of all-cause mortality, CV mortality, and the composite of major adverse CV events compared to continuing use of statin medications. Data in the subgroup analyses of ≥75 years were also consistent with the main findings and showed a possible increased risk of adverse outcomes associated with statin discontinuation.

Given the limited evidence, the decision to continue or stop a statin should be considered a preference decision and should be discussed based upon the individual's healthcare goals and treatment preferences. This is consistent with guidelines which suggest that in the absence of compelling data to stop therapy, it is reasonable to continue statins among healthy, independently functioning adults with a longer life expectancy if it aligns with the patients goals of care. They also suggest that older persons with a limited life expectancy or in which medication therapy no longer aligns with goals of care, statin discontinuation may be reasonable.

Statin discontinuation appears to be becoming more and more common in clinical practice, however, findings suggest that statin discontinuation was consistently associated with an increased relative risk of all-cause mortality, CV mortality and CV events in people not necessarily approaching end of life. Findings of this systematic review solidify the need for more RCTs on this topic. Both the SITE and STREAM trial discussed above should address statin prescribing specifically in older adults with high quality evidence. Until more complete findings are available, providers and patients should work congruently to guide-decision making based on findings in this analysis along with patient-specific factors such as patient goals and preference, overall health status, independent functioning and life expectancy.[16]

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