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Efficacy Of Statin Therapy In The Elderly

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ABSTRACT

Statins are one of the most heavily prescribed medications. The 2018 ACC/AHA guidelines support statin therapy for most older adults, but recommendations are less clear for those over 75. The literature was systematically reviewed for evidence of the efficacy of statin treatment in different patient populations. Significant evidence was found supporting a decreasing association between low-density lipoprotein cholesterol (LDL-C) and mortality as well as decreasing statin efficacy with increasing age. The consequences of unnecessary statin therapy can be severe for older adults. Improved methods for evaluating atherosclerotic cardiovascular disease (ASCVD) risk, such as using negative markers to help identify those who may not benefit from statin therapy, should be more widely employed.

INTRODUCTION

Cardiovascular disease, a leading cause of morbidity, accounts for 1 in 3 deaths in U.S. adults. Statin drugs have become a mainstay in the primary prevention and treatment of ASCVD. From 2002 to 2013, statin use among US adults 40 years and older increased by 80%, from 18% of the general population to 28% (39 million individuals). The Medical Expenditure Panel Survey found that statin use for primary prevention in adults 80 years and older increased 4-fold, from 9% in 1999 to 34% in 2012. Recent meta- and post-hoc analyses have attempted to address whether available clinical evidence supports such widespread statin use.

Early statin trials excluded elderly patients, and less evidence exists for the efficacy of statins in this heterogenous clinical group.[1] Statins are associated with adverse musculoskeletal event: myopathy, muscle weakness and pain, arthropathies, and rhabdomyolysis. This is problematic for the elderly, in whom statins can contribute to deconditioning and frailty. The current literature reflects a complex relationship between statin efficacy and patient age. While no randomized control trials (RCTs) have been conducted of patients older than 80 years at baseline, the independent STAREE trial (NCT02099123) is currently assessing high intensity statin therapy in adults 70 and older.[2]

THERAPEUTIC OUTCOMES

RELATION BETWEEN CHOLESTEROL AND CLINICAL OUTCOMES

Plasma LDL-C has been the principal target of cholesterol-lowering therapy for the past three decades, and statins are effective in lowering LDL-C. Data on the relationship between LDL-C and mortality, however, reveal a paradoxical relationship between LDL-C and ASCVD. In 2016, Ravnskov et al. conducted a review of 19 clinical studies involving 68,094 patients 60 years or older. In 16 different cohorts accounting for 92% of participants, an inverse association was found between LDL-C and all-cause mortality. A population study of 269,391 Korean adults over 40 revealed that changes in total cholesterol within a two-year period increased the risk of subsequent all-cause mortality relative to those who maintained levels in the second tertile.[3]

Among the elderly, frailty and poor health status likely contribute to increased risk of death in those with low cholesterol. Low cholesterol can also be a marker of severe diseases such as cancer. In the general population, LDL is not the best ASCVD predictor. LDL-C was dropped from the 2008 Framingham calculator for 10-year ASCVD risk because it did not improve the model fit. LDL-C is a confounded variable, consisting of several subclasses of particles of different sizes and densities. Small-dense LDL and covalently modified lipoprotein(a) are considerably more atherogenic than larger LDL particles. Other blood lipids such as triglycerides, apolipoprotein B, HDL, and remnant cholesterol are now emerging as more useful ASCVD predictors.

STATINS IN PRIMARY PREVENTION

A 2019 meta-analysis by Ponce et al. included 23 RCTs comprising 60,194 patients 65 and over. For primary prevention in those with no history of ASCVD, statins reduced the risk of coronary artery disease [CAD; relative risk (RR): 0.79, 95% CI: 0.68–0.91] and myocardial infarction (MI; RR: 0.45, 95% CI: 0.31–0.66) but not all-cause or cardiovascular mortality (Figure 1).

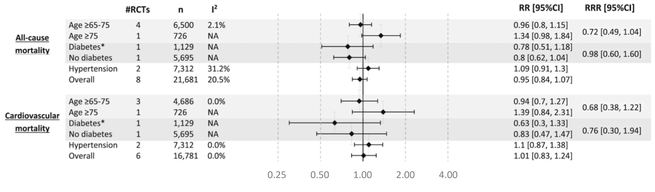

FIGURE 1. Forest plot comparing statin use relative to placebo for primary prevention of ASCVD (RRR: ratio of RRs). *Diabetic patients were 65-75 years. Image reproduced from *J. Clin. Endocrinol. Metab.* 2019; 104:1585.

ELDERLY PATIENTS WITH DIABETES

Ramos et al. conducted a retrospective cohort study of 46,864 participants 75 years and older with no history of ASCVD. To prevent survivor bias, new statin users were selected rather than all statin users. A Cox proportional regression model was used to calculate the hazard ratios of statin use for outcome events. Statins were effective in reducing all-cause mortality [1-year number needed to treat (NNT): 306] and the incidence of ASCVD (NNT: 164) in diabetic patients aged 75–84 (Table 1). The reduction in ASCVD began to lose statistical significance at age 85 and disappeared completely at age 92. The protective effect of statins against all-cause mortality in began to lose significance at age 82 in diabetes patients and disappeared definitively at age 88. Remarkably, statins did not reduce ASCVD or all-cause mortality in patients ≥75 without diabetes.

TABLE 1. Hazard ratios (HR) in new statin users *vs.* non-statin users.*

	Diabetes		No Diabetes	
	75–84 yr N=6,641	**≥ 85 yr** N=1,239	**75–84 yr** N=31,916	**≥ 85 yr** N=7,068
ASCVD (95% Confidence Interval)	0.76 (0.65 - 0.89)	0.82 (0.53 - 1.26)	0.94 (0.86 - 1.04)	1.00 (0.80 - 1.24)
All-Cause Mortality (95% Confidence Interval)	0.84 (0.75 - 0.94)	1.05 (0.86 - 1.28)	0.98 (0.91 - 1.05)	1.00 (0.90 - 1.11)

* Primary prevention, *i.e.*, no history of ASCVD. According to the 2013 ACC/AHA cholesterol guidelines, most of the population was eligible for statin treatment [10% ASCVD risk at 10 years (Ramos 2018)].

34% Seniors over 80 taking a statin for primary prevention

SECONDARY PREVENTION IN THE ELDERLY

The meta-analysis by Ponce et al. also assessed the effect of statins in the treatment of patients diagnosed with clinically significant ASCVD. In contrast to primary prevention, high-certainty evidence was obtained for the use of statins in adults 65 and over for secondary prevention of ASCVD. Compared to placebo, statins significantly decreased the risk of all-cause mortality (RR: 0.80, 95% CI: 0.73–0.89), cardiovascular mortality (RR: 0.68, 95% CI: 0.58–0.79), CAD (RR: 0.68, 95% CI: 0.61–0.77), and myocardial infarction (RR: 0.68, 95% CI: 0.59–0.79). No separate data on subgroups, such as those specifically over 75 years of age or patients with type 2 diabetes, was available from the eight trials reviewed.

CORONARY ARTERY CALCIFICATION

The severity of CAD and plaque formation can be assessed based on the level of coronary artery calcification (CAC) in a computed tomography scan. The CAC score is a robust independent risk factor for ASCVD and all-cause mortality. A meta-analysis was conducted of 49 studies involving 85,000 patients (Sarwar 2009). During a mean follow-up period of 50 months, 0.47% of patients with no CAC suffered a cardiovascular event, compared to 4.1% of patients with CAC, highlighting the metric's negative predictive power.

A retrospective cohort study of 13,644 participants assessed the impact of statins on ASCVD outcomes stratified by baseline CAC score (Mitchell 2018). The median follow-up period was 9.4 years. Compared to those with no CAC, individuals with CAC who took a statin within 5 years of CAC testing had a lower risk of a first major adverse cardiovascular event (MACE). The NNT depended on CAC severity (Table 2). To put this into context, a small longitudinal study of middle-aged adults found that 22% of statin-naïve patients with CAC = 0 were eligible for statins based on the 2013 ACC/AHA guidelines (Pursnani 2015).

TABLE 2. HRs for first MACE in statin-users *vs.* non-statin users.

CAC Score	HR (95% CI)	NNT *
0	1.00 (0.79-1.27)	-
>0	0.76 (0.60-0.95)	-
1–100	0.83 (0.60-1.16)	100
101–400	0.32 (0.21-0.48)	12

*NNT for preventing MACE through 10 years (Mitchell 2018).

TABLE 3. MAJOR STUDIES AND PRINCIPAL FINDINGS

Citation	Study Type	N	Age	Notable Outcomes
STATIN USERS vs. CONTROLS				
Han 2017. *JAMA Intern. Med.* 177:955.	ALLHAT-LLT: open-label RCT; North America	2,867	≥ 65	Increased all-cause mortality [HR = 1.34 (95% CI: 0.98-1.84; *P* = .07)] for patients ≥75 with moderate hyperlipidemia/hypertension taking a moderate intensity statin vs. usual care (primary prevention).
Ponce 2019. *J. Clin. Endocrinol. Metab.* 104:1585.	Meta-analysis, 23 trials	60,194	≥ 65	Statins reduced the risk of all-cause and cardiovascular mortality in secondary but not primary prevention.
Ramos 2018. *BMJ* 362:k3359.	Retrospective cohort, new user design; Spain	46,864	≥ 75	Statins reduced ASCVD and mortality in diabetic patients younger than 82 years. No benefit was observed in non-diabetic patients.
Mitchell 2018. *J. Am. Coll. Cardiol.* 72:3233.	Retrospective cohort	13,644	> 18	Adults who took a statin had a reduced risk of first MACE according to their baseline CAC score. Those with no CAC had no benefit.
IRRESPECTIVE OF STATIN USE				
Ravnskov 2016. *BMJ Open* 6:010401.	Meta-analysis, 30 cohorts	68,094	≥ 60	Inverse association between LDL-C and all-cause mortality for 92% of participants.
Miedema 2019. *JAMA Network Open* 2:e197440.	Multicenter retrospective cohort	22,346	30-49	Patients with CAC > 100 had 10-fold higher CHD mortality (coronary heart disease) than those with CAC = 0.

EVIDENCE-BASED FINDINGS FOR CLINICAL PRACTICE

- 2013 guidelines cite a 28% reduction in RR per mmol LDL-C reduction (39 mg/dL). Meta-analysis of intensive statin therapy found a modest RR of 14% in adults with LDL > 100 (Navarese 2018).
- In adults over 75 with no history of ASCVD or diabetes, statins have not been shown to reduce ASCVD, stroke, or cardiovascular/all-cause mortality.
- In patients with diabetes, statins are protective for primary prevention of ASCVD up to age 85.
- Statins have not been shown to reduce mortality in adults over 65 with no history of ASCVD. Lack of benefit in heart failure may be due to decreased coenzyme Q levels (Alehagen 2015).
- CAC < 10 is a strong negative risk marker that can be used to rule out statin treatment in low-risk individuals.

SPECIAL CONSIDERATIONS

Adverse Musculoskeletal Effects
Muscle weakness can be serious adverse effects in the elderly, potentially leading to life-threatening falls or severe injury.[4] For muscle pain, estimates of the 5-year number needed to harm (NNH) vary from 19 to 47. Statins deplete endogenous levels of coenzyme Q. Ubiquinol supplemention may provide protective benefits.

New-Onset Diabetes
Statins can increase blood glucose and long-term statin use increases the risk of developing diabetes relative to non-users (RR: 1.44, 95% CI: 1.31–1.58).[5] High potency statins had the highest risk (rosuvastatin, RR: = 1.61, 95% CI: 1.30–1.98). 1-year NNH: atorvastatin=172, rosuvastatin=210, simvastatin=363 (Carter 2013).

Cognition
Despite the Food and Drug Administration's 2012 warning about memory loss in statins, meta-analysis of 25 RCTs indicated that statins are not associated with cognitive impairment.[6]

Drug Interactions
Over 36% of older adults take ≥5 prescription medications. Atorvastatin and simvastatin are metabolized by CYP3A4, which metabolizes half of all drugs on the market. St. John's Wort induces CYP3A4, while grapefruit is an inhibitor. Myopathy risk may be increased by drug interactions from polypharmacy as well as comorbidities.

CONCLUSIONS

Statins are often prescribed using a treat-all approach to prevent ASCVD. Despite such widespread use, available evidence does not support the use of statins for primary prevention in very old adults without diabetes. The risk of adverse events is amplified in the elderly population. Healthcare providers could do better to balance the benefits and harms of statin therapy, and treatment recommendations should be individualized for this population. For predicting ASCVD risk, metrics such as CAC are superior to plasma LDL-C and the Framingham risk calculator, which is heavily weighted for age. Future steps in our analysis will involve assessing evidence for the U.S. Preventive Services Task Force recommendation to raise the 10-year risk threshold for treatment from 7.5% to 10% for adults 40–75 with no history of ASCVD.

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For more information, see our publication, "Statin treatment in specific patient groups: Role for improved cardiovascular risk markers," *Journal of Clinical Medicine* 9:3748. DOI: 10.3390/jcm9113748

1. Leya M, Stone NJ. Statin prescribing in the elderly: Special considerations. *Curr. Atheroscler. Rep*. 2017; 19:47.
2. Strandberg TE. Role of statin therapy in primary prevention of cardiovascular disease in elderly patients. *Curr. Atheroscler. Rep*. 2019; 21:28.
3. Jeong S-M et al. Association of change in total cholesterol level with mortality: A population-based study. *PLOS ONE* 2018; 13: e019603.
4. Singh S, et al. Statins for primary prevention in older adults—moving towards evidence-based decision-making. *J. Am. Geriatr. Soc.* 2018; 66:2188.
5. Casula M, et al. Statin use and risk of new-onset diabetes: A meta-analysis of observational studies. *Nutr. Metab. Cardiovasc. Dis.* 2017; 27:396.
6. Ott BR, et al. Do statins impair cognition? A systematic review and meta-analysis of randomized controlled trials. *J. Gen. Intern. Med.* 2015; 30:348.