American Heart Journal Plus: Cardiology Research and Practice 33 (2023) 100315

Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.sciencedirect.com/journal/american-heart-journal-plus-cardiology-research-and-practice

Editorial

Management of dyslipidemia in older adults

Clinicians of different backgrounds disagree about the strength of the evidence concerning the use of statin therapy for the primary prevention of atherosclerotic cardiovascular disease (ASCVD) in otherwise healthy individuals, with some citing the potential for significant side effects, and insignificant impact on total mortality. Sometimes this disagreement is a function of the age of the patient, and therefore the perceived total benefit accrued by the patient.

The fundamental goal of statin use in primary prevention is to reduce both short- and long-term cardiovascular morbidity, including events of significant consequence such as myocardial infarctions and strokes, as well as cardiovascular mortality. While not always fatal, ASCVD events often result in significant disability with high socioeconomic costs, placing a substantial burden on the healthcare system.

In this article, we focus specifically on the use of lipid-lowering therapy in older adults- a heterogenous group of individuals in terms of comorbidities and physical functioning. We discuss how an individualized prevention strategy can be implemented while balancing potential cardiovascular benefits with the risk of adverse effects in this unique patient population.

1. Background

The census of older adults over age 65 is currently 46 million, about 17 % of the US population, and is projected to increase to about 64 million by 2030 [1]. Notably, the number of people over the age of 85 years is expected to increase from 6 million to about 20 million by 2060 [1]. Given these estimates, older adults are undoubtedly an increasingly important focus for prevention in a bid to increase disability-free years and improve quality of life.

Cardiovascular disease continues to be a leading cause of morbidity and mortality among older men and women in the United States [2]. Lipid-lowering therapy is a proven cornerstone in mitigating ASCVD risk, and among older adults, reductions in LDL-cholesterol (LDL-C) have been associated with about a 20–25 % reduction in risk for major atherosclerotic cardiovascular disease per 1 mmol/L of LDL [3,4]. However, while guidelines are clear on thresholds for lipid lowering among adults aged 40–75 years, there is a paucity of data for older adults as most studies have limited elderly participants or excluded them altogether, and much of what is done in clinical practice is extrapolated from a younger demographic [3,5].

2. Summary of evidence

Given the limited number of older adults included in clinical trials, current data for the benefits of statins in the prevention of ASCVD events in older adults is largely limited to post hoc and subgroup analyses of randomized trials and meta-analyses.

The Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) trial was the first major study to evaluate the use of a statin in high-risk older patients. It examined the effects of pravastatin compared to placebo in a cohort of older adults (70–82 years) with and without baseline ASCVD. Over a period of approximately 3 years, pravastatin reduced the incidence of the primary endpoint, which was a composite of coronary death, non-fatal myocardial infarction (MI), and fatal or non-fatal stroke. Notably, there was a 19 % reduction in risk of nonfatal MI and coronary deaths, as well as a 24 % reduction in mortality from coronary disease [6].

Ridker et al. performed a meta-analysis using age-stratified data from two primary prevention statin trials, Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and Heart Outcomes Prevention Evaluation (HOPE-3). They noted that use of rosuvastatin was associated with a 26 % relative risk reduction for the end point of nonfatal MI, nonfatal stroke, or cardiovascular death in subjects >70 years of age initially free of ASCVD [7].

The Copenhagen General Population Study is a large cohort study of over 90,000 individuals aged 20–100 years with no evidence of cardiovascular disease at the time of baseline assessment. In this cohort, there was a direct correlation between elevated LDL-C and the risk of MI and ASCVD that was more prominent among individuals aged 70 years and older, and the estimated number needed to treat to prevent an ASCVD event with a moderate-intensity statin was lowest among older adults >70 years [8]. The benefits of lipid lowering among older adults have also been confirmed in two large meta-analyses which showed reduction in major vascular events among older adults >75 years that was similar to other age groups [4,9].

3. Statin safety

Despite the undeniable efficacy of statins in reducing LDL-C and subsequent ASCVD events in the general adult population, there are often concerns about their side effects, especially among older adults. These include possible cognitive impairment, functional impairment from skeletal muscle symptoms, and diabetes mellitus [10–12].

There is currently no evidence to suggest that statin therapy causes memory loss, cognitive impairment, or dementia [13,14]. In contrast, recent data suggests that statins may actually be associated with improved memory and reduced risk of dementia probably through reduction in cerebrovascular events [15–17].

Statin-associated muscle symptoms are one of the most reported side effects and have been documented across all age groups. Current

https://doi.org/10.1016/j.ahjo.2023.100315
Received 13 July 2023; Accepted 10 August 2023
Available online 12 August 2023

Table 1
Comparison of the ongoing clinical trials among older adults.

Description	STAREE	PREVENTABLE
Full title	A Study of STAtins for Reducing Events in the Elderly (STAREE)	PRagmatic EValuation of evENTs And Benefits of Lipid-lowering in oldEr Adults (PREVENTABLE)
Location	Australia	United States, Puerto Rico
Status	Ongoing, not recruiting	Recruiting
Number of participants	Proposed number: 12,000 Actual number enrolled: 9971	Proposed number: 20,000
Inclusion criteria	Independent community dwelling older adults aged ≥70 years	Independent community dwelling older adults aged ≥75 years, primarily English/Spanish speaking
Exclusion criteria	History of cardiovascular disease, dementia, diabetes, moderate or severe kidney/liver disease, significant illness likely to cause death during the proposed study period, current statin use, contraindications to statin use, long term use of cytochrome P450 3A4 inhibitors	Clinically evident cardiovascular disease, recent heart failure hospitalization, significant disability, dementia, statin intolerance, recent statin use, active liver disease, long term use of daily colchicine, verapamil, diltiazem(>240 mg/day)
Intervention	Atorvastatin 40 mg tablet versus Placebo	Atorvastatin 40 mg tablet versus Placebo
Primary outcomes	Survival free from dementia, persistent physical disability, major cardiovascular event (myocardial infarction, stroke or cardiovascular death)	Patients without new diagnosis of dementia or chronic disability
Secondary outcomes	Fatal cardiovascular events; hospitalizations from any cause; cancer; cognitive impairment, quality of life, cost-effectiveness of statin; stroke; approved need for permanent residential care; dementia; persistent physical disability; all-cause mortality; heart failure; atrial fibrillation; revascularization procedure. New onset diabetes[a]	Cardiovascular disease composite of cardiovascular death, hospitalization for myocardial infarction/unstable angina, heart failure, stroke/TIA, coronary revascularization. Cognitive disability composite of mild cognitive impairment or probable dementia
Masking	Quadruple: Participant, Care Provider, Investigator, Outcomes Assessor	Triple: Participant, Care Provider, Investigator
Follow-up period	6 years	5 years
Sponsor	Monash University	Duke University

[a] Other pre-specified outcome measure.

evidence does not suggest an increased risk of myopathy in older adults compared to the general population; while there may be a slightly increased risk of rhabdomyolysis, the event is quite rare [18,19]. Lastly, statin-associated muscle symptoms are almost always reversible with cessation of the statin.

Statin-induced hyperglycemia appears to be age related but generally occurs among individuals predisposed to develop diabetes or with a history of metabolic syndrome. The Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial showed an increase in diabetes with statin use only among individuals who had a predisposition to the metabolic syndrome and found no increase in diabetes among those with no risk factors. Some other observational and meta-analysis studies however, note a potential link between high dose statin use and development of diabetes [20,21]. In considering the evidence from these studies, it is worth noting that the typical risk for new onset diabetes has been shown to be much less than the expected benefit from reduced ASCVD events [22,23].

Data from several meta-analyses have shown no effect of statin therapy on cancer incidence or death, or non-vascular mortality [4,9]. Importantly, the JUPITER trial also showed a reduction in venous thromboembolism events among individuals on statin therapy- a benefit that might be even more appreciated among older adults [22].

4. Non-statin lipid-lowering medications

While statins have been extensively studied in the general adult population, with some upcoming studies focused on older adults, there are other lipid-lowering medications which have gained increased recognition in the guidelines due to their efficacy both alone and in combination with statin therapy [3]. The Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older (EWTOPIA 75) trial showed a significant reduction in nonfatal cardiovascular events with LDL-C reduction among older adults using ezetimibe monotherapy [24].

The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) showed more lowering of LDL-C and improved outcomes among patients with diabetes on combination therapy with ezetimibe and simvastatin compared to simvastatin and placebo, and showed that lower is better with LDL-C [25]. Additionally, post-hoc analysis of data from the IMPROVE-IT study among older adults >75 years, showed a significant reduction in mortality from ASCVD events with combination lipid therapy compared to statin monotherapy [26].

5. Future perspectives

Two ongoing randomized controlled trials will shed more light on the benefit of intensive lipid-lowering therapy with high intensity statins among older adults (Table 1). The Statin Therapy for Reducing Events in the Elderly (STAREE) trial is a double-blind, placebo-controlled randomized clinical trial that is evaluating the effect of high-intensity statin therapy on two co-primary outcomes including disability-free survival and major cardiovascular events among individuals in Australia aged >70 years with no history of clinical CVD, diabetes or dementia [27].

Similarly, the Pragmatic Evaluation of Events And Benefits of Lipid-lowering in Older Adults (PREVENTABLE) trial is a multi-center, placebo-controlled randomized clinical trial that is evaluating the effect of high-intensity statin on reducing the primary composite of death, dementia, and persistent disability among individuals in the United States aged ≥75 years without clinically evident cardiovascular disease, significant disability, or dementia.

Additionally, the Coronary Artery Calcium in the Pragmatic Evaluation of Events And Benefits of Lipid lowering in the Elderly: CAC PREVENTABLE Ancillary Study will obtain a blinded baseline coronary artery calcium and high sensitivity troponin among participants in the PREVENTABLE trial at enrollment. At trial conclusion, both markers will be used to stratify the participants to determine the heterogenous effects of statins. This study will be particularly elucidating as it will inform the medical community about the clinical utility and accuracy of using these markers to risk stratify individuals and personalize cardiovascular disease risk in the elderly population [28]. Furthermore, the long-term goal is to build a comprehensive online risk prediction tool that will improve on the existing LIFE-CVD model by incorporating these individualized markers [28].

6. Summary of key points and recommendations

In summary, it is not advisable to focus just on longevity or all-cause mortality when it comes to assessing the use of lipid-lowering therapies as part of primary prevention. In particular, the majority of ASCVD events in the elderly are nonfatal events that can have lasting

consequences with significant disability in this population who are already increasingly burdened with chronic disease [29].

An important consideration in the elderly is polypharmacy, the associated risk of drug-drug interactions, and overall life expectancy. While we await more data from RCTs including older adults, it is reasonable to have a risk-benefit decision with each patient, employing available risk prediction tools including consideration of selective use of a coronary artery calcium score to personalize their cardiovascular risk, and integrating screenings for dementia (Mini-Cog), frailty (5-item FRAIL score: Fatigue, Resistance, Ambulation, Illnesses, & Loss of Weight), and overall functional status [3].

A larger proportion of US older adults are active and productive well into their 80's, with the proportion of older adults engaging in employment projected to increase steadily through 2030 [30]. While there is a role for careful weighting of potential harms and benefits prior to initiating statin therapy in those with limited life expectancy [31], overall, older adults should be offered therapies to get them to the recommended lipid thresholds associated with reduced cardiovascular events while bearing in mind their comorbidities. Additionally, given the recommendations for non-statin lipid-lowering therapies to attain more intensive therapy targets among younger adults, it is worth considering if the beneficial effects of these therapies also extend to older adults, and what combination of therapies provide cardiovascular benefit with the least side effect profile.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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