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REVIEW

Cholesterol Lowering in Older Adults: Should We Wait for Further Evidence?

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Abstract

Purpose of Review Current guidelines for primary and secondary prevention of cardiovascular events in adults up to age 75 years are well-established. However, recommendations for lipid-lowering therapies (LLT), particularly for primary prevention, are inconclusive after age 75. In this review, we focus on adults ≥ 75 years to assess low-density lipoprotein-cholesterol (LDL-C) as a marker for predicting atherosclerotic cardiovascular disease (ASCVD) risk, review risk assessment tools, highlight guidelines for LLT, and discuss benefits, risks, and deprescribing strategies.

Recent Findings The relationship between LDL-C and all-cause mortality and cardiovascular outcomes in older adults is complex and confounded. Current ASCVD risk estimators heavily depend on age and lack geriatric-specific variables. Emerging tools may reclassify individuals based on biologic rather than chronologic age, with coronary artery calcium scores gaining popularity. After initiating LLT for primary or secondary prevention, target LDL-C levels for older adults are lacking, and non-statin therapy thresholds remain unknown, relying on evidence from younger populations. Shared decision-making

Key Points

- Few ASCVD risk scores (SCORE2-OP and QRISK) have been validated in older adults after age 84, and all scores heavily weight age and lack considerations for life expectancy and time to benefit.
- LDL-C levels may not be reliable markers for future ASCVD in older adults without prior CVD.
- Limited data on using CAC in older adults suggests that those with a score of zero may be less likely to benefit from LLT and can aid in risk reclassification.
- Despite scarcity of trial evidence among older adults ≥ 75 years, there is some evidence that statins reduce ASCVD, even among high risk patients (dementia and frail).
- It is crucial to evaluate drug-drug interactions before initiating statins due to known interactions with common cardiovascular medications. While statins may increase myalgias and creatinine kinase levels, rates are generally low and do not appear higher among older adults. New onset diabetes mellitus has been reported, especially among those at risk for diabetes, but the rates are low per year and may be less relevant to older adults. No robust evidence exists linking statins to poor cognitive performance.
- Non-statin therapies are second-line agents and have been shown to lower LDL-C and improve cardiovascular outcomes, especially for secondary prevention. However, their role in primary prevention for older adults (≥ 75 years) remains unknown.
- Deprescribing remains challenging, and more evidence is needed to guide the approach (e.g., dose reduction and patient selection) since observational studies suggest a potential increase in ASCVD.

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is crucial, considering therapy's time to benefit, life expectancy, adverse events, and geriatric syndromes. Deprescribing is recommended in end-of-life care but remains unclear in fit or frail older adults.

Summary After an ASCVD event, LLT is appropriate for most older adults, and deprescribing can be considered for those approaching the last months of life. Ongoing trials will guide statin prescription and deprescribing among older adults free of ASCVD. In the interim, for adults ≥ 75 years without a limited life expectancy who are free of ASCVD, an LLT approach that includes both lifestyle and medications, specifically statins, may be considered after shared decision-making.

Keywords Dyslipidemia · Aging · Cardiovascular Diseases · Primary Prevention · Secondary Prevention · Lipid lowering therapy

Introduction

The population aged 80 and older is rapidly growing, expected to reach 426 million worldwide by 2050 [1]. Older adults experience high rates of atherosclerotic cardiovascular disease (ASCVD) [2], with as many as 1/3 men and 1/5 women experiencing coronary artery disease (CAD) and more than 1/10 men and women experiencing strokes [3]. In the context of geriatric syndromes, ASCVD in older adults often results in reduced quality of life, financial burden, functional decline, polypharmacy, hospitalizations, and mortality [2, 4].

Lipid-lowering therapies (LLT) are effective for secondary ASCVD prevention, but uncertainty remains for benefits in primary prevention in older adults [5]. Factors such as time to benefit, limited life expectancy, competing mortality risks, concerns for adverse effects, polypharmacy, drug interactions, and prevalent geriatric syndromes such as frailty and cognitive impairment complicate decision-making [6–8]. Furthermore, a scarcity of age-specific evidence contributes to weak recommendations for LLT in national guidelines for primary prevention [9, 10] and corresponding low use of statins for primary prevention among older adults [11–13], particularly women, underweight individuals, and those with heart failure and dementia [14–16].

In this review we 1) assess the utility of low-density lipoprotein-cholesterol (LDL-C) as a marker for predicting ASCVD risk in older adults; 2) review existing ASCVD risk assessment tools in the context of the geriatric population, 3) highlight current guidelines and recommendations for LLT, with a focus on primary prevention, and 4) discuss benefits and risks of LLT (statin and non-statin therapies) in older adults, including strategies for deprescribing.

Primary Prevention of ASCVD in Older Adults

LDL-C as a Marker for Future ASCVD

For primary prevention, the association between LDL-C levels, cardiovascular events and all-cause mortality among older adults has been mixed [17–20]. In a systematic review of cohort studies with 68,094 participants, LDL-C was inversely associated with all-cause mortality among adults ≥ 60 years, with a U-shaped association with cardiovascular mortality, suggesting low levels of LDL-C may be harmful [21]. A US cohort of 2,667 adults ≥ 75 years free of ASCVD reported no association between LDL-C and ASCVD, even among those with risk factors such as smoking, diabetes, and hypertension [22]. On the other hand, the Copenhagen General Population study included 91,131 individuals followed for a median 7-year period. Among those without prior LLT, CVD, or diabetes, each 1 mmol/L increase in LDL-C was associated with an elevated risk of myocardial infarction (MI) (HR 1.34, 95% CI 1.27–1.41), even among those aged 70–100 years. Moreover, among those aged 70–100, moderate-intensity statins provided the greatest absolute risk reduction in ASCVD events and the lowest number needed to treat [23].

The paradox of low LDL-C and increased mortality in older adults could reflect changes in cholesterol metabolism, terminal decline, catabolic states, subclinical disease markers, or confounding conditions such as frailty and malnutrition [22, 24]. However, the lack of association in some studies could reflect a survivor effect. Long-term observational studies are needed to better understand LDL-C as a risk factor for ASCVD in older adults.

Life-expectancy and Biological Aging

Differentiating between chronologic age (time elapsed since birth) and biologic age (physiologic age) by incorporating geriatric assessments (frailty, cognition, function, mental health, multimorbidity, etc.) allows for better phenotypic differentiation of older adults [25]. For example, median survival for a non-frail ≥ 85-year-old is 7.4 years while a 66 year old with severe frailty has an estimated survival of 4.6 years, highlighting the importance of refining life expectancy beyond chronologic age alone, particularly when considering time to benefit from a given therapy [26]. For primary prevention, at least up to age 75 years, 2.5 years are needed to prevent one MACE for every 100 patients treated with a statin [27]. Online tools, such as ePrognosis.com, can

assist clinicians in estimating time to benefit from treatment to aid decision-making [28].

Considering life expectancy and geriatric syndromes during shared decision-making may refine statin selection for primary prevention. This would ensure patients have sufficient time to accrue benefits while minimizing potential risks in those with limited life expectancy or advanced geriatric conditions.

Risk Score Tools & their Flexibility

Multiple ASCVD risk scores exist, highlighted in Table 1. All current risk scores heavily weight age, making them less relevant for stratifying risk at older ages. Tools such as PREVENT in the US have a maximum age of 79, while the UK QRISK3 has a maximal age of 84 [29]. The SCORE2-OP score was developed in Europe for adults ≥ 70 years and demonstrated improved accuracy stratifying risk in older adults, though it also heavily weights chronologic age [30]. Non-standard risk factors such as carotid intima-media thickness, malignancy, albuminuria, or education level have been considered with some improvement in prediction [31]. Biomarkers such as high-sensitivity C-reactive protein, only incrementally improve CVD risk prediction [32–34]. To date, geriatric domains, such as frailty and cognitive function, have not been incorporated into the existing risk scores despite evidence that frailty is a modifiable risk factor [35]. Future research must consider these factors to help stratify health outcomes in older adults.

Coronary Artery Calcium Score

Coronary artery calcium (CAC) scores can re-stratify ASCVD risk among adults up to age 80 with a low burden of risk factors for whom the benefit of LLT is unclear [36]. While subclinical ASCVD rises with age, the Multi-Ethnic Study of Atherosclerosis found that 16% of adults ≥ 75 years had a CAC score of zero, indicating very low ASCVD risk [39]. In an analysis of 3 pooled US population-based studies including 1,478 participants (mean age 70), adults with a CAC score of zero had a 90% probability of remaining ASCVD event–free over 12 years [40]. Notably, risk is associated with coronary calcium burden; for example, in 1,795 individuals without pre-existing ASCVD (mean age 71), the relative risk of coronary events was 3.1 (95% CI, 1.2 to 7.9) for CAC scores 101–400, 4.6 (95% CI, 1.8 to 11.8) for CAC scores 401–1000, and 8.3 (95% CI, 3.3 to 21.1) for CAC scores > 1000 compared to CAC scores of 0–100 [41]. Additionally, among 2,290 participants in the Atherosclerosis Risk in Communities study aged ≥ 75 years free of ASCVD, CAC ≥ 1000 was associated with an increased risk of impaired physical function, dementia, and hearing loss compared to those with CAC scores of zero [42]. Finally, among 13,644 adults without ASCVD or malignancy followed for 9 years, those with CAC scores of 0 taking statins did not have lower MACE risk (HR: 1.00; 95% CI: 0.79–1.27) compared to no statin [43]. The ongoing CAC-PREVENTABLE (Pragmatic Evaluation of Events And Benefits of Lipid-lowering in Older Adults) study will evaluate the role of CAC in adults aged 75 and older, free of clinical ASCVD to guide statin recommendations [44].

Lipid Lowering Therapy for Primary Prevention in Older Adults

Lifestyle interventions remain the first line strategy, followed by lipid-lowering therapies, including statins, ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and bempedoic acid (Table 2).

Up to age 75, the ACC/AHA guidelines report clear LDL-C targets following LLT for primary prevention, with an approach to intensification including adding non-statin therapy. For adults ≥ 75 years, the guidelines recommend an approach of shared decision-making, highlighting possible benefits while balancing the risk of adverse events and incorporating comorbidities and life expectancy. For adults ≥ 75 years at high or very high cardiovascular risk, ESC/EAS recommends statin use be individualized through shared decision-making, without specific LDL-C cut-offs. Even among older adults with diabetes, the 2023 American Diabetes Association relies on functional and cognitive status when considering LLT for primary prevention [56]. Below, we review the data for these strategies in adults aged ≥ 75 years, recognizing that few have been included in randomized controlled trials.

Lifestyle Interventions

Comprehensive lifestyle modifications, before introducing LLT medications are the cornerstone of primary ASCVD prevention. However, evidence for primary prevention is limited among older adults, especially for those ≥ 75 years. Nevertheless, lifestyle interventions include diet, physical activity, weight management, moderate alcohol intake, and smoking cessation [9, 36]. Dietary interventions demonstrate a consistent pattern of improved cardiovascular outcomes, emphasizing reduced saturated and trans fats and increased fiber intake through fruits, vegetables, whole grains, foods rich in phytosterols, and 2–3 portions of fish per week [9]. The 2021 AHA Scientific Statement notes that DASH/DASH-style diets are particularly effective for LDL-C reduction [57]. Exercise and weight loss are also recommended, targeting 30 min/day or ≥ 150 min/week of moderate-intensity or 75 min/week of vigorous-intensity physical activity. A 2023 meta-analysis of 20 randomized trials demonstrated

Table 1 Current recommendations for older adults from several national guidelines

Guideline, year	Risk score	Age cut-off	Recommendation for older adults ≥ 75 years
American College of Cardiology/American Heart Association (ACC/AHA), 2019 [36, 37]	PCE: US-derived pooled cohort equations	79 years	**Primary prevention** 1. Weak recommendation for statins in people > 75 years old. Rely on clinical assessment and risk discussion) ○ May be reasonable to initiate a moderate intensity statin in adults 75 years or older with an LDL-C of 70–189 mg/dl ○ It may be reasonable to stop statin therapy when functional decline, multimorbidity, frailty, or reduced life expectancy limit the potential benefits 2. Diabetes mellitus ○ Reasonable to continue statin therapy. *Class IIa* ○ Reasonable to initiate statin therapy after a clinician-patient discussion of potential benefits and risks. *Class IIb* **Secondary prevention** 1. Not at very high-risk *Class IIa* *a*. Start a moderate or high intensity statin *b*. Continue a high-intensity statin if it is well tolerated after a clinician-patient discussion of the risks, benefits, and costs associated with statin therapy and a consideration of patient frailty 2. Very high-risk patients: Add ezetimibe for LDL ≥ 70 mg/dL, followed by PCSK9. *Class IIa*
European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) 2019 [9]	SCORE2 (Systematic Coronary Risk Evaluation), SCORE2-OP (Older people)	65–70 years SCORE2-OP (≥ 70 years)	**Primary prevention (> 75 years)** Patients at high or very high cardiovascular risk, statin is to be individualized and shared decision-making. *(Class IIb)* **Secondary prevention** - No special recommendation for older adults; the recommendation is the same for the older (≥ 65 years) and younger patient subset with LLT *(Class I)* **Titration for older adults** - Initiate at low dose and titrate to reach target goal *(Class IIa)* - Initiate at low dose if there is significant renal impairment and/or the potential for drug interactions. *(Class I)*
National Institute for Health and Care Excellence (NICE) [29]	QRISK3	84 years	**Primary prevention** - Regardless of diabetes status and age, atorvastatin 20 mg for cardiovascular risk reduction following QRISK3 assessment (≥ 10%) - ≥ 85 years, consider treatment with atorvastatin 20 mg **Secondary prevention** - No special recommendation according to age **Titration/special population** Before initiation/escalation, consider life expectancy and frailty

Table 1 (continued)

Guideline, year	Risk score	Age cut-off	Recommendation for older adults ≥ 75 years
Canadian Cardiovascular Society (CCS), 2021	Framingham risk score	74 years	**Primary/secondary prevention** - No special recommendation based on age cut-offs. Risk score is limited up to 75 years
U.S. Preventive Services Task Force (USPSTF) [38]	PCE: US-derived pooled cohort equations	75 years	**Primary prevention** Insufficient evidence for primary prevention, *Grade: Insufficient* Selective prescription of statins for adults between the 65 to 75 years of age with ≥ 1 risk factors (dyslipidemia, diabetes, hypertension, or smoking), and a 7.5% to 10% risk of a cardiovascular event in 10 years

significant reductions in total cholesterol, triglycerides, and LDL-C with aerobic and resistance exercise in older adults, with combined training offering the most significant LDL-C reduction [57, 58].

Statins

Evidence for Statins

Evidence for statins for primary ASCVD prevention for adults ≥ 75 years is sparse. In a 2019 meta-analysis from the Cholesterol Treatment Trialists' Collaboration, only 8% of the 186,854 participants across 28 trials were ≥ 75 years at randomization. The overall risk reduction among statin users (both primary and secondary prevention) and the effects on MACE per 1 mmol/L reduction in LDL-C was non-significant for those ≥ 75 years in the primary prevention subgroup (0.92, 95% CI [0.73–1.16]), reflecting the small sample size included [59].

To date, six randomized controlled trials included adults ≥ 75 to test the effect of statins on ASCVD outcomes for primary prevention (Table 2).

1. Medical Research Council/British Heart Foundation (MRC/BHF) Heart Protection Study (2002) randomized 20,546 participants with and without ASCVD to 40 mg simvastatin vs placebo; 5,806 were ≥ 70 years old. There was a significant reduction in all-cause mortality (12.9% vs. 14.7%), CHD death (5.7% vs. 6.9%), MI or coronary death (8.7% vs. 11.8%), first occurrence of any major vascular events (19.8% vs. 25.2%), and stroke rates [45]. However, this study did not report subgroups by age or history of ASCVD.
2. PROSPER (A Prospective Study of Pravastatin in the Elderly at Risk) (2002) enrolled 5,804 adults aged 70–82 years, with and without ASCVD, randomized to pravastatin 40 mg daily or a placebo. There was a significant reduction in the combined end-points of CHD death, MI, and CVA (Hazard Ratio (HR): 0.85, 95% CI 0.74–0.97) and no differences in cognitive function, disability, or stroke. For primary prevention specifically, there was no reduction in all-cause mortality, stroke risk, or composite cardiovascular outcomes in the statin group vs placebo [46].
3. ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm) (2003) included 19,342 hypertensive participants aged 40–79 years (6,570 > 60 years) with at least three other cardiovascular risk factors randomized to atorvastatin 10 mg or placebo. After a median of 3.3 years, the primary endpoint (nonfatal MI and fatal CHD) was significantly lower in the atorvastatin group, HR of 0.64 (95% CI 0.50–0.83,

Table 2 High-quality studies on lipid-lowering therapies among older adults for primary/secondary prevention

Name/Year/Type	Number, Age (years)	Patient characteristics	Inclusion of geriatric syndromes*	Outcomes
Statins				
MRC/BHF Heart Protection Study (2002) [45]	20,546 participants, 5,806 were ≥ 70 years	Primary/Secondary prevention With/without ASCVD with 35% having no CAD	None	40 mg simvastatin vs placebo - All-cause mortality (12.9% vs. 14.7%), - CHD death (5.7% vs. 6.9%), - MI or coronary death (8.7% vs. 11.8%), - First occurrence of any major vascular events (19.8% vs. 25.2%) - CVA (4.3% vs. 5.7%; $p < 0.0001$) No grouping based on age
PROSPER (2002) [46]	5,804 adults aged 70–82 years	Primary/Secondary prevention With and without ASCVD	None	Pravastatin 40 mg daily or a placebo. (Primary/secondary prevention): - Reduction in the combined end-points of CHD death, MI, and CVA (HR: 0.85, 95% CI 0.74–0.97) - No differences in cognitive function, disability, or stroke Exclusively among primary prevention: - No relative risk reduction in all-cause mortality, stroke risk, or composite cardiovascular outcome
ASCOT-LLT (2003)	19,342 adults, ranging 40–79 years. (Mean age: 71 years) 23% > 70 years	Primary prevention HTN and CV risk factors	None	Atorvastatin 10 mg compared to placebo, **Primary endpoint (nonfatal MI and fatal CHD),** (HR 0.64; 95% CI 0.50–0.83, $p = 0.0005$)
JUPITER, 2010 [47]	17,802 participants (5,695 ≥ 70 years)	Primary prevention, CRP ≥ 2 mg/L but without diabetes or uncontrolled HTN	None	Among older adults ≥ 70 years, there was a significant reduction of: - Primary endpoint (MI, CVA, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes), HR: 0.61 (0.46–0.82)), - CVA, HR: 0.55 (0.33–0.93) - Revascularization or hospitalization for unstable angina, HR: 0.51 (0.33–0.80) - No reduction in MI, cardiovascular death, or all-cause mortality
HOPE-3, 2016 [48]	12,705 participants (3,086 ≥ 70 years)	Primary prevention, no known ASCVD but with risk factors such as smoking, elevated blood glucose, and family history of premature coronary disease	None	Rosuvastatin 10 mg versus placebo Among llder adults (mean age: 70 years) randomized to statins, there was a reduction in: - 1st co-primary outcome (cardiovascular causes, nonfatal MI, or nonfatal stroke) by 25% - 2nd coprimary outcome (cardiac arrest, heart failure, and revascularization) by 26%
ALLHAT (2017) Secondary Analysis	1,467 participants (mean age 71.3 years)	Primary prevention Age ≥ 65 years without ASCVD Mean LDL-C: 147.7 mg/dL	None	Pravastatin 40 mg compared to usual care, **All-cause mortality:** - ≥ 65 years: (1.18; 95% CI, 0.97–1.42; $p = 0.09$) - 65–74 years: (1.08; 95% CI, 0.85–1.37; p = 0.55) - ≥ 75 years: (1.34; 95% CI, 0.98–1.84; $p = 0.07$) **No significant differences in CHD rates**

Table 2 (continued)

Name/Year/Type	Number, Age (years)	Patient characteristics	Inclusion of geriatric syndromes*	Outcomes
Secondary analysis ASPREE, 2020 [49]	18,096 participants Mean age: 74.2 years	Primary prevention Australia/U.S ≥ 65 years of age, free of documented CVD, dementia, and disability	Dementia, Persistent physical disability	Statin vs placebo - **Primary outcome** (death, dementia, or persistent physical disability) did not differ significantly (HR, 0.92; 95% CI: 0.83–1.03; $p=0.17$) - **Lower risk for physical disability** (HR, 0.75; 95% CI: 0.58–0.96), but not significant when analyzed for primary prevention - **MACE** (HR, 0.68; 95% CI: 0.57–0.82), - **Fatal CVD** (HR, 0.71; 95% CI: 0.51–0.99), - **MI** (HR, 0.56; 95% CI: 0.43–0.75), - **Stroke** (HR, 0.75; 95% CI: 0.58–0.96)
Secondary prevention				
ALLIANCE, 2009 RCT	2442 patients, 65–78 years	CAD w/wo CKD	None	Atorvastatin targeting LDL-C to ≤ 80 mg/dL compared to usual care **Primary endpoint** (time to first cardiovascular event such as cardiac death, nonfatal MI, resuscitated cardiac arrest, cardiac revascularization, and unstable angina requiring hospitalization) - **Patients with CKD:** reduced RR by 28% (HR, 0.72; 95% CI, 0.54 to 0.97; $P=0.02$) - **Patients without CKD:** reduced RR by 11% (HR, 0.89; 95% CI, 0.74 to 1.07; $P=0.3$)
SAGE, 2007 [50] Secondary analysis	893 patients 65–85 years	CAD (episode of myocardial ischemia that lasted ≥ 3 min during 48-h ambulatory ECG)	None	Atorvastatin 80 mg vs. pravastatin 40 mg **Primary efficacy parameter** (absolute change from baseline in total duration of ischemia at month 12) not significant difference between the treatment groups **Atorvastatin-treated patients** - Greater LDL-C reductions - Trend toward fewer MACE (HR, 0.71; 0.46–1.09), - Greater reduction in all-cause death (HR 0.33; 0.13–0.83;)
Gencer et al., 2020 [7] Systematic review and meta-analysis	244,090 patients from 29 trials 21,492 (8.8%) ≥ 75 years	Primary/Secondary prevention, Adults receiving any: statin, ezetimibe, evolocumab, and alirocumab	None	LDL-C lowering significantly reduced the risk of: - **Major vascular events** per 1 mmol/L reduction in LDL-C (0.74; 0.61–0.89) - **Cardiovascular death** (0.85; 0.74–0.98), - **MI** (0.80; 0.71–0.90), - **stroke** (0.73; 0.61–0.87), - **Coronary revascularization** (0.80; 0.66–0.96) No difference in cancer rates For non-statin LLT: No differences in hemorrhagic stroke, new onset DM or neurocognitive adverse event
IMPROVE-IT 2019 [51] Secondary analysis	5173 participants 65–74 years old: 28.5% ≥ 75 years: 2798 (15.4%)	Post ACS	None	Simvastatin-ezetimibe vs. simvastatin-placebo **- Primary Endpoint Rates:** - < 65 years: 0.9% (HR: 0.97; 95% CI: 0.90–1.05) - 65–74 years: 0.8% (HR: 0.96; 95% CI: 0.87–1.06) - ≥ 75 years: 8.7% absolute risk reduction (HR: 0.80; 95% CI: 0.70–0.90) - No differences in the rate of adverse events

Table 2 (continued)

Name/Year/Type	Number, Age (years)	Patient characteristics	Inclusion of geriatric syndromes*	Outcomes
Post-hoc analysis of the RACING [52]	574 (15.2%) aged ≥ 75 years from the original cohort	MI, ACS, PCI, CABG, arterial revascularization procedures, CVA or PAD	None	Ezetimibe with moderate-intensity statin vs high-intensity statin Lower rates of intolerance-related drug discontinuation or dose reduction among patients aged ≥ 75 years (2.3% vs. 7.2%; $P = 0.010$), but with no reduction in cardiovascular events
FOURIER [53]	40 and 85 years	History of ASCVD MI: 81.1% CVA: 19.4% PAD: 13.2% 69.3% on high-intensity statin	None	Evolocumab vs Placebo Reduction in primary endpoints (cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization), HR of 0.85 (0.76–0.95)
ORION 9, 10, and 11 [54]	< 75 years, or ≥ 75 years, with 492 (13.4%) ≥ 75 years	Among older adults (≥ 75 year) Stage 3 CKD (31.2%), HTN (88.1%) and DM (38.0%)	None	Percentage change in LDL-C with inclisiran was similar across all ages, with 51.0% among ≥ 75 years at day 510
ODYSSEY OUTCOMES (2020) [55] RCT	18,924 adults ≥ 75 years: 1007 (5.3%) ≥ 85 years: 42 (0.2%)	Post ACS, with LDL-C > 70 mg/dL despite high intensity statin/max tolerated		**MACE dichotomized by age,** $P_{interaction} = 0.19$ - ≥ 75 years: HR 0.85 (95% CI 0.64–1.13) - < 75 years: HR 0.85 (95% CI 0.78–0.93) **NNT for MACE at 3 years:** - Age 45 years: NNT = 43 (95% CI 25–186) - Age 75 years: NNT = 26 (95% CI 15–97) - Age 85 years: NNT = 12 (95% CI 6–81)

*Inclusion of geriatric syndromes defined as reporting geriatric syndromes in the outcomes, which includes cognitive impairment, falls, polypharmacy, frailty, falls, functional independence

Cerebrovascular Accident (CVA); Major Adverse Cardiovascular Events (MACE); Percutaneous Coronary Intervention (PCI); Coronary Artery Bypass Grafting (CABG); Number Needed to Treat (NNT); Randomized Controlled Trial (RCT); Acute Coronary Syndrome (ACS); Low-Density Lipoprotein Cholesterol (LDL-C); Chronic Kidney Disease (CKD); Diabetes Mellitus (DM); Hypertension (HTN); Hazard ratio (HR); Atherosclerotic Cardiovascular Disease (ASCVD); Peripheral Artery Disease (PAD); Electrocardiogram (ECG); United States (U.S.); Cardiovascular Disease (CVD); Coronary Heart Disease (CHD); C-reactive Protein (CRP)

Aggressive Lipid-Lowering Initiates Abates New Cardiac Events (ALLIANCE); Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial - Lipid-Lowering Trial (ALLHAT-LLT); Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA); ASPirin in Reducing Events in the Elderly (ASPREE); A Prospective Study of Pravastatin in the Elderly at Risk (PROSPER); Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY); Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER); Heart Outcomes Prevention Evaluation (HOPE-3); Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT); Justification for the Use of Statins in Primary Prevention (JUPITER); Medical Research Council/British Heart Foundation (MRC/BHF) Heart Protection Study; Randomized Comparison of Routine Angiography Versus Initial Conservative Treatment in Elderly Patients With Non-ST Elevation Myocardial Infarction (RACING); Study Assessing Goals in the Elderly (SAGE)

$p = 0.0005$), as was fatal and non-fatal stroke [60] Importantly, among all participants > 60 years, HR for the primary endpoint was 0.64 (0.47–0.86) $p = 0.0027$.

4. JUPITER (Justification for the Use of Statins in Primary Prevention) enrolled 17,802 participants (5,695 ≥ 70 years) free of ASCVD or risk factors with elevated high-sensitivity C-reactive protein > 2.0 mg/L randomized to rosuvastatin 20 mg. After a median follow-up of 1.9 years, and among older adults ≥ 70 years, there was a significant reduction for primary endpoint (MI, CVA, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes) (0.61 (0.46–0.82)), CVA (0.55 (0.33–0.93)), revascularization or hospitalization for unstable angina (0.51 (0.33–0.80)), but not MI, cardiovascular death, or all-cause mortality [47].
5. HOPE-3 (Heart Outcomes Prevention Evaluation) randomized 12,705 participants (3,086 ≥ 70 years) with no known ASCVD but with risk factors such as smoking, elevated blood glucose, and a family history of premature coronary disease to rosuvastatin 10 mg versus placebo. In sub-group analysis, among older adults (mean age 70 years), there was a reduction in co-primary outcome (cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) by 25%. Furthermore, the second coprimary outcome (cardiac arrest, heart failure, and revascularization) was reduced by 26% [48].

   When the JUPITER and HOPE-3 were meta-analyzed together to focus on adults ≥70 years, there was a 26% relative risk reduction in endpoints of nonfatal MI, nonfatal CVA, or cardiovascular death (HR, 0.74; 0.61-0.91) for rosuvastatin 10-20mg vs placebo [61].
6. ALLHAT-LLT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial—Lipid-Lowering Trial) trial randomized 10,355 participants with hypertension and one additional ASCVD risk factor to pravastatin 40 mg vs placebo. In a subgroup analysis focused on 1,467 participants ≥ 65 years (mean age: 71) stratified by age (65–74 y and ≥ 75 y), there was no significant benefit for ASCVD outcomes or mortality in both age groups [62].

Given the limited trial data, observational studies using real-world data have been conducted to examine the role of statins in older adults. A recent target trial emulation study using electronic health records and propensity score matching (1:1 initiators and non-initiators; 42,680 matched patients aged 75 to 84 years) evaluated the risk/benefit of statins among older adults (≥ 75 years) with no known ASCVD in Hong Kong. Statins use was associated with reduced cardiovascular events (intention-to-treat analysis: HR 0.94 [CI, 0.90–0.98] and a 5-year standardized absolute risk reduction of 1.20% [CI, 0.57%-1.82%] in the 75–84 year group) and lower risk of all-cause mortality, even among the very old group (≥ 85 years), without an increase in adverse events [63]. A 2021 systematic review and meta-analysis of 10 observational studies (n = 815,667) found that using statin among adults ≥ 65 years for primary prevention was associated with reduced all-cause mortality, CVD death, and CVA, but not MI. However, the association with reduced all-cause mortality was not evident in the absence of diabetes [64]. Furthermore, among 326,981 US veterans ≥ 75 years with no known ASCVD, new statin use was associated with a 20% lower risk of death from any cause and an 8% lower risk of an ASCVD event [65]. The protective association of statins extended to high-risk populations, such as those with dementia, frailty, and even those over the age of 90 years [66, 67, 68]. These observational studies have to be interpreted with caution due to multiple limitations and cannot be considered causal. A few of these limitations revolve around the variability in LDL-C measurements, residual risk, and adherence. There is variability in LDL-C measurements such as non-protocol driven time of measurement, whether initial or repeat. Another limitation includes baseline differences among participants. Third, there may be residual risk, including unmeasured confounders, population heterogeneity, and incomplete risk factor assessment or control, which may obscure residual cardiovascular risk after lowering LDL-C. Finally, adherence to therapy in observational studies is often unknown. For example, in patients with cognitive impairment, adherence rates might be lower than those with normal cognition, impacting the observed clinical outcomes between LLT, LDL-C levels, and cardiovascular outcomes.

The exclusion of older adults and those with geriatric syndromes from clinical trials has resulted in limited data on the efficacy and safety of statins for primary prevention in this population. Importantly, this lack of evidence does not imply benefit or harm but highlights the need for further research. Observational data suggest that older adults are at high risk for ASCVD events and might benefit the most from preventive interventions, supported by the JUPITER and HOPE-3 meta-analysis. However, few individuals over age 75 were included. Therefore, rather than a 'whole or none' approach, a more tempered risk-based approach may be the preferred method for using statins as primary prevention among high-risk older adults while balancing the risk of adverse events.

Nevertheless, older adults are less likely to receive optimal statin intensity, have low tolerance, and adherence remains suboptimal, with rates as low as 45% in one year (in those aged ≥ 65 years who initiated statin therapy). These challenges highlight the complexities of statin use in this age group [69, 70].

Challenges with Statins

Drug-Drug Interactions

Commonly reported drug/drug interactions have been reported with statins and cardiovascular medications, including antiarrhythmics (amiodarone), blood pressure, and rate control medications (calcium channel blockers), antiplatelets, anticoagulants [71]. Most interactions are seen with statins that exhibit CYP3A4 metabolism. The interactions are of importance since the prevalence of atrial fibrillation increases with aging, requiring rate and rhythm control in addition to anticoagulation [72]. Therefore, this raises the importance of utilizing non-statin LLT, such as ezetimibe, which may lower the risk of drug-drug interactions [73–75].

Adverse Events

Muscle-related (myopathy, rhabdomyolysis, elevated creatine kinase, skeletal muscle dysfunction), functional dependence, diabetes mellitus, and cognitive impairment are the most commonly reported events with statins [6]. However, not all adverse events have been well replicated in studies.

1- Muscle-related adverse events: In a meta-analysis from Cholesterol Treatment Trialists' Collaboration, (n = 154,664) with a mean age of 63 years, with close to 50% receiving statin for primary prevention, there was a small excess risk of muscle symptoms (absolute excess rate of 11 events per 1000 person-years) with statins. However, when analyzed by age (≥ 75 years), the rate ratio for any muscle pain or weakness was 1.04 (0.95–1.13) vs placebo. Additionally, after 1 year, there was no significant excess in first reports of muscle pain or weakness [76]. Furthermore, in older adults (> 75 years) from the Provider Assessment of Lipid Management (PALM) Registry, older individuals were less likely to report any adverse symptoms (41.3% vs 46.6%; $P = 0.003$) or myalgias specifically (27.3% vs 33.3%; $P < 0.001$) [77]. Another phenomenon related to myalgia is the nocebo effect, or an individual's awareness and concerns of an adverse effect may have a significant impact on their expectations and lead to a negative outcome [78]. In the SAMSON trial (Self-Assessment Method for Statin Side-effects Or Nocebo), randomized participants were given a 12-month prescription of 20 mg of atorvastatin, 4 placebo, and 4 empty. Although statin and placebo prescriptions had higher mean symptom scores, they were not statistically significant [79]. In summary, the impact of statin-associated muscle symptoms in older adults remains unclear, however a strategy of rechallenging a statin, either at a lower dose or another statin, could be considered when the decision is made to pursue treatment.

2- Cognitive function: Despite the 2012 black box warning from the U.S. Food and Drug Administration for possible adverse effects of statins on cognitive function, there is no evidence that statins or very low LDL-C levels lead to cognitive impairment [80]. A systematic review and meta-analysis of 57 observational studies of statins reported a decreased risk of any dementia [OR 0.80 (CI 0.75–0.86)] and Alzheimer's dementia [OR 0.68 (CI 0.56–0.81)] with high potency statins associated with higher risk reduction vs low potency statins [81]. High quality evidence from randomized trials does not support the association between statins or lowering LDL-C levels and adverse cognitive events or worsening cognitive test scores, events with potent agents such as PCSK9 inhibitors, and the benefit with ASCVD seems to overweight the observational evidence of cognitive impairment [82].

3- Diabetes Mellitus: Multiple studies have reported an increased risk of new-onset diabetes. In a Cholesterol Treatment Trialists' Collaboration meta-analysis, low-intensity or moderate-intensity statins vs. placebo resulted in a 10% relative increase in new-onset diabetes, with an absolute excess of 0.12% (95% CI 0.04–0.20) during each year of treatment, mainly among those with pre-diabetes [83]. When extrapolating to older adults, given the incidence risk is 0.12% per year, the risk of starting a statin at age 75 may be less of a concern than younger adults. Nevertheless, among statins, pravastatin was associated with the lowest risk for new-onset diabetes mellitus, while rosuvastatin carried the highest risk [84].

Non-statin Therapies for Primary Prevention

No specific guidelines for non-statin therapy in primary prevention exist for older adults (≥ 75 years) due to the lack of evidence [37]. Despite the release of the 2022 ACC Expert Consensus Decision Pathway on the Role of Non-statin Therapies, relevant cut-offs for this age group (≥ 75 years) are not defined due to the lack of data. In general, non-statin therapies are reserved for secondary prevention in patients who fail to achieve established LDL-C goals or for individuals with diabetes or elevated risk scores who fail to reach target LDL-C levels according to their risk scores despite the maximally tolerated statin dose.

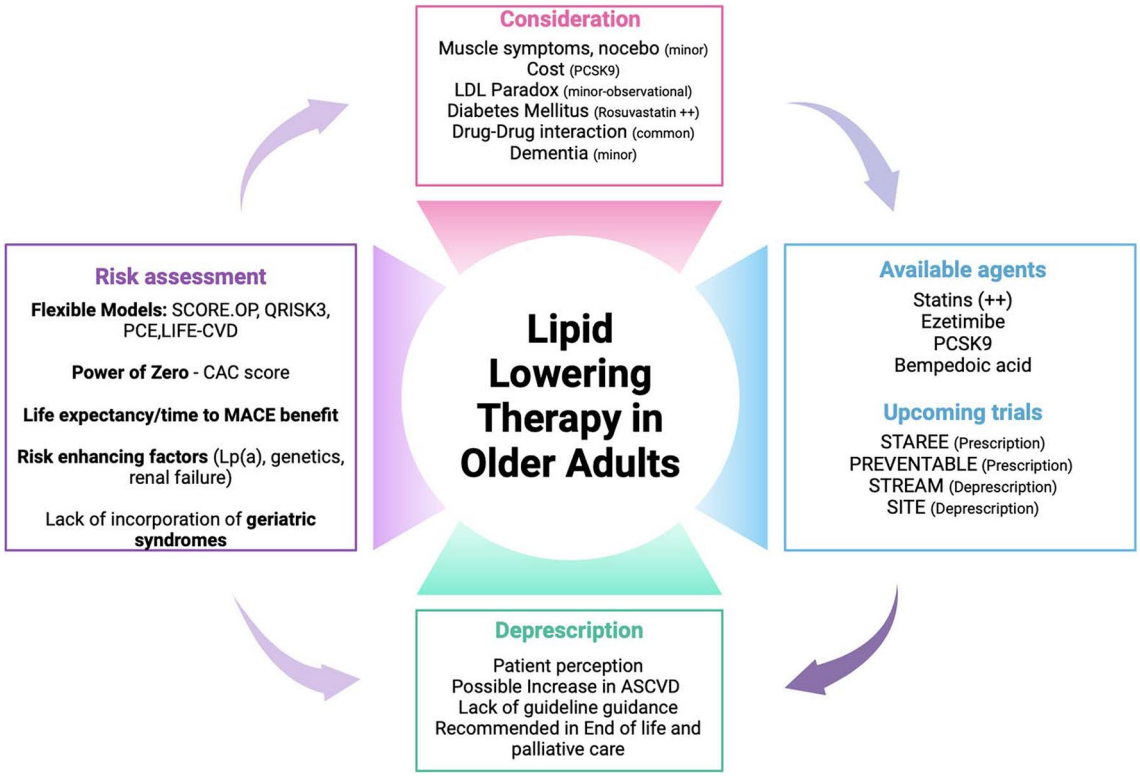

Fig. 1 Central illustration

Ezetimibe

Evidence suggests adding non-statin LLT benefits older adults by reducing adverse events from higher statin doses, but most trials focused on secondary prevention or those under 75. In the EWTOPIA 75 (Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older) [85], ezetimibe reduced the incidence of the primary outcome (sudden cardiac death, MI, coronary revascularization, or stroke and reduced cardiac events) (HR, 0.66; 95% CI, 0.50–0.86; $P = 0.002$) when prescribed for primary prevention. No differences were seen in the incidence of stroke, all-cause mortality, or adverse events. However, there were limitations related to design (open-label, early termination, and follow-up).

Proprotein Convertase Subtilisin/Kexin 9 (PCSK9)

PCSK9 increases LDL-receptor degradation, consequently reducing LDL-receptors and thus lowering LDL clearance from the circulation. PCSK9 inhibitors have been of growing use, effectively lowering LDL and apoB-lipoproteins by inhibiting the above mechanism. Multiple sites of action exist: (1) free plasma PCSK9 (alirocumab and evolocumab) and (2) small interfering RNA-altering the transcription of PCSK9 (Inclisiran) [86]. Most evidence for PCSK9 inhibitors and inclisiran in older adults comes from trials on secondary prevention rather than primary prevention [53, 55].

Bempedoic Acid

Works through adenosine triphosphate–citrate lyase inhibition, an earlier step in cholesterol synthesis than HMG-CoA reductase [87]. While it effectively reduces cholesterol levels and cardiovascular events, its use among older adults, especially those over 75, remains limited due to scarce evidence. The CLEAR (Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen Outcomes) trial randomized patients 18 to 85 years of age (mean age: 65.5 ± 9.0 years, with more than $50\% \geq 65$ and $15\% \geq 75$ years) for primary/secondary prevention to bempedoic acid vs. placebo showed a reduction in cardiovascular events with bempedoic acid, particularly benefiting people with diabetes. However, it did not significantly impact stroke or overall mortality [88, 89]. Adverse effects, including liver enzyme elevation, muscle-related symptoms, and tendon disorders, were more common in older adults, making the role of bempedoic acid unclear for older adults [90].

Secondary Prevention of ASCVD in Older Adults

The use of LLT (statin or non-statin) for LDL-C reduction among older adults following ASCVD has been well studied and supported in national guidelines (Table 2).

LDL-C Target Levels and Risk Scores

Similar to primary prevention, LDL-C targets are not specific to adults ≥ 75 years. According to ACC/AHA guidelines, among very high-risk adults with established ASCVD, clinicians should target an LDL-C reduction by ≥ 50% and LDL-C < 55 mg/dL, a high-intensity statin is recommended, while adding a non-statin (ezetimibe, PCSK9, bempedoic acid or Inclisiran) following LDL-C target failure. In contrast, LDL-C target is < 70 mg/dL for those not at very high risk. Specifically for adults ≥ 75 years, it is reasonable to resume moderate-high intensity statin if well tolerated and to individualize therapy when planning to initiate. The ESC/EAS recommends treating older adults (≥ 65 years) similarly to younger patients, adding a non-statin therapy when LDL-C ≥ 55 mg/dL despite maximally tolerated statin dosage. (Class I). However, they advise starting with a low dose and titrating up to reach LDL-C goals, particularly in the presence of renal impairment and drug-drug interactions.

Evidence on Lipid Lowering (Statin and Non-statin)

This reflects evidence from high-quality studies, such as a systematic review and meta-analysis of 29 randomized controlled trials for primary/secondary prevention (24 trials from the Cholesterol Treatment Trialists' Collaboration meta-analysis plus five individual trials). LDL-C lowering significantly reduced the risk of major vascular events in older patients by 26% per 1 mmol/L reduction in LDL-C (RR, 0.74; 95% CI 0.61–0.89). Other endpoints showing benefit included cardiovascular death (15% per 1 mmol/L reduction), MI, 20%, stroke by 27% (higher benefit with non-statin), and coronary revascularization by 20%, but no impact on all-cause death [7]. Importantly, irrespective of age, reduction in major vascular events was similar among those with prior ASCVD [59]. Several trials from non-statin LLT yielded positive results in reducing cardiovascular endpoints among older adults reduction in the primary endpoint including cardiovascular death, major coronary events, and stroke, and reduction in statin intolerance when combined with ezetimibe [51, 52, 55]. Medications like inclisiran offer several advantages that may be beneficial for older adults with polypharmacy and cognitive impairment. First, its extended dosing interval every six months may reduce the medication burden. Second, subcutaneous injection by a healthcare professional simplifies administration and allows for adherence monitoring, which can be a challenge for this population [37].

Nevertheless, despite the proven benefit of LLT for secondary prevention, older adults still face a pattern of underprescription. In a multicenter retrospective cohort study from 14 commercial health plans geographically dispersed across the U.S. of older adults (≥ 75 years) with ASCVD, less than 50% were on statins, and very few received non-statin therapies (eg, ezetimibe) [8].

Deprescribing

Physicians caring for older adults often face the question of deprescribing. However, only 18 of 33 guidelines include recommendations for discontinuing statins, primarily due to side effects, with only three explicitly addressing older adults with poor health status [91]. Discontinuation of LLT therapy should be patient-centered, considering life expectancy, risk of harm, functional status, frailty, and ASCVD risk-enhancing factors. Observational studies show an increased risk of ASCVD following statin discontinuation, such as in a Danish study involving 67,418 adults aged ≥ 75 years on long-term statin treatment. This study found that discontinuation led to an adjusted HR of 1.32 (95% CI, 1.18–1.48), indicating one excess MACE per 112 persons who discontinued statins yearly. Other studies also noted a similar trend for primary prevention, with higher MACE associated with discontinuation [92, 93].

In contrast, a palliative care randomized trial of 189 adults, mean age of 74 years, with and without ASCVD and a life expectancy of less than one year, found no significant difference in 60-day mortality rates after statin discontinuation. However, these patients experienced a higher quality of life, as assessed by the McGill Quality of Life Questionnaire, particularly in the support domain. It is important to note that these findings apply specifically to a unique palliative population and may not be relevant to older adults with a life expectancy exceeding one year and who are free from cancer. Additionally, the study was unblinded and included more patients with cognitive impairment in the discontinuation arm, which could have influenced the outcomes, especially quality of life measures [94]. During end-of-life care, the ADA recommends reducing intensity and withdrawing LLT [56].

Two trials are expected to improve the knowledge of statin deprescription among older adults. The SITE (Statins In The Elderly) trial, an open-label randomized trial of older adults ≥ 75 years old investigating the quality-adjusted life years gained and mortality at 3 years following statin discontinuation, was initially prescribed for primary prevention [95]. STREAM (Statins in Multimorbid Older Adults Without Cardiovascular Disease) in Switzerland will randomly assign participants to

continuation/discontinuation of statins prescribed for primary prevention. The primary outcome of composite endpoint of all-cause death and major non-fatal cardiovascular events (non-fatal myocardial infarction non-fatal ischemic stroke, and with secondary outcomes encompassing falls, strength, and quality of life changes [NCT05178420].

Conclusion/Future Directions

The question "Cholesterol Lowering in Older Adults: Should We Wait for Further Evidence?" presents a complex and ongoing challenge, particularly for primary prevention. While comprehensive evidence on the efficacy and safety of LLT is limited, available data (largely observational and from secondary analyses) increasingly suggests benefits for high-risk older adults, including those who are frail and without a very limited life expectancy (< 1 year).

Following a comprehensive cardiovascular risk assessment, patient-centered decisions should incorporate patient priorities and preferences while considering potential adverse effects and the complexities of geriatric care (functional status, cognitive status, polypharmacy) and competing mortality risks. Additionally, utilizing noninvasive assessments like CAC scoring can be considered to evaluate biological age beyond chronological age, potentially reclassifying patients with intermediate scores or those hesitant about therapy.

The ultimate goal for patients and their clinicians is to optimize healthy longevity while enhancing the quality of life, ideally through the maintenance of independence and cognitive function. Upcoming trials will refine the selection of ideal older adults for LLT. In the interim, for adults aged 75 and older without a life limiting illness, consideration of LLT for prevention of both ASCVD events and mortality can be included as part of a larger conversation of healthy aging (Fig. 1).

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