

Aspirin and statin therapy for primary prevention of cardiovascular disease in older adults

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ABSTRACT

The value of primary preventative therapies for cardiovascular disease (CVD) in older adults (age ≥ 75 years) is less certain than in younger patients. There is a lack of quality evidence in older adults due to underenrolment in pivotal trials. While aspirin is no longer recommended for routine use in primary prevention of CVD in older adults, statins may be efficacious. However, it is unclear which patient subgroups may benefit most, and guidelines differ between expert panels. Three relevant geriatric conditions (cognitive impairment, functional impairment and polypharmacy) may influence therapeutic decision making; for example, baseline frailty may affect statin efficacy, and some have advocated for deprescription in this scenario. Evidence regarding statins and incident functional decline are mixed, and vigilance for adverse effects is important, especially in the setting of polypharmacy. However, aspirin has not been shown to affect incident cognitive or functional decline, and its lack of efficacy extends to patients with baseline cognitive impairment or frailty. Ultimately, the utility of primary preventative therapies for CVD in older adults depends on potential lifetime benefit. Rather than basing treatment decisions on absolute risk alone, consideration of comorbidities, polypharmacy and life expectancy should play a significant role in decision making. Coronary calcium score and new tools for risk stratification validated in older adults that account for the competing risk of death may aid in evaluating potential benefits. Given the complexity of therapeutic decisions in this context, shared decision making provides an important framework.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death and a major cause of functional impairment in older adults.¹ Accordingly, effective primary prevention of CVD in the older adult population could have a significant impact on public health. Several preventive approaches in younger patients can be applied similarly in older adults: for example, the principles of a lifestyle that includes regular exercise, healthy eating and smoking cessation apply across the age spectrum. However, for medication management, there are different considerations in older adults. Historically, these individuals were underenrolled in pivotal clinical trials, leading to a paucity of evidence regarding which subgroups benefit most.² Furthermore, concerns about medication side effects, multimorbidity and medical futility complicate therapeutic decision making.

One target for primary prevention of CVD risk in older adults is hypertension, and recent evidence from the SPRINT (Systolic Blood Pressure Intervention Trial) trial and others has supported more aggressive blood pressure targets in older adults than were previously believed to be beneficial.^{3,4} However, hypertension is an extensive topic (and an area of active debate) that we believe warrants its own review. In the current manuscript, we therefore focus on two other preventive medications, aspirin and lipid-lowering therapy, that have also been actively debated with recent updates to consensus guidelines for older adults. For lipid-lowering therapy, we will focus on statins, which are by far the most extensively studied drug class. We will review evidence regarding the efficacy of each of these therapies and highlight relevant ongoing trials. Additionally, we will discuss common geriatric considerations as they relate to the potential benefits versus harms. Finally, we discuss the use of precision approaches in the older adult population that incorporate both a lifetime benefit approach and shared decision making. While ‘older adults’ generally refers to individuals age ≥ 75 years, when the physiological changes of ageing become much more common, we acknowledge that some have used other definitions (eg, age ≥ 70 years) which we have noted when relevant.

Aspirin for primary prevention in older adults

Aspirin is one of the most widely used medications worldwide. Although its role in secondary prevention of CVD is well established, its role for primary prevention in older adults is questionable.² Prior to 2018, the evidence for aspirin use in primary prevention was derived from subgroup analyses of larger studies (table 1).^{2,5} These data suggested a benefit from aspirin in reducing incident myocardial infarction (MI) and stroke.^{2,5} In 2018, results from three major randomised trials of aspirin for primary prevention (A Study of Cardiovascular Events in Diabetes, Aspirin to Reduce Risk of Initial Vascular Events and Aspirin in Reducing Events in the Elderly) challenged this evidence, with all three finding minimal benefit and significant bleeding risks with aspirin in older adults.⁵ Most notably, the ASPREE trial, a large, randomised controlled trial evaluating aspirin use for primary prevention in healthy older adults (age ≥ 70 years) in Australia and the USA, observed significantly higher all-cause mortality in the aspirin group⁶ and no difference between aspirin and placebo groups in CVD or a composite endpoint of death, dementia or physical



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Table 1 2018 randomised controlled trials for aspirin primary prevention therapy

Name	Population	Age for subgroup analysis	Size*	Outcome measures	Findings†
ARRIVE ⁵	▶ Average CV risk. ▶ No diabetes.	65+ years	5517	1. Time to first occurrence of CV death, MI, unstable angina, stroke or TIA.	1. (HR 1.04; 0.84–1.30)
ASCEND ⁵	▶ Patients with diabetes. ▶ No evidence of CV risk.	70+	3643	1. First serious vascular event (stroke, MI, TIA, or death from any vascular cause).	1. (RR 0.95; 0.81–1.10)
ASPREE ⁵	▶ Healthy older adults. ▶ No CVD, dementia, physical disability or chronic illness limiting life expectancy <5 years.	70+ years (65+ years if black or Hispanic in USA)	19114	1. Composite of death, dementia and persistent disability. 2. All-cause mortality.	1. (HR 1.01; 0.92–1.11) 2. (HR 1.14; 1.01–1.29)

Summary of major randomised controlled trials of aspirin for primary prevention. Results specific to older adults are presented.

*Size and findings refer to specified age group.

†Significant results are bolded.

ARRIVE, Aspirin to Reduce Risk of Initial Vascular Events; ASCEND, A Study of Cardiovascular Events in Diabetes; ASPREE, Aspirin in Reducing Events in the Elderly; CV, cardiovascular; MI, myocardial infarction; TIA, transient ischaemic attack.

disability.⁷ Participants receiving aspirin also experienced significantly increased rates of major haemorrhage.⁷

The findings from the 2018 trials led to a shift in the 2019 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines to recommending against routine aspirin use for primary prevention in adults older than 70 years (table 2).⁸ This shift is in line with other international guidelines recommending against routine aspirin use for primary prevention.⁹ However, the ACC/AHA guidelines acknowledged that more research is needed to identify subgroups of older adults with CVD risk factors that may derive benefit.⁸ Coronary artery calcification may potentially improve the risk/benefit ratio of aspirin, although this has not yet been demonstrated in large trials.¹⁰

Statins for primary prevention in older adults

Evidence regarding statin therapy for primary prevention of CVD in adults older than 75 years is sparse and conflicting (table 3). The PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) trial, the first randomised trial to study statin use specifically in older adults (aged 70–82 years) found no significant benefit for primary prevention with statins compared with placebo for the composite outcome of coronary death, non-fatal MI and fatal or non-fatal stroke.¹¹ Secondary analyses focusing on older adults in primary prevention statin trials have led to conflicting results,^{12–13} and two large meta-analyses found no significant reduction of vascular events with statin use.^{14–15}

Given the paucity of clinical trial data, retrospective cohort studies have been employed to evaluate statin use for primary prevention in older adults (table 3). These analyses have also yielded mixed results, variably showing no protective effect of statins,¹⁶ protective effects of statins for cardiovascular events and/or mortality¹⁷ or differential effects, with statin efficacy limited to patients with diabetes or other modifiable risk factors.^{18–19} Two recent analyses found favourable results, showing reduced cardiovascular and all-cause mortality with statin use.^{20–21} Additionally, in contrast with previous studies suggesting a lack of relationship between low-density lipoprotein (LDL) and CVD risk in older adults, a recent analysis of the Copenhagen General Population Study demonstrated that the oldest age group (70–100 years old) had the highest absolute risk of MI and ASCVD with increased LDL-C and the lowest number needed to treat for MI prevention, thus supporting statin use in this population.²²

However, the reliance on observational studies with unmeasured confounding and underpowered subgroup analyses of clinical trials makes interpretation difficult. Reflecting this

conflicting evidence, primary prevention guidelines in older adults range from a strong recommendation for statin therapy in older adults 75–85 years (National Institute for Health and Care Excellence – UK (NICE-UK)) to a weak IIB recommendation with encouraged discussion of risks for anyone over 75 (European Society of Cardiology/European Atherosclerosis Society 2019, ACC/AHA 2018) (table 2).^{8,23–25} Two ongoing randomised trials, PREVENTABLE and STAREE, will provide more clarity (table 4). PREVENTABLE is a randomised study in the USA comparing atorvastatin versus placebo among community-dwelling adults age 75 years and older to evaluate incident dementia and disability (primary outcomes) and cardiovascular mortality (secondary outcome).²⁶ STAREE is a randomised study comparing atorvastatin and placebo in healthy older adults (70 years and older) without ASCVD in Australia with primary outcome measures of death or development of dementia and major cardiovascular events.²⁷

Considerations specific to older adults

Geriatric syndromes are defined as multifactorial, non-disease-specific conditions that are increasingly common with advancing age. Traditionally, clinical trials have either not measured these syndromes, or they have served as explicit exclusion criteria (eg, cognitive impairment). However, there is increasing recognition that geriatric syndromes are important prognostically for cardiovascular patients and should influence treatment plans.²⁸ Three syndromes that are relevant in the consideration of primary cardiovascular prevention are cognitive impairment, functional impairment and polypharmacy. We discuss each syndrome and its relevance below.

Cognitive impairment

Cognitive impairment is defined as impairment in any domain of normal brain activity (eg, memory, language and judgement), while dementia is defined as cognitive impairment plus impairment in daily function. In practice, baseline cognitive impairment may complicate the decision to initiate preventative therapy due to even more limited evidence in this group than in the general older adult population.²⁹ For aspirin, ASPREE excluded patients with baseline cognitive impairment, and for statins, STAREE and PREVENTABLE will do so as well. For aspirin, one randomised trial in patients with Alzheimer's disease (AD) did not show an effect of aspirin on mortality or dementia progression.²⁹ For statins, while patients with cognitive impairment were excluded from pivotal trials, a retrospective cohort study by Orkaby *et al*²¹ demonstrated that significant reductions in all-cause and

Table 2 Guidelines for primary prevention of cardiovascular disease in older adults

Name and year	Risk calculator	Recommendation for older adults 75+ years	Other comments
Aspirin			
ACC/AHA 2019 Guideline on the Primary Prevention for Cardiovascular Disease ⁸	PCE Not well validated after 79 years of age.	Class III: harm 'Low-dose aspirin (75–100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age'.	'Prophylactic aspirin in primary-prevention adults >70 years of age is potentially harmful and, given the higher risk of bleeding in this age group, difficult to justify for routine use... However, one caveat is that, although routine use is not recommended in these settings, there is also insufficient evidence to comment on whether there may be select circumstances in which physicians might discuss prophylactic aspirin with adults <40 years of age or >70 years of age in the context of other known ASCVD risk factors'.
ESC 2021 European Society of Cardiology ⁹	SCORE Not validated in patients over 65 years	Class III: not recommended 'Antiplatelet therapy is not recommended in individuals with low/moderate CV risk due to the increased risk of major bleeding'. ^a Class IIb: may be considered 'In patients with DM or very high CVD risk, low-dose aspirin may be considered for primary prevention in the absence of clear contraindications'. [*]	'In general, risk factor treatment recommendations are based on categories of CVD risk ('low-to-moderate', 'high', and 'very high'). The cut-off risk levels for these categories are numerically different for various age groups to avoid undertreatment in the young and to avoid overtreatment in older persons. As age is a major driver of CVD risk, but lifelong risk factor treatment benefit is higher in younger people, the risk thresholds for considering treatment are lower for younger people' 'The role of antithrombotic therapy in primary prevention in (very) high-risk individuals remains to be established'.
Statins			
NICE-UK 2014/2016 National Institute for Health and Care Excellence ²⁴	QRISK † Use up to 84 years of age.	Strong recommendation, 'except for people ≥85 years who can consider atorvastatin 20 mg'.	'No/limited evidence exists to validate CV benefits and side effects of LLDs in oldest patients. Yet, the important effect of age on CV risk suggests all older people should be offered a LLD. Take benefits from lifestyle modifications, patient preference, comorbidities, polypharmacy, frailty and life expectancy into account'.
ACC/AHA 2018 Guideline on the Management of Blood Cholesterol ²³	PCE Not well validated after 79 years of age.	Class IIb (weak) recommendation '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'.	'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'. ²¹ '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 CAC score of zero to avoid statin therapy'.
ACC/AHA 2019 Guideline on the Primary Prevention for Cardiovascular Disease ⁸	PCE Not well validated after 79 years of age.	No specific recommendation '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'.	'Coronary artery calcium may even refine ASCVD risk estimates among lower-risk women (<7.5% 10 year risk), younger adults (<45 years of age), and older adults (≥75 years of age), but more data are needed to support its use in these subgroups. A coronary artery calcium score of zero identifies individuals at lower risk of ASCVD events and death over a ≥10 year period who appear to derive little or no benefit from statins for ASCVD risk reduction. Thus, the absence of coronary artery calcium could reclassify a patient downward into a lower risk group in which preventive interventions (eg, statins) could be postponed'.
ESC/EAS 2019 European Society of Cardiology and European Atherosclerosis Society ²⁵	SCORE Not validated in patients over 65 years	Class IIb (weak) recommendation 'Initiation of statin treatment for primary prevention in older people aged >75 may be considered, if at high risk or above'.	

Summary of society guidelines for primary prevention in older adults with respect to statin and aspirin therapies.

*The 2021 ESC guidelines recommendations for antithrombotic therapy do not vary by age.

†All adults 75+ years will be >10% risk using QRISK calculator.

ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; NICE-UK, National Institute for Health and Care Excellence – UK; PCE, pooled cohort equation; SCORE, Systematic Coronary Risk Equation.

cardiovascular mortality with statin therapy extended to patients with baseline dementia. However, baseline cognition may still be relevant in terms of limited life expectancy, potentially rendering preventative therapy futile.

Another relevant question is whether preventative therapies inhibit the onset of cognitive impairment; however, to date, there is no definitive evidence. Early evidence from epidemiological studies suggested a protective effect of aspirin use for the development of dementia,³⁰ although this has not been supported by subsequent research. Recently in the ASPREE trial, there was no difference between aspirin and placebo groups in the development of dementia, mild cognitive impairment, probable AD or cognitive decline.³⁰

Statin therapy has been associated with mixed effects on cognition, but the weight of evidence has found no association between statins and negative cognitive impacts. Initially, a series of case reports and subsequent findings from the JUPITER trial

showed reversible cognitive impairments with statin use, leading to the FDA's label change in 2012 to note possible cognitive side effects.³¹ At the same time, observational studies showed a protective effect of statins on cognition.³¹ However, numerous recent studies have not corroborated either of these findings in older adults, with no associations found between cognition and statin use.³² These inconsistencies may be related to differential effects by age, with older adults less likely to derive any protective benefit on cognition.³³ The STAREE and PREVENTABLE trials will provide more definitive evidence in this area, as they include progression to dementia as key endpoints (table 4).^{26 27}

Functional impairment

Functional impairment generally refers to the inability to perform physical activities necessary for independent living, although some also use the term to refer to other functions (eg,

Table 3 Evidence for statin therapy for primary prevention in older adults

Name and year	Type	Age (years)	Size*	Primary prevention population characteristics	Outcome measures	Findings†
Randomised controlled trials and subgroup analyses						
PROSPER (2002) ¹¹	RCT pravastatin versus usual care	70–82	3239	<ul style="list-style-type: none"> ▶ Elevated risk such as smoking, hypertension or diabetes. ▶ Total cholesterol 4–9 mmol/L. ▶ Triglyceride <6 mmol/L. 	1. Combined endpoint of definite or suspect death from CHD, non-fatal MI, fatal or non-fatal stroke.	1. (HR 0.94; 0.77–1.15).
ALLHAT-LLT Subgroup Analysis (2017) ¹²	Subgroup analysis of RCT pravastatin versus usual care	75+	726	<ul style="list-style-type: none"> ▶ Ambulatory with stage 1 or 2 hypertension and at least one other CHD risk factor. ▶ Fasting LDL 120–189 mg/dL. ▶ Fasting triglyceride <350 mg/dL. 	1. All-cause mortality. 2. CHD events.	1. (HR 1.34; 0.98–1.84; p=0.07). 2. (HR 0.70; 0.43–1.13; p=0.14).
HOPE-3 and JUPITER Subgroup Analysis (2017) ¹³	Meta-analysis of two RCTs rosuvastatin versus usual care	>70	8781	<p>JUPITER</p> <ul style="list-style-type: none"> ▶ No CV disease. ▶ LDL <130 mg/dL, CRP >2 mg/L. <p>HOPE-3:</p> <ul style="list-style-type: none"> ▶ No CV disease. ▶ Intermediate risk (1% annual risk of major CV events). ▶ Must have one additional risk factor.‡ 	1. Non-fatal MI, non-fatal stroke or CV death.	1. (HR 0.74; 0.61–0.91; p=0.0048) 26% RR reduction in statin users.
Meta-analyses						
Cholesterol Treatment Trialists' Collaboration (2018) ¹⁴	Meta-analysis of 28 RCTs	75+	6449	▶ No known vascular disease (MI, coronary heart disease or heart failure).	1. Major vascular events (major coronary events, strokes and revascularisation). 2. Mortality.	1. (RR 0.92; 0.73–1.16). 2. Not reported for 75+ years.
Gencer (2020) ¹⁵	Meta-analysis of 29 trials of lipid-lowering therapy.§	75+	Not provided.‡‡	▶ No established ASCVD at baseline.	1. Major vascular events.	1. (RR 0.61; 0.25–1.51; p=0.29).
Retrospective cohort and case control studies						
Heusch (2018) ¹⁶	Retrospective cohort (SPRINT)	70+	3054	<ul style="list-style-type: none"> ▶ No history of CVD. ▶ 22%–25% 10-year Framingham risk. 	1. Primary composite event rate (MI, ACS, stroke, HF or CV death). 2. Time to composite event.	1. (ARR 0.018; –0.005 to 0.04; p=0.13). 2. (ARR 84.6; –50.7 to 220.0; p=0.22).
Ramos (2018) ¹⁹	Retrospective cohort (Primary Care System Data in Catalan, Spain)	75+	38 557	<ul style="list-style-type: none"> ▶ No history of CVD. ▶ No cancer, dementia, paralysis, dialysis or previous organ transplant. ▶ Not in residential care. 	1. Incidence of ASCVD. 2. All-cause mortality.	In patients without diabetes: 1. (RR 0.98; 0.91–1.05). 2. (RR 0.93; 0.82–1.06). In patients with diabetes:¶ 1. (RR 0.76; 0.65–0.89) . 2. (RR 0.84; 0.75–0.94) .
Jun <i>et al</i> (2019) ¹⁷	Case–control (National Health Insurance Service in Korea)	75+	11 017 cases 55 085 controls	▶ No history of CVD.	1. MI. 2. Stroke. 3. All-cause mortality.	1. (OR 1.12; 0.90–1.41). 2. (OR 0.74; 0.61–0.89)** . 3. (OR 0.73; 0.66–0.81)** .
Bezin <i>et al</i> (2019) ¹⁸	Retrospective cohort (French Health Insurance System Data)	75+	7284	▶ New statin users.	1: ACS or all-cause mortality.	In patients without modifiable risk factors:†† 1. (HR 1.01; 0.86–1.18). In patients with modifiable risk factors:†† 1. (HR 0.93; 0.89–0.96; p<0.01) .
Kim (2020) ²⁰	Retrospective cohort (National Health Insurance Corporation)	75+	1370	<ul style="list-style-type: none"> ▶ New statin users. ▶ Total cholesterol >200 mg/dL. 	1. All-cause mortality. 2. MACE.	In new statin users: 1. (HR 0.83; p=0.04) . 2. (HR 1.24; p=0.003) . In statin users >5 years: 1. (HR 0.76; p=0.01) . 2. (HR 0.88; p=0.36).
Orkaby <i>et al</i> (2020) ²¹	Retrospective cohort (Veteran's Health Administration)	75+	326 981	<ul style="list-style-type: none"> ▶ New statin use. ▶ No history of ASCVD. ▶ 97% men. ▶ Included patients with cancer, dementia or mental illness. 	1. All-cause mortality. 2. CV mortality.	1. (HR 0.75; 0.74–0.76) . 2. (HR 0.80; 0.78–0.81) .

Summary of RCTs, meta-analyses and observational studies evaluating statin therapy for primary prevention in older adults.

*Size, participant characteristics and outcomes are all specific to primary prevention group in the age range specified.

†Significant results are bolded.

‡Must have 1+ of the following: elevated waist-to-hip ratio, history of a low level of high-density lipoprotein cholesterol, current or recent tobacco use, dysglycaemia, family history of premature coronary disease and mild renal dysfunction.

§Lipid-lowering therapies in the primary prevention subgroup included statins and ezetimibe.

¶This effect decreased after age 85 years and disappeared in nonagenarians.

**This effect disappeared for statin users <1 year.

††Modifiable risk factors defined as diabetes or use of antihypertensive drugs, antiplatelet agents or anticoagulants.

‡‡Sample size for primary prevention subgroup not available in published materials.

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; HOPE-3, Heart Outcomes Prevention Evaluate; JUPITER, Justification for Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL, low-density lipoprotein; MACE, major adverse cardiovascular events; MI, myocardial infarction; RCT, randomised controlled trial.

Table 4 Ongoing trials relevant to primary prevention of cardiovascular disease in older adults

Name	Design	Population characteristics	Primary outcomes	Secondary outcomes
PREVENTABLE ²⁶	<ul style="list-style-type: none"> ▶ RCT comparing atorvastatin versus placebo. ▶ 20 000 participants. ▶ 75 years and older. ▶ 5-year follow-up. ▶ End date: July 2026. 	Community-dwelling older adults without clinically evident ASCVD, significant disability or dementia. Major exclusion criteria*: <ul style="list-style-type: none"> ▶ Clinically evidenced CVD. ▶ Hospitalisation for HF in prior 12 months. ▶ Dementia. ▶ Dependence in any Katz Basic ADLs, with the exception of urinary or bowel incontinence. 	<ul style="list-style-type: none"> ▶ New diagnosis of dementia. ▶ Persistent disability. 	<ul style="list-style-type: none"> ▶ CV mortality measured as a composite of CV death, hospitalisation for MI/unstable angina, HF, stroke/TIA or coronary revascularisation. ▶ Cognitive disability measured as a composite of MCI or probable dementia.
STAREE ²⁷	<ul style="list-style-type: none"> ▶ RCT comparing atorvastatin versus placebo. ▶ 18 000 participants. ▶ 70 years and older. ▶ 8-year follow-up. ▶ End date: December 2023. 	Healthy participants 70 and older Major exclusion criteria†: <ul style="list-style-type: none"> ▶ CVD. ▶ Diabetes. ▶ Dementia or 3 MS score <78 on screening. ▶ Total cholesterol >7.5 mmol/L. ▶ Moderate or severe CKD. ▶ Moderate or severe liver disease. ▶ Serious intercurrent illness likely to cause death within the next 5 years. 	<ul style="list-style-type: none"> ▶ Death or development of dementia or development of disability. ▶ Major fatal or non-fatal cardiovascular event. 	<ul style="list-style-type: none"> ▶ Cardiovascular death. ▶ Fatal and non-fatal MI. ▶ Hospitalisations. ▶ New-onset diabetes. ▶ Fatal and non-fatal cancer. ▶ Cognitive decline. ▶ Quality of life. ▶ Cost-effectiveness of statin. ▶ Fatal and non-fatal stroke. ▶ Approved need for permanent residential care. ▶ All-cause dementia. ▶ Frailty/disability.
Statins in the Elderly (SITE) ⁴⁸	<ul style="list-style-type: none"> ▶ RCT of statin continuation versus cessation. ▶ 1230 participants. ▶ 75 years and older. ▶ 36 months follow-up. ▶ End date: December 2022. 	Treated with a statin for at least 1 year for primary prevention. Exclusion: <ul style="list-style-type: none"> ▶ Life prognosis below 6 months. ▶ Dementia. ▶ Familial hypercholesterolaemia. 	<ul style="list-style-type: none"> ▶ Incremental cost per QALY gained. ▶ Overall mortality. 	<ul style="list-style-type: none"> ▶ Quality of life. ▶ Clinical events occurrence. (CV events, diabetes and cognitive disorders).

Summary of ongoing trials relevant to primary prevention in older adults.

*Not all exclusion criteria are listed. More detailed exclusion criteria can be found at: <https://clinicaltrials.gov/ct2/show/NCT04262206> (PREVENTABLE).

†Not all exclusion criteria are listed. More detailed exclusion criteria can be found at: <https://clinicaltrials.gov/ct2/show/NCT02099123> (STAREE).

ADLs, activities of daily living; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure; MCI, mild cognitive impairment; MI, myocardial infarction; PREVENTABLE, Pragmatic Evaluation of Events and Benefits of Lipid-Lowering in Older Adults; QALY, quality-adjusted life year; 3 MS Score, Mini-Mental State Examination; STAREE, A Clinical Trial of Statin Therapy for Reducing Events in the Elderly; TIA, transient ischaemic attack.

cognitive and sensory). Frailty is a related concept that refers to an increased physiological vulnerability to stressors; impaired physical function is an element of the 'frailty phenotype'.³⁴ Function has been increasingly recognised as important in the context of aspirin and statin therapies, largely due to an ageing patient population that places a high priority on preservation of independent living.³⁵

In this context, trials have increasingly included function as an outcome. For example, in the ASPREE trial, participants randomised to receive aspirin for primary prevention showed no difference in disability-free survival, a measure that included physical disability based on ability to perform activities of daily living.³⁶ The ongoing STAREE and PREVENTABLE statin trials are both measuring disability as a primary outcome, and STAREE is also measuring incident frailty.^{26 27}

A specific functional issue familiar to many practicing clinicians is statin-associated muscle symptoms (SAMS), which include patient-reported myalgias, cramps and weakness, potentially impairing daily function.^{2 37} While several recent studies have shown consistent tolerability of statins across age groups,³⁸ SAMS still may prompt medication switching or interval dosing to limit side effects. Beyond SAMS, there is a broader question of whether statins lead to accelerated functional decline over time, although studies have been mixed. Several retrospective studies examining the effects of statins on various measures of function in older adults (including falls, strength and mobility) have not found any association,^{39 40} although others demonstrated

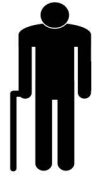
increased falls and impaired balance.^{40 41} These discrepancies likely relate to inconsistent study populations (community dwelling vs long-term care facility based) and differing measures of function.⁴⁰ In this context, vigilance and monitoring for adverse effects, as well as individualised therapy plans, are crucial.³⁹

In older adults with preexisting functional impairment, which is associated with an increased risk of mortality, there is less theoretical benefit of statins for primary prevention given that it takes several years for benefits to accrue. Accordingly, clinicians need to be cautious about initiating statin medications in this setting given the question of clinical futility. While some have called for a clinical trial of primary prevention in functionally impaired older adults to generate additional evidence,⁴² such a trial is difficult to undertake in practice. For example, trials examining function as an outcome (such as PREVENTABLE) cannot enroll patients with functional impairment at baseline.

Polypharmacy

Polypharmacy is common among older adults and is defined as the long-term prescription of five or more medications. Studies have shown that polypharmacy is associated with higher risk of adverse drug reactions as well as reductions in physical and cognitive function.⁴³ Aspirin and statins are common culprits.¹ Given the clinical equipoise about primary preventative therapies in older adults, deprescribing these medications is warranted

Current Paradigm: One Size Fits All



- Limited evidence
- Conflicting guidelines
- Polypharmacy
- 10-year risk paradigm

Novel Paradigm: Precision Medicine



- Consider geriatric conditions
- Consider biomarkers (calcium score)
- Lifetime benefit
- Shared decision-making

Figure 1 A novel paradigm for primary prevention of CVD in older adults. Traditional care is based on limited evidence and does not suit the needs of older adults. We propose a precision medicine approach incorporating geriatric considerations and biomarkers to inform lifetime benefit and guide shared decision making. CVD, cardiovascular disease.

in some situations. However, there is limited guidance on safety and best practices.

While the 2019 ACC/AHA guidelines recommend against aspirin use for primary prevention in older adults,⁸ these guidelines are based on aspirin initiation rather than deprescription.⁴⁴

Aspirin deprescription is not without risk; in 2017, a large, Swedish cohort study evaluating spontaneous aspirin interruption in long-term primary prevention users found a 28% increased risk of cardiovascular events with aspirin discontinuation.⁴⁵ This risk was greater with older age.⁴⁵ In theory,

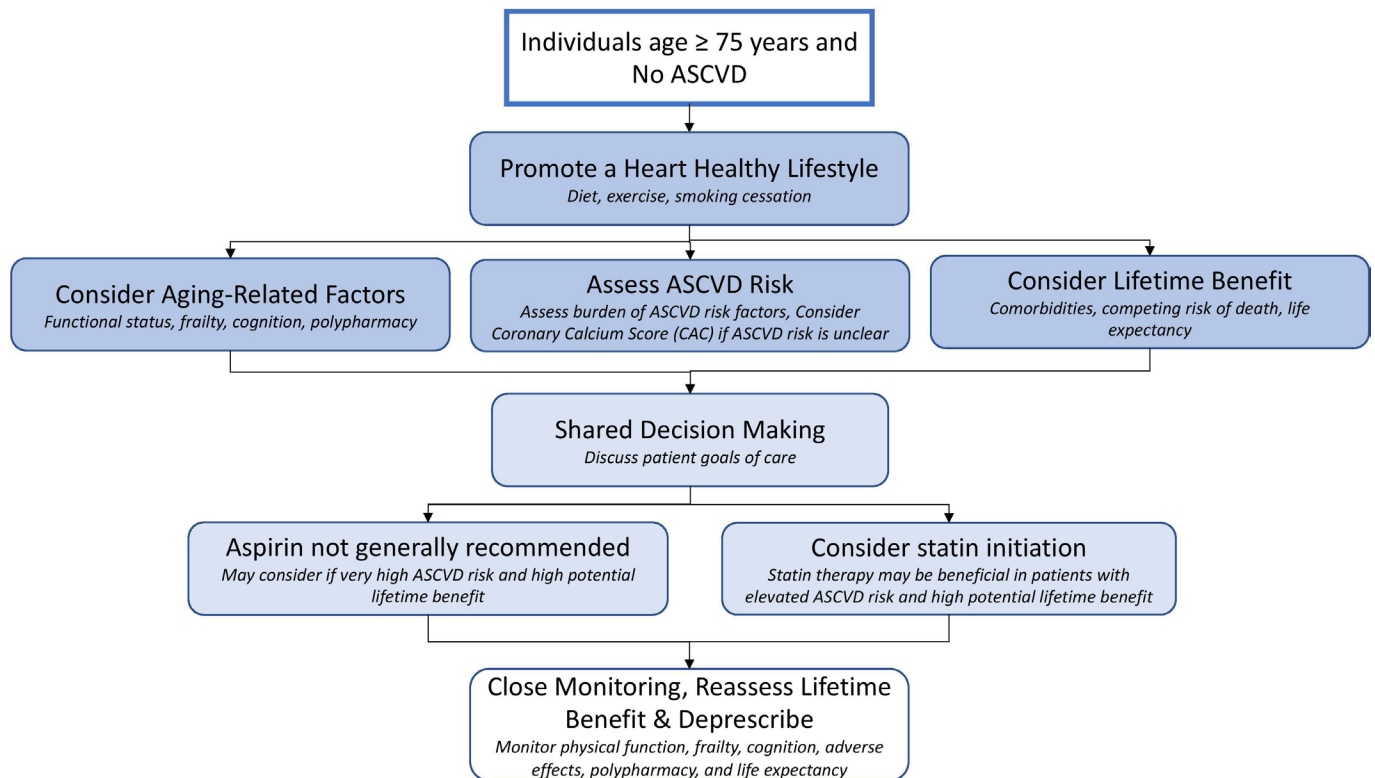


Figure 2 Proposed treatment algorithm for primary prevention of CVD in older adults. In addition to promoting a heart healthy lifestyle and assessing CVD risk, clinicians considering primary prevention of CVD in older adults should consider ageing-related factors and lifetime benefit before initiating preventative therapies. Shared decision making and close monitoring are important in this age group. ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease.

these observational findings could better be elucidated by a randomised clinical trial of aspirin deprescription, which some have advocated for.⁴⁴

The 2018 ACC/AHA guidelines mention that deprescription of statins may be reasonable in the setting of 'functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy'²³; however, no specific guidance is included for the exact timing of deprescribing. The safety of statin discontinuation appears to be situation dependent: while one study observed a 33% increased risk of cardiovascular events after cessation of statins for primary prevention in older adults,⁴⁶ another in patients with limited life expectancies found that statin discontinuation was safe and improved quality of life.⁴⁷ Significant adverse effects or limited life expectancy may be optimal indicators for statin discontinuation³⁷ given the time to clinical benefit of statins (2–3 years) and the safety of statin discontinuation observed in individuals with limited life expectancies.³⁷ The upcoming SITE study (table 4), a randomised controlled trial of statin cessation versus continuation in adults 75 years and older will provide further data regarding the safety and cost benefit of statin discontinuation.⁴⁸

Future directions: moving towards a precision approach

Assessing risk and lifetime benefit

Many guidelines regarding statin therapy in older adults encourage clinicians to consider individual risk. However, current models for risk evaluation have several limitations (figure 1). First, these tools were generally validated in younger populations. Based on age alone, nearly every older adult is eligible for statin therapy.³⁷ Additionally, the interaction between risk factors such as LDL and CVD outcomes may differ by age.⁴⁹ Coronary artery calcium (CAC) scoring is a promising indicator of biological age that may better discriminate CVD risk in older adults.⁵⁰ CAC has robust negative predictive value for CVD and all-cause mortality in older adults,⁵⁰ and the 2019 ACC/AHA guidelines highlighted CAC as a way to 'de-risk' older patients with low scores and avoid statin therapy.⁸ CAC is not necessarily appropriate for every older patient; the high prevalence of subclinical atherosclerosis in this age group lessens its specificity.⁴⁹ However, it provides a valuable option to further elucidate CVD risk when considering preventative therapy in selected patients.

Beyond risk measurement tools, another central issue with the current risk assessment paradigm in older adults is the reliance on a model of 10-year risk of CVD.³⁷ While elevated 10-year risk of CVD in middle-aged adults clearly supports statin use, extrapolation of this paradigm is not always appropriate for older patients, for whom multimorbidity and competing risk of death may render CVD prevention futile.⁴⁹ Therefore, while in middle-aged adults the goal is to identify and aggressively treat those who are most at risk of CVD, in older adults, this goal shifts to identifying patients most likely to benefit from treatment. The key goal of therapy in this context is therefore to extend healthy life expectancy and reduce disability life span. In an attempt to implement this concept into practice, Kleipool *et al.*³⁷ recently developed a new tool for calculating risk of CVD in older adults that accounts for life expectancy and competing risk of death. Although this tool was validated in populations that included older adults, it still has limited applicability to very frail patients or patients with very limited life expectancy who were not adequately represented.³⁷ Nevertheless, it provides a theoretical model for risk calculation that moves away from the 10-year risk framework. This kind of tool could support

approach to CVD prevention that prioritises potential lifetime benefit.

Shared decision making (SDM)

SDM is an approach where clinicians and patients discuss treatment options, risks and preferences to guide decisions.² While SDM is broadly an important framework for therapeutic decisions, this approach is especially important with older adults, for whom the uncertain value of primary prevention therapies, aging-related factors such as functional status, cognition and polypharmacy, and heterogeneous goals of care complicate decision making. SDM in this context could be used to guide decision making regarding initiation of preventative therapies,² diagnostic testing³¹ or deprescribing.⁴³

Decision aids are evidence-based tools with clear graphics and information that facilitate SDM.² SDM with decision aids has been shown to improve both patient knowledge as well as alignment of patient values and treatment choices.² Decision aids have been developed for primary prevention therapies, but they have not been widely adopted.² Limited clinical encounter time, as well as impairments that preclude use of these tools among older patients (eg, vision and cognition), are often cited as barriers to implementation.² Additionally, decision aids present population-level estimates of risks and benefits that are not necessarily generalisable among older adults due to their clinical complexity.² While decision aids may be difficult to implement among heterogeneous older adult populations, the framework of SDM is nonetheless still important in discussions between clinicians and patients about primary prevention of CVD to promote patient education and care that is aligned with patients' goals.

CONCLUSION

Current data regarding the use of aspirin and statins in older adults largely consists of conflicting observational studies and underpowered secondary analyses of clinical trials, providing an uncertain landscape for clinical practice. However, the weight of evidence to date does not support aspirin for primary prevention in older adults but does support statin therapy for selected high-risk patients. The PREVENTABLE, STAREE and SITE trials will provide further important information; however, these trials focus on well-defined patient populations with exclusion criteria that, like any clinical trial, will still leave some questions unanswered.

With this in mind, we believe the most useful strategy for primary prevention in older adults would be to offer treatments to those most likely to gain meaningful years of life rather than considering 10-year risk estimates, with this broad goal further informed by considerations that include geriatric syndromes and shared decision making (figure 2). Future research and development of guidelines should support clinicians in this approach by elucidating the impact of geriatric conditions on treatment decisions and developing better tools to evaluate the utility of preventative therapy, with improved methods to appraise CVD risk in this population, lifetime benefit and patient values.

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