Statins for Primary Prevention in Older Adults

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Learning Objectives

1. Describe statins' place in therapy for atherosclerotic cardiovascular disease (ASCVD)

2. Summarize available evidence regarding statin use for primary prevention in older adults, with emphasis on age >75 years

3. Describe risks versus benefits of statin use for primary prevention in older adults

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Statins Overview

- Also known as 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG)-CoA reductase inhibitors
- Available products:

Generic Name	Brand Name(s)	Available Dosage Strengths
Atorvastatin	Lipitor®	10 mg, 20 mg, 40 mg, 80 mg
Fluvastatin	Lescol®	20 mg, 40 mg, 80 mg, 80 mg XL
Lovastatin	Mevacor®, Altoprev®	10 mg, 20 mg, 40 mg
Pitavastatin	Livalo®	1 mg, 2 mg, 4 mg
Pravastatin	Pravachol®	10 mg, 20 mg, 40 mg, 80 mg
Rosuvastatin	Crestor®	5 mg, 10 mg, 20 mg, 40 mg
Simvastatin	Zocor®	5 mg, 10 mg, 20 mg, 40 mg, 80 mg

Statin Mechanism of Action
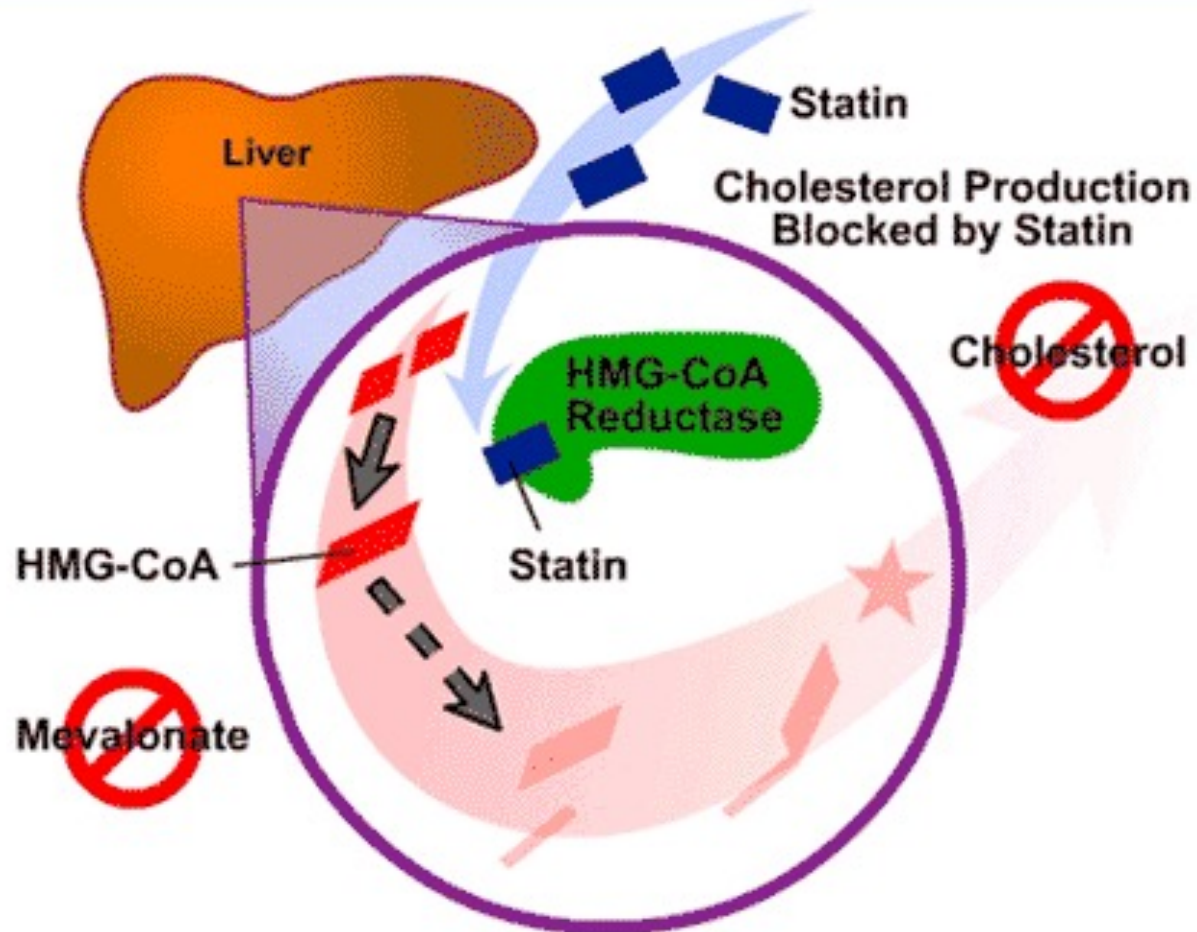
Statin Therapeutic Effects

- Lipid lowering with statins is beneficial for primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD)
    - Considered first-line agents
    - Generally provide the most effective lipid lowering compared to other classes
- Mechanism of benefit not completely understood

Statin Adverse Effects

- Myalgia
- Myopathy
- Arthralgia
- Gastrointestinal (nausea/vomiting/diarrhea)
- Hepatotoxicity
- Rhabdomyolysis

Statin Properties

| Statin	Lipophilicity	Hepatic Metabolism
Atorvastatin	High	CYP3A4
Fluvastatin	High	CYP2C9
Lovastatin	High	CYP3A4
Pitavastatin	High	Glucuronidation
Pravastatin*	Low	Sulfonation
Rosuvastatin*	Low	Minimal CYP2C9 and CYP2C19
Simvastatin	High	CYP3A4

*It has been suggested that statins with low lipophilicity (i.e., hydrophilic statins: pravastatin and rosuvastatin) are less likely to lead to adverse muscle-related effects

Statin Intensity

High Intensity Daily dose lowers LDL-C by approximately ≥50%	Moderate Intensity Daily dose lowers LDL-C by approximately 30% to <50%	Low Intensity Daily dose lowers LDL-C by <30%
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2-4 mg	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg

Statin Drug-Drug Interactions

- Drug-drug interactions with statins are common
- Examples of medications that have clinically relevant drug-drug interactions with statins
  - Cytochrome P-450 (CYP450) enzyme inhibitors
    - Amiodarone
    - Azole antifungals
    - Calcium channel blockers
    - Macrolide antibiotics
    - Protease inhibitors
  - Fibrates → increased risk of myopathy and rhabdomyolysis when a statin and fibrate are co-administered
    - Fenofibrate preferred over gemfibrozil if co-administered with a statin
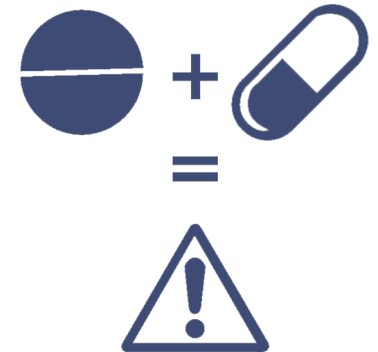
General Considerations for Statin Use in Older Adults

- More susceptible to risks of statin use
  - Pharmacokinetic/pharmacodynamic changes of aging
- Polypharmacy
- Life expectancy versus time to benefit
- Importance of individualized treatment plans and shared decision-making

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USPSTF Recommendations (2016)

Adults aged 40 to 75 years with no history of CVD, 1 or more CVD risk factors, and a calculated 10-year CVD event risk of 10% or greater	The USPSTF recommends that adults without a history of cardiovascular disease (CVD) (ie, symptomatic coronary artery disease or ischemic stroke) use a low- to moderate-dose statin for the prevention of CVD events and mortality when all of the following criteria are met: 1) they are aged 40 to 75 years; 2) they have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking); and 3) they have a calculated 10-year risk of a cardiovascular event of 10% or greater. Identification of dyslipidemia and calculation of 10-year CVD event risk requires universal lipids screening in adults aged 40 to 75 years. See the "Clinical Considerations" section for more information on lipids screening and the assessment of cardiovascular risk.	**B**
Adults aged 40 to 75 years with no history of CVD, 1 or more CVD risk factors, and a calculated 10-year CVD event risk of 7.5% to 10%	Although statin use may be beneficial for the primary prevention of CVD events in some adults with a 10-year CVD event risk of less than 10%, the likelihood of benefit is smaller, because of a lower probability of disease and uncertainty in individual risk prediction. Clinicians may choose to offer a low- to moderate-dose statin to certain adults without a history of CVD when all of the following criteria are met: 1) they are aged 40 to 75 years; 2) they have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking); and 3) they have a calculated 10-year risk of a cardiovascular event of 7.5% to 10%.	**C**
Adults 76 years and older with no history of CVD	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of initiating statin use for the primary prevention of CVD events and mortality in adults 76 years and older without a history of heart attack or stroke.	**I**

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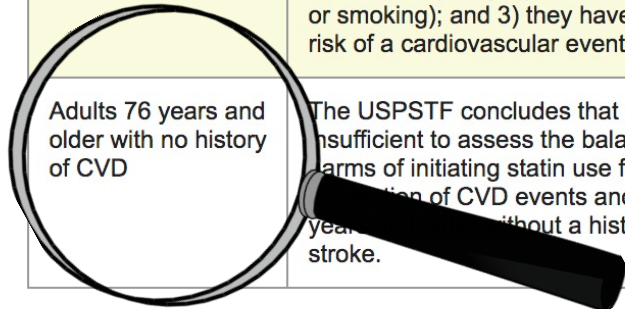
Choosing Wisely®

Cholesterol drugs for people 75 and older
When you need them—and when you don't

Choosing Wisely®

Adults age 75 and older may not need statins.

Many older adults have high cholesterol. Their doctors usually prescribe statins to prevent heart disease.

But for older people, there is no clear evidence that high cholesterol leads to heart disease or death. In fact, some studies show the opposite— that older people with the lowest cholesterol levels actually have the highest risk of death.

Choosing Wisely®

Weigh the risks and benefits.

You and your doctor should look carefully at the risks and benefits of statins, especially if you are older and do not have heart disease.

Older people may not live long enough to get the important benefits from statins. You and your family should speak with your doctor about your health concerns. Are you more concerned about preventing a heart attack that might never happen? Or do you want to avoid side effects that can lead to frailty, injury, and memory problems?

Choosing Wisely®

When should older adults take statins?

You should take statins if you have had a heart attack, stroke, or mini-stroke (transient ischemic attack, or TIA). Statins can help prevent a second heart attack or stroke.

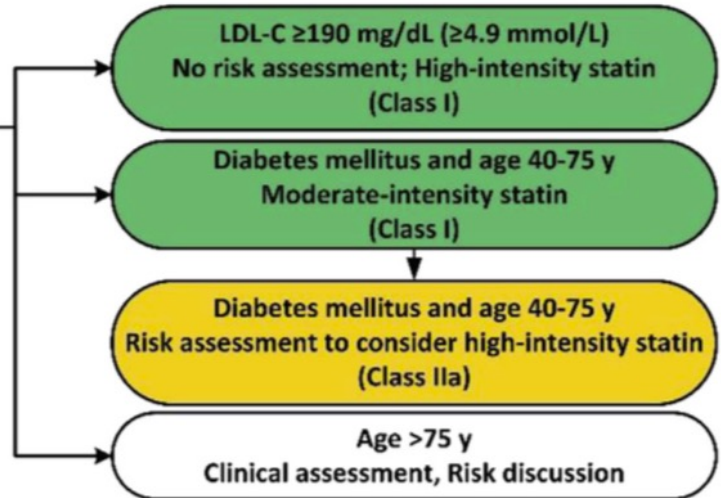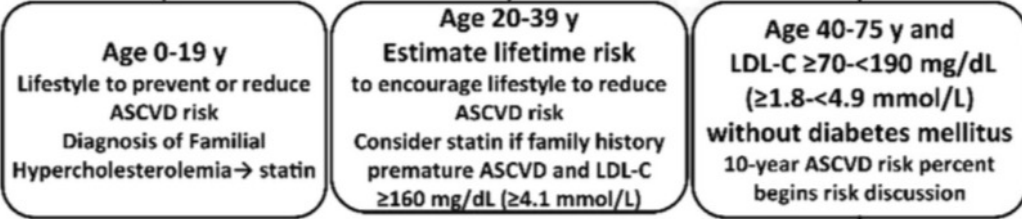# 2018 AHA/ACC* Guideline on Management of Blood Cholesterol

- Updated from 2013 AHA/ACC guideline
- Some notable changes between 2013 and 2018 guidelines:
  - Additional risk assessment strategies
  - Identification of ASCVD risk-enhancing factors
  - Use of coronary artery calcium (CAC) scoring
  - **More guidance regarding older adults**

*AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA

Grundy et al. 2018. J Am Coll Cardiol.

Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

LDL-C ≥190 mg/dL (≥4.9 mmol/L)
No risk assessment; High-intensity statin
(Class I)

Diabetes mellitus and age 40-75 y
Moderate-intensity statin
(Class I)

Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin
(Class IIa)

Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of Familial Hypercholesterolemia→ statin

Age 20-39 y
Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)

Age 40-75 y and LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L) without diabetes mellitus
10-year ASCVD risk percent begins risk discussion

Age >75 y
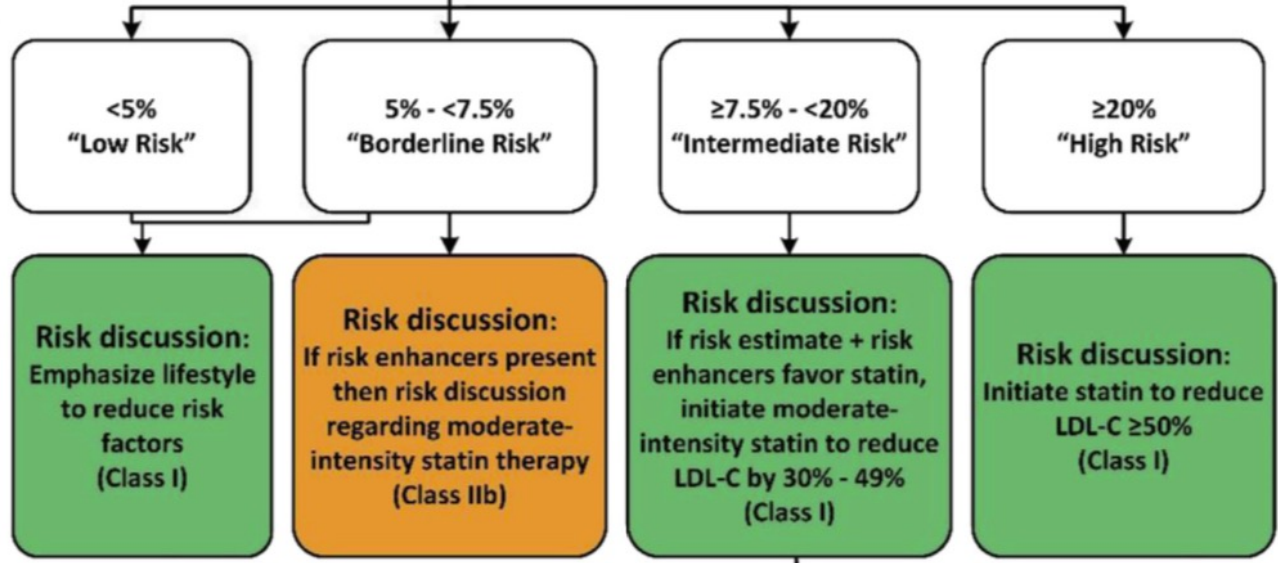Clinical assessment, Risk discussion

ASCVD Risk Enhancers:

- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g., South Asian ancestry)

Lipid/Biomarkers:
- Persistently elevated triglycerides (≥175 mg/dL, (≥2.0 mmol/L))

In selected individuals if measured:
- hs-CRP ≥2.0 mg/L
- Lp(a) levels >50 mg/dL or >125 nmol/L
- apoB ≥130 mg/dL
- Ankle-brachial index (ABI) <0.9

<5%
"Low Risk"

5% - <7.5%
"Borderline Risk"

≥7.5% - <20%
"Intermediate Risk"

≥20%
"High Risk"

Risk discussion:
Emphasize lifestyle to reduce risk factors
(Class I)

Risk discussion:
If risk enhancers present then risk discussion regarding moderate-intensity statin therapy
(Class IIb)

Risk discussion:
If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49%
(Class I)

Risk discussion:
Initiate statin to reduce LDL-C ≥50%
(Class I)

If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
CAC = 1-99 favors statin (especially after age 55)
CAC = 100+ and/or ≥75th percentile, initiate statin therapy

TABLE 7	Checklist for Clinician-Patient Shared Decision-Making for Initiating Therapy

Checklist Item	Recommendation

ASCVD risk assessment	■ Assign to statin treatment group; use ASCVD Risk Estimator Plus.*
	   ■ In lower-risk primary-prevention adults 40-75 y of age with LDL-C ≥70 mg/dL (≥1.8 mmol/L).
	   ■ Not needed in secondary prevention, in those with LDL-C ≥190 mg/dL (≥4.9 mmol/L), or in those 40-75 y of age with diabetes mellitus.
	■ Assess other patient characteristics that influence risk. See Risk-Enhancing Factors (Section 4.4.1.3. and **Table 6**)
	■ Assess CAC (Section 4.4.1.4.) if risk decision is uncertain and additional information is needed to clarify ASCVD risk.
	   ■ Use decision tools to explain risk (e.g., ASCVD Risk Estimator Plus,* Mayo Clinic Statin Choice Decision Aid†).

Lifestyle modifications	■ Review lifestyle habits (e.g., diet, physical activity, weight or body mass index, and tobacco use). ■ Endorse a healthy lifestyle and provide relevant advice, materials, or referrals. (e.g., CardioSmart‡, AHA Life's Simple 7§, NLA Patient Tear Sheets‖, PCNA Heart Healthy Toolbox¶, cardiac rehabilitation, dietitian, smoking cessation program).
Potential net clinical benefit of pharmacotherapy	■ Recommend statins as first-line therapy. ■ Consider the combination of statin and nonstatin therapy in selected patients. ■ Discuss potential risk reduction from lipid-lowering therapy. ■ Discuss the potential for adverse effects or drug–drug interactions.
Cost considerations	■ Discuss potential out-of-pocket cost of therapy to the patient (e.g., insurance plan coverage, tier level, copayment).
Shared decision-making	■ Encourage the patient to verbalize what was heard (e.g., patient's personal ASCVD risk, available options, and risks/benefits). ■ Invite the patient to ask questions, express values and preferences, and state ability to adhere to lifestyle changes and medications. ■ Refer patients to trustworthy materials to aid in their understanding of issues regarding risk decisions. ■ Collaborate with the patient to determine therapy and follow-up plan.

*ASCVD Risk Predictor Plus is available at: http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/ and http://static.heart.org/riskcalc/app/index.html#!/baseline-risk. Accessed September 1, 2018.
†Mayo Clinic Statin Decision Aid information is available at: https://statindecisionaid.mayoclinic.org.
‡CardioSmart health information is available at: https://www.cardiosmart.org/About
§AHA Life's Simple 7 information is available at: https://www.heart.org/en/healthy-living/healthy-lifestyle/my-life-check-lifes-simple-7
‖NLA Patient Tear Sheets information is available at: https://www.lipid.org/practicetools/tools/tearsheets
¶PCNA Heart Healthy Toolbox information is available at: http://pcna.net/clinical-tools/tools-for-healthcare-providers/heart-healthy-toolbox

  AHA indicates American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CKD, chronic kidney disease; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; PCNA, Preventive Cardiology Nurses Association and NLA, National Lipid Association.

ASCVD Risk Calculator

AHA/ACC ASCVD risk calculator to accompany guideline available at:

- http://static.heart.org/riskcalc/app/index.html#!/baseline-risk

- http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/

Older Adults Aged ≥75 Years

General Recommendations

COR	LOE	RECOMMENDATIONS
IIb	B-R	1. 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 (S4.4.4.1-1–S4.4.4.1-8)
IIb	B-R	2. 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 (S4.4.4.1-9).
IIb	B-R	3. 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 (S4.4.4.1-10, S4.4.4.1-11).

Recommendations in Patients with Diabetes Mellitus

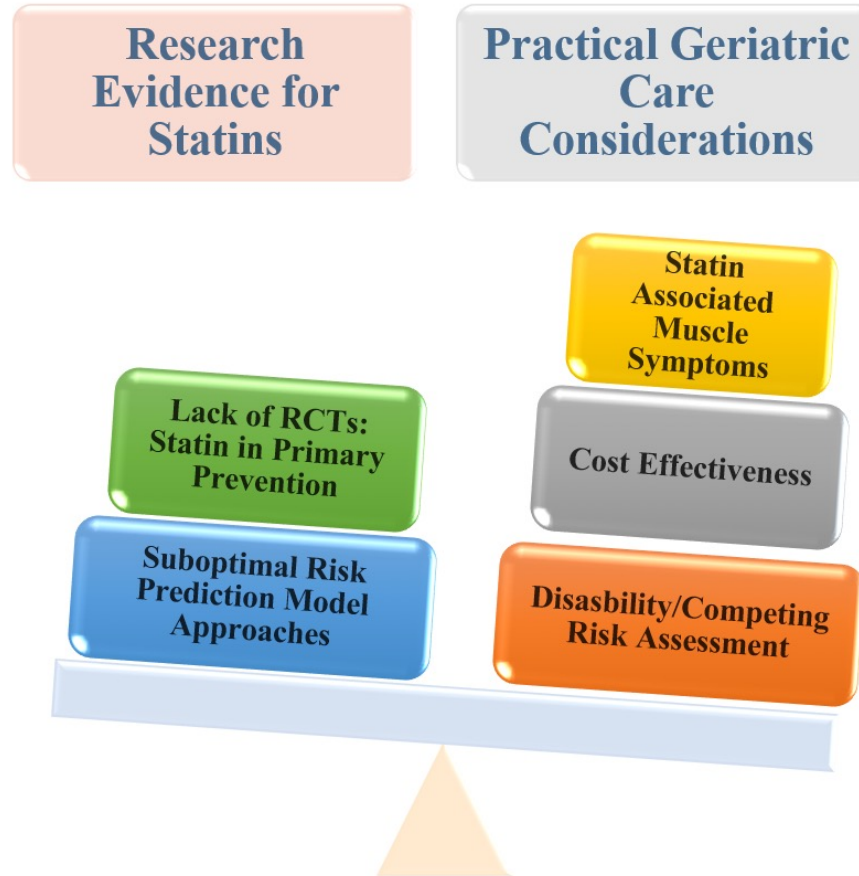| COR	LOE	RECOMMENDATIONS
IIa	B-NR	4. In adults older than 75 years of age with diabetes mellitus and who are already on statin therapy, it is reasonable to continue statin therapy (S4.3-5, S4.3-8, S4.3-13).
IIb	C-LD	6. In adults older than 75 years with diabetes mellitus, it may be reasonable to initiate statin therapy after a clinician–patient discussion of potential benefits and risks (S4.3-5, S4.3-8, S4.3-13).

Grundy et al. 2018. J Am Coll Cardiol.

Older Adults Aged ≥75 Years: Summary of Evidence Used for Guideline

- Overall inconsistent evidence
  - Some RCTs and a meta-analysis support statin use for primary prevention up to age 79, though other studies do not
- Data is lacking for individuals ≥80 years

Grundy et al. 2018. J Am Coll Cardiol.

Older Adults Aged ≥75 Years

Research Evidence for Statins

Practical Geriatric Care Considerations

Statin Associated Muscle Symptoms

Lack of RCTs: Statin in Primary Prevention

Cost Effectiveness

Suboptimal Risk Prediction Model Approaches

Disasbility/Competing Risk Assessment

"For patients ≥75 years of age, RCT evidence for statin therapy is not strong, so clinical assessment of risk status in a clinician-patient risk discussion is needed for deciding whether to continue or initiate statin treatment."

Grundy et al. 2018. J Am Coll Cardiol.

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Older Adults Aged ≥75 Years: Other Considerations in Guideline

- Discussion of risks versus benefits is very important
  - Potential for additive risks that may outweigh benefits
  - Deprescribing statins is important to consider with regard to risks
- Decisions are not always intuitive
  - Some frail or complex older adults may prefer to stay on statins given their cardiovascular risk
- Use of CAC scoring may inform decision making
- Shared decision-making is important, and discussions should happen regularly

Grundy et al. 2018. J Am Coll Cardiol.

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Meta-Analysis by Ridker et al.

Meta-analysis of age-specific outcome data from 2 RCTs: JUPITER and HOPE-3

Objective: Evaluate statin use for primary prevention in older adults

Interventions:
- JUPITER: Rosuvastatin 20 mg daily
- HOPE-3: Rosuvastatin 10 mg daily

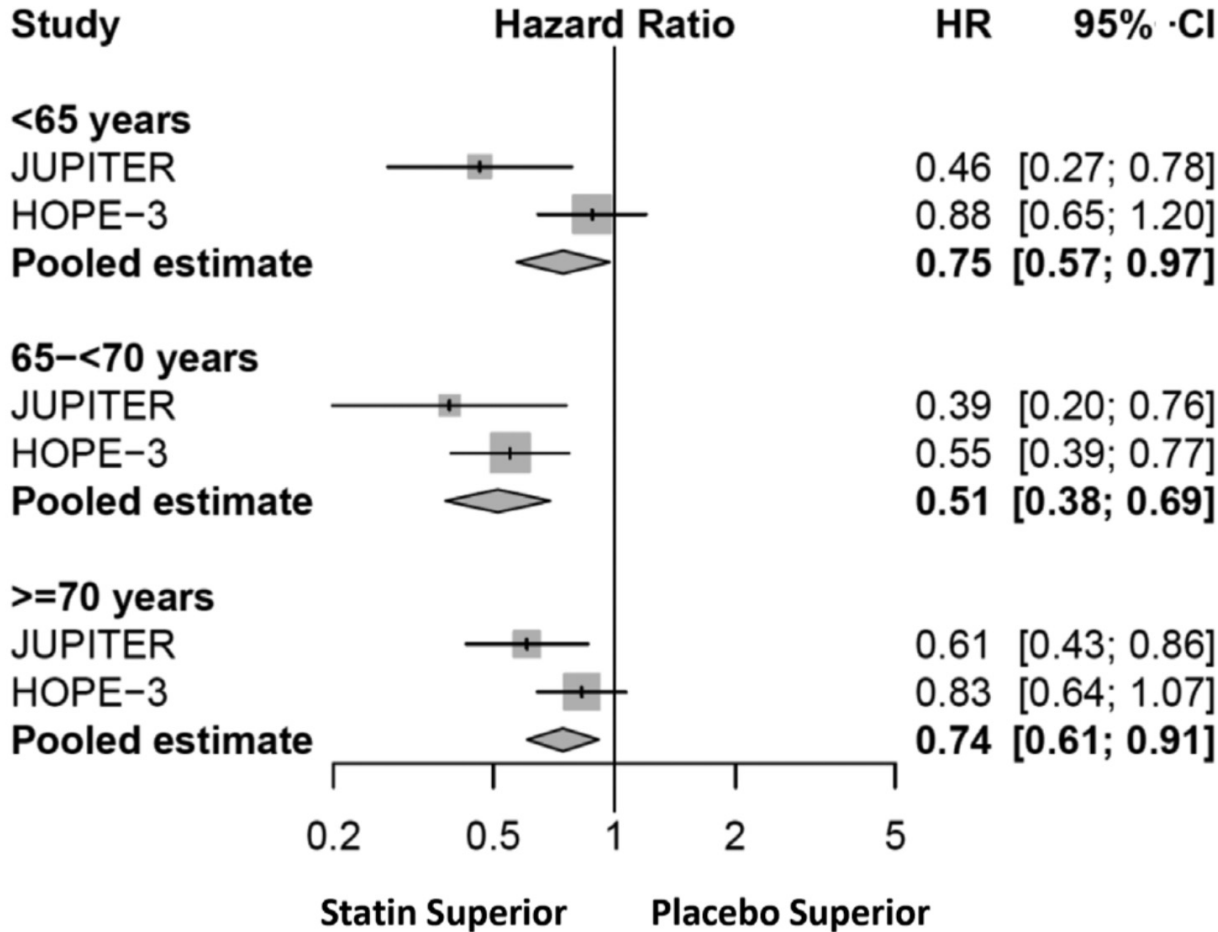Ridker et al. 2017. Circulation.

Meta-Analysis by Ridker et al.

Effects of rosuvastatin on the composite endpoint of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death in the JUPITER and HOPE-3 primary prevention trials, stratified by age.

Age Group	Trial	N	Rosuvastatin N (IR*)	Placebo N (IR*)
< 65 years	JUPITER	7,458	20 (0.27)	45 (0.59)
	HOPE-3	6,059	78 (0.46)	88 (0.53)
65-< 70 years	JUPITER	4,649	12 (0.24)	30 (0.61)
	HOPE-3	3,559	50 (0.50)	91 (0.91)
≥ 70 years	JUPITER	5,695	51 (0.82)	82 (1.36)
	HOPE-3	3,086	107 (1.25)	125 (1.50)

*rates are per 100 person-years. The test for heterogeneity by age for the effects of statin therapy on clinical outcomes was non-significant (P=0.10).

Ridker et al. 2017. Circulation.

Meta-Analysis by Ridker et al.

Ridker et al. 2017. Circulation.

Meta-Analysis by Ridker et al.

Conclusions:

- Results support statin use for primary prevention in individuals ≥70 years of age

- Given consistency of benefits seen in individuals <70 years and >70 years of age, some benefit is likely even in individuals ≥80 years of age

  - Must be weighed against potential for modest impact on longevity
  - Must take into account personal preferences

Ridker et al. 2017. Circulation.

Meta-Analysis by Ridker et al.

Limitations and Considerations:

- Included only small number of individuals ≥80 years
  - Extrapolation of results should be done with caution
- Does not address certain concepts relevant to clinical practice, such as adherence, drug-drug interactions, quality of life, cost-effectiveness, etc.

Ridker et al. 2017. Circulation.

ALLHAT-LLT RCT by Han et al.

Objective: Examine statin treatment among adults aged 65 to 74 years and ≥75 years for primary prevention

Intervention: Pravastatin 40 mg daily

Outcomes:

- Primary: All-cause mortality
- Secondary: Cause-specific mortality and nonfatal MI or fatal coronary heart disease combined

Han et al. 2017. JAMA Internal Medicine.

ALLHAT-LLT RCT by Han et al.

Subjects (≥75 years group):

	Pravastatin	Usual Care
Number	375	351
Age, mean (SD)	78.5 (3.6) years	78.6 (3.6) years
% Female	57.1%	56.4%

Han et al. 2017. JAMA Internal Medicine.

ALLHAT-LLT RCT by Han et al.

Results (≥75 years group):
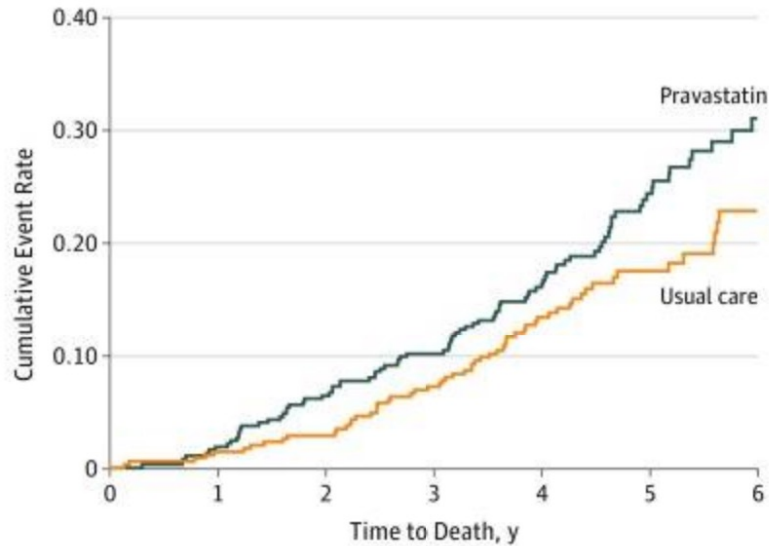
Pravastatin versus Usual Care

| Outcome	Hazard Ratio	P-value
All-cause mortality	1.34 (0.98-1.94)	0.07
CVD deaths	1.39 (0.94-2.32)	0.20
CHD deaths	0.99 (0.49-2.00)	0.97
Stroke deaths	2.27 (0.59-8.79)	0.23
Stroke (fatal and nonfatal)	1.09 (0.63-1.90)	0.76
Fatal CHD and nonfatal MI	0.70 (0.43-1.13)	0.14

Han et al. 2017. JAMA Internal Medicine.

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ALLHAT-LLT RCT by Han et al.

Results (≥75 years group):
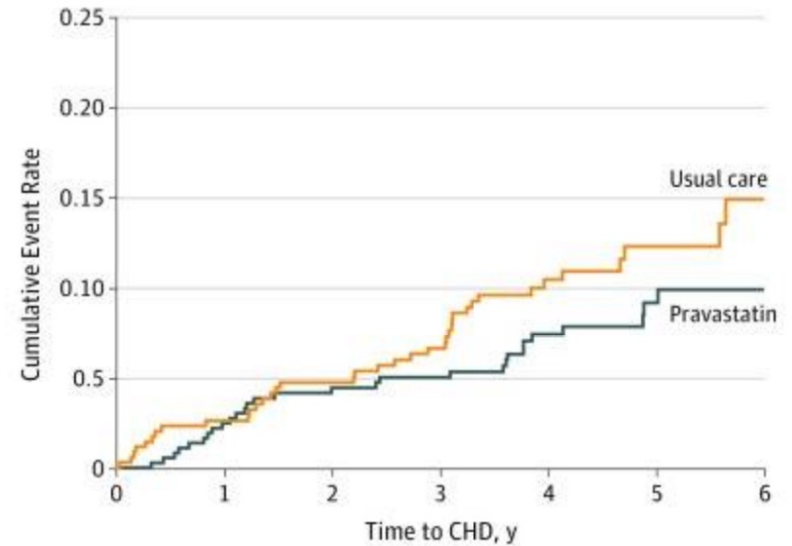
Han et al. 2017. JAMA Internal Medicine.

ALLHAT-LLT RCT by Han et al.

Conclusions:

- No benefit found with pravastatin for primary prevention in older adults

- Nonsignificant direction toward increased all-cause mortality with pravastatin in individuals ≥75 years

- Statin use may produce undesirable effects in health or function of older adults that could offset potential cardiovascular benefit

Han et al. 2017. JAMA Internal Medicine.

ALLHAT-LLT RCT by Han et al.

Limitations and Considerations:

- Post-hoc secondary analysis of an ALLHAT-LLT subgroup
- Excluded individuals on lipid-lowering treatment at baseline
- Small sample size of subjects in the ≥75 years group
- Did not assess specific adverse effects

Han et al. 2017. JAMA Internal Medicine.

Observational Study by Orkaby et al. (2020)

Objective: Evaluate the role of statin use for mortality and primary prevention of ASCVD in Veterans 75 years and older

Design: Retrospective cohort study

Exposure: Any new statin prescription

Outcomes:
- Primary: All-cause and cardiovascular mortality
- Secondary: Composite of ASCVD events (myocardial infarction, ischemic stroke, and revascularization with coronary artery bypass graft surgery or percutaneous coronary intervention)

Orkaby et al. 2020. JAMA.

Observational Study by Orkaby et al. (2020)

Table 1. Demographics of 326 981 Veterans 75 Years and Older, Free of Atherosclerotic Cardiovascular Disease, Before and After Propensity Score Overlap Weighting

	Crude			After propensity score weighting		
Variable	No statin (n = 326 981)[a]	Statin (n = 57 178)	Standardized difference	No statin (n = 326 981)	Statin (n = 57 178)	Standardized difference
Age, mean (SD), y	80.7 (4.0)	81.2 (3.6)	14.4	81.1 (1.5)	81.1 (3.0)	0.0
Body mass index, mean, (SD)[b]	26.7 (4.4)	27.5 (4.3)	18.6	27.4 (1.6)	27.4 (3.6)	0.0
Sex, %						
Men	97.3	97.3	0.3	97.3	97.3	0.0
Women	2.7	2.7	0.3	2.7	2.7	0.0
Race, %[c]						
White	90.7	90.2	1.8	90.3	90.3	0.0
Black/African American	7.5	7.9	1.5	7.9	7.9	0.0
Other	1.7	1.9	1.0	1.9	1.9	0.0

Orkaby et al. 2020. JAMA.

Observational Study by Orkaby et al. (2020)

Results:

Table 2. Association Between Statin Use, All-Cause Mortality, and Major Cardiovascular Events in 326 981 US Veterans 75 Years and Older Free of Atherosclerotic Cardiovascular Disease at Baseline, After Propensity Score Overlap Weighting

Outcome	Crude rate/1000 person-years		Weighted incidence rate difference/1000 person-years (95% CI)[a]	HR (95% CI)	P value
	Statin user (N = 57 178)	Statin nonuser (N = 269 803)			
Primary outcomes					
All-cause mortality (n = 206 902)	78.7	98.2	−19.45 (−20.38 to −18.52)	0.75 (0.74 to 0.76)	<.001
All CV death (n = 53 296)	22.6	25.7	−3.09 (−3.63 to −2.55)	0.80 (0.78 to 0.81)	<.001
Secondary outcomes					
ASCVD composite (n = 123 379)[b]	66.3	70.4	−4.05 (−5.09 to −3.02)	0.92 (0.91 to 0.94)	<.001
Myocardial infarction (n = 24 951)	13.2	12.6	0.56 (0.13 to 0.98)	0.99 (0.97 to 1.03)	.94
Ischemic stroke (n = 35 630)	18.4	18.2	0.25 (−0.26 to 0.76)	0.98 (0.96 to 1.01)	.20
CABG surgery/PCI (n = 74 362)	35.2	39.2	−3.38 (−4.12 to −2.64)	0.89 (0.88 to 0.91)	<.001

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass graft; CV, cardiovascular; HR, hazard ratio; PCI, percutaneous coronary intervention.

[a] Weighted incidence rate difference comparing statin users to nonusers after overlap weighting was applied.

[b] ASCVD composite: time to first MI or ischemic stroke or CABG/PCI. There were fewer composite ASCVD events compared with total individual events, as participants were censored at first event of interest.

Orkaby et al. 2020. JAMA.

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Observational Study by Orkaby et al. (2020)

Conclusions:

- Among Veterans 75 years and older and free of ASCVD at baseline, new statin use was significantly associated with a lower risk of all-cause and cardiovascular mortality

- Further research, including from RCTs, is needed to more definitively determine the role of statin therapy in older adults for primary prevention of ASCVD

Orkaby et al. 2020. JAMA.

Orkaby et al. (2020)

Limitations and Considerations:

- Observational study design
- VA population limits generalizability (e.g., very few women included)
- Adverse effects not evaluated
- Simvastatin was most commonly used statin, which does not reflect current practices

Orkaby et al. 2020. JAMA.

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Evidence from Other Studies

Study	Design	Subjects	Intervention/ Exposure	Results
PROSPER: Shepherd et al. (2002)	Double-blind randomized controlled trial	N=5,804 subjects aged 70-82 years	Pravastatin 40 mg daily	HR for composite of coronary death, non-fatal MI, fatal or non-fatal stroke: 0.85 (0.7-0.97), p=0.014
Glynn et al. (2010)	Exploratory analysis of JUPITER	N=5,695 subjects ≥70 years with elevated CRP	Rosuvastatin 20 mg daily	HR for 1st major CV event: 0.61 (0.46-0.82), p<0.001
Orkaby et al. (2017)	Prospective cohort study of Physicians' Health Study participants	N=7,213 male physicians ≥70 years without CVD	Statin use	HR for major CV event: 0.86 (0.70-1.06), p=0.17; HR for all cause mortality: 0.82 (0.69-0.98), p=0.03

Outline

Background

Clinical Guidelines/Recommendations

Evidence Summary

Other Considerations

Highlights from Review: "Primary Prevention with Statins in the Elderly"

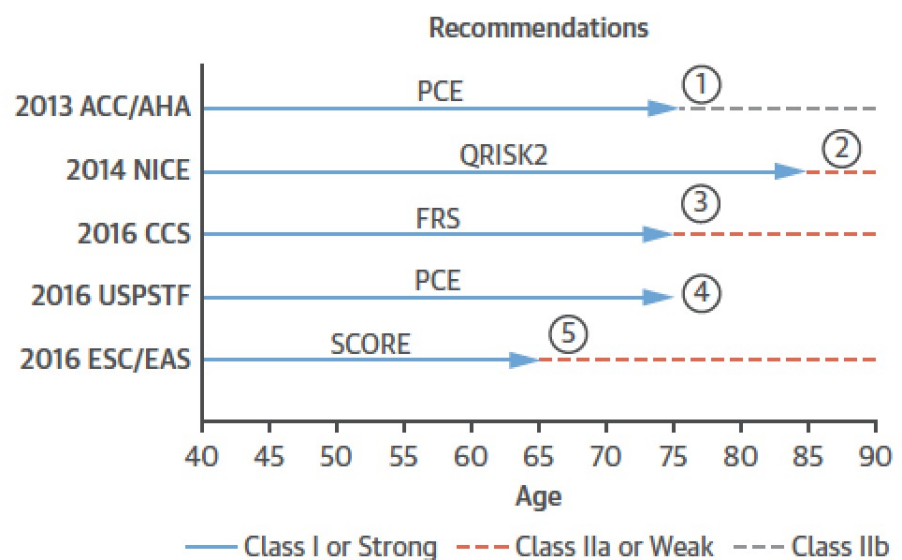**TABLE 2** Enrollment of Elderly and Very Elderly in Primary Prevention Statin Trials

Study Name, Year (Ref. #)	No.	Mean Age (yrs)	Age Range (yrs)	Elderly	Very Elderly (≥75 yrs of Age)
WOSCOPS, 1995 (10)	6,595	55	Men 45-64	0	0
AFCAPS/TexCAPS, 1998 (11)	6,605	Men 58 Women 62	Men 45-73 Women 55-73	Men 20% ≥65 yrs of age Women 33% ≥65 yrs of age	0
ALLHAT-LLT, 2002 (12)	10,355	66	≥55	28% ≥65 yrs of age*	7%*
PROSPER, 2002 (13)	3,239 (no ASCVD)	75 (whole cohort)	70-82 (whole cohort)	100% ≥70 yrs of age	NR
ASCOT-LLA, 2003 (14)	10,305	63	40-79	64% >60 yrs of age 23% >70 yrs of age	NR
CARDS, 2004 (15)	2,838	62	40-75	40% ≥65 yrs of age 12% >70 yrs of age	0
MEGA, 2006 (16)	7,832	58	40-70	23% ≥65 yrs of age	0
JUPITER, 2008 (17)	17,802	66	Men ≥50 Women ≥60	58% ≥65 yrs of age† 32% ≥70 yrs of age†	NR
HOPE-3, 2016 (18)	12,705	66	Men ≥55 Women ≥65/60	52% ≥65 yrs of age† 24% ≥70 yrs of age†	NR

*Primary prevention data reported by Han et al. (19). †Reported by Ridker et al (20).

AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid Lowering Trial; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; CARDS = Collaborative Atorvastatin Diabetes Study; HOPE-3 = Heart Outcomes Prevention Evaluation-3; JUPITER = Justification for the Use of Statins in prevention: An Intervention Trial Evaluating Rosuvastatin; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; NR = not reported; PROSPER = Pravastatin in elderly individuals at risk of vascular disease; WOSCOPS = West of Scotland Coronary Prevention Study.

Highlights from Review: "Primary Prevention with Statins in the Elderly"

FIGURE 1 Recommendations for Primary Prevention With Statins in Apparently Healthy People

Handling of individuals >65 years of age differs substantially among contemporary European and North American guidelines, partly because of the performance (applicability) of the risk model used. ACC/AHA = American College of Cardiology/American Heart Association; CCS = Canadian Cardiovascular Society; ESC/EAS = European Society of Cardiology/European Atherosclerosis Society; FRS = Framingham Risk Score for general cardiovascular disease; NICE = National Institute for Health and Care Excellence; PCE = pooled cohort equation; SCORE = Systematic COronary Risk Evaluation; USPSTF = U.S. Preventive Services Task Force.

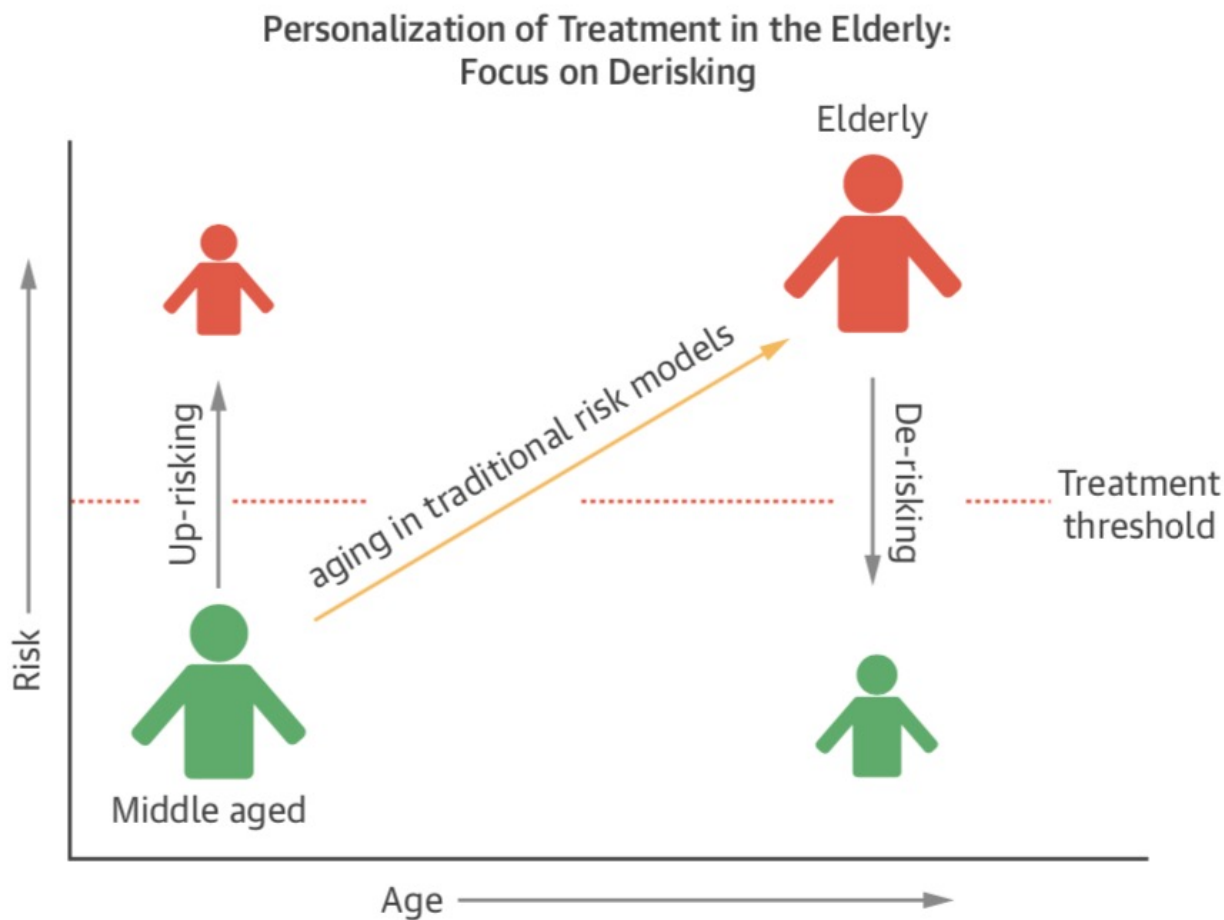# Highlights from Review: "Primary Prevention with Statins in the Elderly"

CENTRAL ILLUSTRATION Age-Dependent Implementation of Guidelines in Clinical Practice

Sex: Male	SBP: 135 mm Hg	HDL cholesterol: 37 mg/dL	Race: White
Smoker	Total cholesterol: 232 mg/dL	Diabetes: No	No antihypertensives

	Age 56	Age 66	Age 76	Age 86
PCE:	18%	26%	34%	NA
QRISK2:	17%	28%	43%	NA
Framingham:	31%	49%	NA	NA
SCORE:	4%	NA	NA	NA

Guideline Recommendation

	Age 56	Age 66	Age 76	Age 86
ACC/AHA	✓ Class I	✓ Class I	— Class IIb	— Class IIb
NICE	✓ Strong	✓ Strong	✓ Strong	— Specific recommendation for individuals ≥85 years
CCS	✓ Strong	✓ Strong	—	—
USPSTF	✓ Level B	✓ Level B	✗	✗
ESC/EAS	✗	— Class IIa	— Class IIa	— Class IIa

✓ : Strong Statin Recommendation   — : Weak Statin Recommendation   ✗ : Not Recommended for Statin

Mortensen, M.B. et al. J Am Coll Cardiol. 2018;71(1):85-94.

Highlights from Review: "Primary Prevention with Statins in the Elderly"

FIGURE 5 The Concept of Derisking in Elderly People

Take-Aways from Review: "Primary Prevention with Statins in the Elderly"

- Recommendations for statin therapy in older adults differ significantly among 5 major clinical practice guidelines
- Clinical trial data support statin use for primary prevention of nonfatal ASCVD events in older adults aged 66-75 years
- Evidence for individuals >75 years of age is sparse
  - Cannot base decision to initiate statin for primary prevention directly on available evidence
  - Must extrapolate data from those <75 years with caution, taking into account comorbidity, polypharmacy, adverse effects, and life expectancy
  - Until more evidence is available for individuals >75 years of age, use of statins for primary prevention must be based on well-informed shared decision making

Take-Aways from Review: "Primary Prevention with Statins in the Elderly"

- Considering potential harms is a crucial part of the decision-making process
  - Risk of statin-associated symptoms (e.g., musculoskeletal issues) may be increased by frailty, comorbidity, and polypharmacy
- Statin initiation must involve careful weighing of risks versus benefits
  - Consider polypharmacy and potential drug-drug interactions
- Discontinuing statin for primary prevention is reasonable to consider in older adults who are frail with increased risk of statin-associated symptoms and limited life expectancy
  - Benefit of statin therapy persists after discontinuation

Future Directions: STAREE Trial

STAtin therapy for Reducing Events in the Elderly (STAREE)

- **Objective:** Evaluate whether atorvastatin 40 mg daily will extend length of disability-free life in healthy participants aged 70 years and above

- **Design:** Double-blind, randomized, placebo-controlled trial

- **Primary endpoint:** Time to 1) death or development of dementia or development of disability, or 2) major fatal or non-fatal cardiovascular event

- **Estimated enrollment:** 18,000 subjects

- **Estimated study completion date:** December 2023

Future Directions: PREVENTABLE Trial

<u>PR</u>agmatic <u>EV</u>aluation of ev<u>ENT</u>s <u>A</u>nd <u>B</u>enefits of <u>L</u>ipid-lowering in old<u>E</u>r adults (PREVENTABLE)

- **Objective:** Demonstrate the benefit of atorvastatin 40 mg daily in participants aged 75 years and above
- **Design:** Multi-center, randomized, parallel group, placebo-controlled superiority study
- **Primary endpoint:** 1) Number of participants without diagnosis of new dementia, and 2) Number of participants without persistent disability
- **Estimated enrollment:** 20,000
- **Estimated study completion date:** July 2026

Questions?

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