# Dyslipidemia in Older Adults [1,2,3,4,5,6,7,8]



## An Area of Limited Evidence and Some Uncertainty

Statin use in adults >80 years, especially for primary (1°) prevention is an area of some uncertainty and debate. RCTs have included patients up to age ~82, although most participants have been age <75. A systematic review in those over age 80 suggests that the benefit of statins may be attenuated, harms may be more common, and an association of higher total cholesterol and LDL with cardiovascular event risk is no longer clear.[8]

## Primary (1°) vs Secondary (2°) Prevention [9,10,11,12,13,14]

- Potential to benefit will differ for 1° or 2° prevention. 1° prevention delays or prevents the first cardiovascular (CV) event, whereas 2° prevention delays or prevents another cardiovascular event. Individuals who are on a statin for 2° prevention are at higher risk and more likely to benefit than those who are on a statin for 1° prevention. For 1° prevention in those age 65-75, statins reduce major adverse cardiac events (MACE) by a relative ~25%. {For those age >75, a significant benefit of newly initiated statins on MACE is not longer evident.}[2,3]

**Outcomes for Both 1° and 2° Prevention Based on RCT Meta-Analyses (in Age 65-82)**

| | Primary Prevention[10] | Secondary Prevention[14] |
|---|---|---|
| **All-Cause Mortality** | - | RR=0.78, 95%CI 0.65-0.89 NNT=28/~5 yrs |
| **CV Mortality** | - | RR=0.70, 95%CI 0.53-0.83 NNT=34/~5 yrs |
| **Myocardial Infarction** | RR=0.61, 95%CI 0.42-0.85 NNT= 84/~3.5yrs | RR=0.74; 95%CI 0.60-0.89 NNT=38/~5 yrs |
| **Stroke** | RR=0.76, 95%CI 0.62-0.93; NNT= 143/~3.5yrs | RR=0.75; 95%CI 0.56-0.94 NNT=28/~5 yrs |

1° Prevention: meta-analysis included 8 RCTs, 24,674 patients **aged 65 to 82 years** old with **~3.5 years** of follow-up.
2° Prevention: meta-analysis included 9 RCTs, 19,569 patients **aged 65 to 82 years** old with **~5 years** of follow-up.

## Should a Statin be Started In the Older Adult (age >75)? Considerations for Primary Care, Canada

**Primary Prevention** [2 (PEER Simplified Guideline Update 2023); 2 (CCS Dyslipidemia 2021)]

- There currently is no validated risk assessment tool and limited evidence for benefit with statin therapy for individuals >75 years of age. Clinical judgement and shared decision making is important when considering statin therapy in this population.
- PEER Simplified Guideline Update 2023 and Age >75 [(Guideline and Systematic Evidence Review) 2,3]
  - Recommend against lipid testing and assessment of risk using a CVD calculator
  - Suggest against routine initiation of statin therapy for 1° prevention in age >75
  - Note it may be reasonable to discuss benefits and risks of statin therapy for 1° prevention in some patients age >75 whose overall health status is good
  - Recommend against stopping/reducing statin just because patient has aged beyond >75
  - Evidence summary, Age >75[3]: a) Major adverse cardiovascular events (MACE) benefit with statins appears to diminish with advancing age (non-significant reduction, RR=0.92; 95%CI 0.73-1.16); and, b) there is no statistically significant ↓ in CV or all-cause mortality.

**Secondary Prevention** [2 (PEER Simplified Guideline Update 2023); 2 (CCS Dyslipidemia 2021)]

- A statin may be recommended for secondary prevention, regardless of age.
- PEER Simplified Guideline Update 2023
  - Recommends clinicians discuss the benefits and risks and encourage initiation of a statin
- CCS guideline: suggests therapy guided by LDL targets. Simplified Lipid Guideline: prefers the highest intensity statin an individual can tolerate, and without targeting a specific LDL.
- {Additional therapy, e.g. ezetimibe or a PCSK9i, may be considered in certain circumstances.}

## High versus Moderate Intensity Statins

- High-intensity statins (e.g. atorvastatin 80mg daily) have evidence of lowering the risk of CV events more than low-intensity (e.g. atorvastatin 10mg daily) in select, very high-risk individuals (although average age was only ~60 to 63 years). However, there was no significant difference in all-cause mortality between the two doses. For example,
  - The **TNT** trial compared high-intensity to low-intensity atorvastatin in post-ACS patients (average age was ~60 years, 65 to 69 years: 20.4%, ≥70 years: 16.8%). There was a ↓ in overall CV events (NNT=46 over ~5years), but no statistically significant difference in all-cause mortality.[15]
  - The **SPARCL** trial evaluated the efficacy of atorvastatin 80mg daily versus placebo for the prevention of stroke recurrence (both fatal & non-fatal) after a recent stroke or transient ischemic attack (TIA) in patients with "normal" cholesterol levels (LDL: 2.6 to 4.9 mmol/L) & no known history of coronary heart disease.[16] The mean age was ~63 years. **SPARCL** demonstrated benefits to treatment including: ↓ 2° stroke (NNT=53 over 4.9 years), ↓ TIA (NNT=43), ↓ major coronary events (NNT=59), ↓ CV events (NNT=32), but no ↓ in overall mortality. A risk of hemorrhagic stroke was also found (NNH=112 over 4.9 years).
- High-intensity statins are generally well tolerated in those age >75. Use of a low-moderate-intensity statin is reasonable when renal function is significantly impaired, tolerability is a concern, or there is significant potential for drug interactions, etc. [17,18]

| Statin intensity: | LOWEST | MODERATE | HIGH |
|---|---|---|---|
| **Atorvastatin** LIPITOR | 5mg daily | 10 to **20**mg daily | 40-80mg daily |
| **Pravastatin** PRAVACHOL | 10-20mg daily | **40** to 80mg daily | |
| **Rosuvastatin** CRESTOR | 2.5mg daily | 5 to **10**mg daily | 20-40mg daily |
| **Simvastatin** ZOCOR | 5-10mg daily | **20** to **40**mg daily | |

- A few additional considerations for statin therapy: a) Atorvastatin levels have been shown to be higher in older adults due to reduced renal function and drug interactions; b) Recent systematic reviews have not found any difference in cancer incidence.[2,3]
  {A possible cancer signal was linked to early data on pravastatin & adults >65 years.[PROSPER initial & long-term f/u]}

## Does High Cholesterol = ↑ Risk in Older Adults?[8,9,20,21]

Hyperlipidemia is a major modifiable risk factor for CV events. The relationship between mortality & elevated cholesterol in older adults is uncertain. In older adults, cholesterol levels appear unrelated to mortality between the ages of 70 to 90. Any protective effect of statins observed in the very old appears to be independent of total cholesterol.

## Treatment Targets [1,2,22]

- The PEER Simplified Lipid Guidelines (as well as the USA Veterans Affairs and USPSTF) recommend treatment (e.g. statin high-intensity as tolerated) without specific cholesterol targets and without repeating lipid levels.[2]
- The CCS Dyslipidemia Guideline recommends a treat-to-target approach, i.e. target LDL-C <2mmol/L or >50% reduction (alternative: ApoB <0.8g/L, or non-HDL-C <2.6mmol/L).[1]
- High-risk individuals on a statin, irrespective of LDL-C achieved, have demonstrated a ↓ in CV events [4S, CARDS, HPS].[23] {In the **4S Trial**, mean LDL-C went from 4.9 to 3.2mmol/L with simvastatin 20 to 40mg/d; results: a ↓ in all-cause death NNT=31; ↓ in MACE NNT=12.}[23]

# Dyslipidemia in Older Adults continued

## Weighing the Benefit vs the Risk[24]

In patients with tolerability or other issues on statins, the amount of effort to continue statin therapy should be related to their CV risk.[CCS] Those at higher CV risk stand to benefit more.

- As patients get older, it may be reasonable to re-evaluate their need and desire for risk reduction therapy before considering alternative option.

## Should Statins be Continued Indefinitely into Old Age (e.g. >~85 years)?

A statin does not need to be stopped or be dose reduced solely because of age.[2] Rather, consider the following to assess risk versus benefit, and potential value/role in each patient:

- Patient values or preferences (e.g. fewer pills, AE, QoL, differing priorities at this stage of life).
- Patient's baseline CV risk - primary (1°) vs secondary (2°) prevention; recency of a CV event
- Number of other risk factors (e.g. male, smoker, family history).
- Concomitant illness & general health status. (Are there other health priorities.)
- Prognosis & life expectancy beyond 2 years to allow for time-to-benefit.

Observational data suggests that continuing statin use in those age >75 is associated with ↓major CV events (composite of MI, ischemic stroke/transient ischemic attack, revascularization, or CV death).[25]
{Upcoming RCTs examining withdrawal (SITE) and 1° prevention of patients >70 years (STAREE) will provide insight.}

### *YES – continue because…*

- Statins generally do more good than harm in RCTs and seldom associated with harms.
- Evidence for statin benefit in general is more extensive & consistent than many other CV risk prevention options, especially for 2° prevention.
- Benefit generally increases as CV risk increases, & CV risk increases with age.
- Generally well tolerated; most tolerability & safety concerns can be managed individually.
- Statins are a relatively low-cost, risk-reduction option with extensive evidence and experience.
- Want to be less aggressive? Consider a lower dose rather than stopping completely.

### *NO – consider decreasing or stopping when…*[26,27,28,29]

… the potential harms or burden of treatment may be greater than potential benefits.

- **Most of the evidence for statin use is for those age <75** with minimal study in those over age >85.[26]
- There is little evidence that statins offer a mortality benefit as people get older (e.g. the potential for ↓ CV events does not translate into ↓ mortality). The importance of cholesterol as a risk factor for CV disease ↓ with age & epidemiologic data suggest that higher cholesterol levels may be associated with ↑ survival for age ≥85 years.[8,28]
- There is some evidence that suggests that older adults may be more susceptible to statin adverse events (AEs), such as myalgia, fatigue, & exercise intolerance.[30,31,32] Some may be wary of rare/uncertain but severe AEs such as myositis, rhabdomyolysis, liver damage, and cognitive impairment. Patients with complex medical conditions are often excluded from randomized control trials, thus limiting the applicability of findings to many older adults in the real world.
- Older adults may be taking medications that interact with statins (& ↑ the risk of toxicity). (**Note**: pravastatin & rosuvastatin do not have CYP3A4 drug interactions.)
- If an individual has severe physical or cognitive impairments, or limited life expectancy (e.g. cancer with poor prognosis, advanced dementia), consider discontinuation.

## When to Discuss Discontinuation – Using Shared Decision Making

Good opportunities to discuss potential moderation of the dose, or withdrawal of statins may include:

- Comprehensive medication reviews by clinicians (e.g. physician, pharmacist, nurse practitioner, etc.).
- Assessments on admission to, or discharge from hospital.
- On entry to a long-term care home or palliative care; when health status declines.[33]
- Individual or family wish to discuss/change goals of care (e.g. away from prolonging life).
- Individual is older than patients included in the studies (e.g. >85 years).

## Adverse Events (AE) Associated with Statin Use [34,35,36]

Evidence suggests there is little to no difference in overall, or serious AEs in older adults.[36] In older adults, exposure to higher doses of statins may not greatly ↑ their effectiveness but may ↑ the risk of AE. Older adults are less resilient to AEs. AEs vary between the statins type & intensity. The risk of AEs ↑ with statin potency & exposure (Potency: rosuvastatin > atorvastatin > simvastatin > lovastatin > pravastatin & fluvastatin). With aging, there is a ↓ in body size, ↓ muscle mass, ↓ hepatic function, and/or ↓ renal function; the same dose will result in a greater degree of exposure in older adults than in younger adults. **Most common AEs**: gastrointestinal (e.g. abdominal pain, constipation, nausea) & myalgias. (Also potential lifestyle AEs: ?↓ exercise & ↑ caloric intake belief: statins can compensate for poor dietary choices & a sedentary life.) [37]

### Muscle Symptoms (myalgia occurs in 5 to 10%, myositis Rare: occurs in 0.1%, & rhabdomyolysis Rare: occurs in 0.01%)

- Musculoskeletal AE: Difference vs placebo ≤1% in first year; no difference thereafter.[2,3]
- Complaint of myopathy is common (~15% @1yr) for both placebo & statin groups in RCTs.
- Can be associated with, or result in, the discontinuation of therapy.
- With advancing age, there may be ↑ risk of muscle concerns due to age-associated factors (multiple medications, comorbidities & sarcopenia loss of muscle tissue as a natural part of the aging process). Statin myopathy is likely to have a greater impact in older adults (limited musculoskeletal reserve - ↓ muscle mass, muscle strength & mobility).

See RxFiles Q&A: Statin Intolerance – Management Considerations

### Liver Enzyme Increases (ALT >3X normal)[38]

- Incidence of ↑ hepatic transaminases is 0.5% to 2% with statins & is dose-dependent.
- The transaminases may normalize if the statin dose is reduced. Elevations do not always recur if an individual resumes the statin after discontinuation.
- The effect of aging on the risk of hepatic damage with statins is not known.

### Cognitive Impairment [2,3,]

- The early effects of statins on cognition had been somewhat conflicting.[37,38,39,40,41,42,43]
- Best evidence indicates that statins do not negatively affect cognition, memory, cognitive decline or dementia compared to no statin.[3] (SR of RCTs & long-term observational studies)
  {Some studies report reversible cognitive impairment with statins; some suggest improvement in cognition. The best data is reassuring! If cognitive effects are suspected within 1-3 months of starting a statin, or increasing the dose, may try stopping the statin to confirm if the statin is implicated. If no change, may restart at the same or lower intensity.}

### Acute Kidney Injury (AKI)[45]

- Although rare, the use of high potency statins (≥: 10mg rosuvastatin, 20mg atorvastatin, 40mg simvastatin) is associated with a small ↑ rate of diagnosis for AKI in hospital admissions compared with low potency statins. The effect seems to be strongest in the first 4 months after initiation of statin therapy.

### Diabetes[46,47,60]

- Diabetes-new onset, is slightly more common (~1/250) in those taking higher intensity statins. However, when the potential to benefit from statins is high, the risk of new onset diabetes (a surrogate marker) is not a significant concern (e.g. studies demonstrate that the CV outcome benefit in high-risk individuals outweighs harm from new diabetes diagnosis). Important patient outcomes outrank less important surrogate outcomes.

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## Statin Drug Interactions

**CYP Enzymes, P-glycoproteins (P-GPs) & Organic Anion-Transporting polypetides (OATPs)**

- Atorvastatin, lovastatin & simvastatin are CYP 3A4 [less extent for atorvastatin] & P-GP substrates. Pravastatin & rosuvastatin do not have CYP3A4 drug interactions. Fluvastatin is primarily metabolized by CYP2C9. Other interactions can affect statins as well (see below).

| Interacting Medications [Mechanism of interaction 48,49] | |
|---|---|
| **Amiodarone** Cordarone 1A2, 2C9, 2D6, 3A4, P-GP | **Grapefruit/Grapefruit Juice** 3A4, P-GP |
| **Azole Antifungals** | **Macrolide Antibiotics** |
| Fluconazole Diflucan 2C9, 2C19, 3A4, P-GP | Clarithromycin Biaxin 3A4, P-GP |
| Itraconazole Sporanox 3A4, P-GP | Erythromycin EES, Eryc 3A4, P-GP |
| Ketoconazole Nizoral 3A4, P-GP | **mTOR inhibitors** |
| Posaconazole Posanol 3A4 | Sirolimus Rapamune 3A4, P-GP |
| Voriconazole Vfend 2C9, 2C19, 3A4 | Everolimus Certican 3A4, P-GP |
| **Bile Acid Sequestrants** | **Niacin** (Combination niacin/statin products include Advicor) Additive effects |
| Cholestyramine Olestyr ↓ statin absorption due to binding | **Phenytoin** Dilantin 3A4-Inducer, P-GP |
| **Calcineurin Inhibitors** | **Protease Inhibitors** |
| Cyclosporine Neoral 3A4, P-GP | Atazanavir Reyataz 2C8, 3A4, P-GP |
| Tacrolimus Prograf 3A4, P-GP | Boceprevir Victrelis 3A4, P-GP |
| **Calcium Channel Blockers** | Darunavir Prezista 2D6, 3A4 |
| Amlodipine Norvasc 3A4 | Fosamprenavir Telzir 3A4 |
| Diltiazem Cardizem, Tiazac 3A4, P-GP | Indinavir Crixivan 3A4 |
| Verapamil Isoptin 3A4, P-GP | Lopinavir/Ritonavir Kaletra 2D6, 3A4, P-GP, OATP |
| **Cimetidine** Tagamet 1A2, 2C19, 3A4 | Nelfinavir Viracept 3A4, P-GP |
| **Colchicine** 3A4, P-GP | Ritonavir Norvir 2D6, 3A4, P-GP, OATP |
| **Danazol** Cyclomen 3A4 | Saquinavir Invirase 3A4, P-GP |
| **Digoxin** Lanoxin P-GP | Telaprevir Incivek 3A4, P-GP |
| **Dronedarone** Multaq 3A4, P-GP | Tipranavir Aptivus 3A4 |
| **Fibric Acid Derivatives** | **Rifampin** inducer of: 1A8, 2C8, 2C9, 2C19, 3A4, P-GP, OATP |
| Fenofibrate Lipidil 2C9 | **Telithromycin** Ketek 3A4, P-GP |
| Gemfibrozil Lopid 2C8, 2C9 | **Ticagrelor** Brilinta 3A4, P-GP |
| **Glyburide** Diabeta 2C9 | **Warfarin** Coumadin 3A4-Substrate |

Increased risk for myopathy/rhabdomyolysis due to decreased metabolism of the statin (most commonly: lovastatin & simvastatin, & to a lesser extent, atorvastatin).

## Lifestyle

Lifestyle interventions remain the cornerstone of chronic disease prevention, including CVD

❑ **Optimize lifestyle modification if appropriate & suitable to patient.**

| | | |
|---|---|---|
| Diet (Mediterranean diet, alcohol in moderation)<br>Activity / Exercise<br>- (Link to Physical Activity Rx Pad) | Weight Loss<br>Waist Circumference<br>(men<102 cm, female < 88cm)<br>Smoking Cessation | Education<br>(lifestyle modification should be ongoing) |

⇨ as one moves more toward declining health and frailty, quality of life & patient preference may take precedence over life prolonging measures.

## Alternative Lipid Therapies

Statin therapy is usually preferred as initial treatment over alternate lipid lowering medications due to more limited clinical outcome evidence for non-statin medications.

- In 2° prevention, may consider adding **ezetimibe** or **a PCSK9** to statin if additional risk reduction desired[2]. **Icosapent** a less attractive option due to AEs (atrial fib, ?bleeding).[2]

### Ezetimibe Ezetrol (Note: little to no evidence in 1◦ prevention)

- Ezetimibe may modestly ↓ CV event risk when added to a moderate dose statin (simvastatin 40mg)[NNT = 50 over 7 years; study limitations].[50] See RxFiles IMPROVE-IT Trial Summary.
- Lacks evidence for lowering CV or mortality risk in combination with a statin compared to placebo in individuals with mild-to-moderate asymptomatic aortic stenosis.[51] SEAS
- When combined with a proven therapy (e.g. simvastatin) in chronic kidney disease & individuals on dialysis (stage 3 to 4 CKD) a benefit for ezetimibe was seen; however, this benefit could have been due to the statin alone.[52] SHARP
- Ezetimibe may be a reasonable medication to deprescribe if looking to ↓ pill burden.

### Proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors

- Little to no evidence for non-familial hypercholesterolemia (FH) patients in 1◦ prevention.
- **Evolocumab** Repatha for secondary prevention, in addition to a statin, evolocumab 140mg SC every 2 weeks or 420mg SC every month reduced risk of composite CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization (9.8% vs. 11.3% placebo, HR=0.85, 95% CI, 0.79 to 0.92, NNT=67 in 2.2 years).[53] FOURIER
- **Alirocumab** Praluent for heterozygous familial hypercholesterolemia or CVD, alirocumab plus a statin reduced risk of composite CV death, MI, stroke, or hospitalization for unstable angina (9.5% vs. 11.1% placebo [statin] group, NNT=63 in 2.8 years).[54] ODYSSEY

For individuals with cardiovascular disease (CVD) already on maximally tolerated statins, adding **evolocumab** or **alirocumab** decreases new CV events for an additional one in 65 patients compared to placebo over ~2.5 years. Routine use of these agents is not cost-effective at current prices. [52 Choosing Wisely] See RxFiles FOURIER Trial Summary

**Icosapent** VASCEPA; [55] REDUCE-IT RCT See RxFiles REDUCE-IT Trial Summary

Icosapent was compared to mineral oil in very high-risk patients with elevated TG levels (1.52-5.63 mmol/L). Over 4.9years, CV events were lower (5-point MACE - CV death, nonfatal MI, non-fatal stroke, revascularization, unstable angina; 17.2% vs 22.0%; NNT=21/4.9yrs), but harms were higher (atrial fibrillation NNH=82, peripheral edema NNH=67; serious bleeding, although not statistically significant, was also increased 2.7% vs 2.1%, p=0.06).

### Fibrates

- As monotherapy, the evidence is mixed or lacking for CV & mortality benefit for fibrates in contrast to statins.
- May be used preventatively in some patients with hypertriglyceridemia-induced pancreatitis (HTGP) once high triglyceride levels resolve (e.g. ≤5.6mmol/L).

In combination (e.g. fenofibrate + simvastatin) fibrates are not more effective than simvastatin monotherapy. ACCORD-Lipid See RxFiles ACCORD-Lipid Trial Summary.

### Niacin [51,52]

- There is no role for niacin in CV risk reduction.[2] No benefit compared to statin monotherapy.[54,55]

## GERI-RXFILES DYSLIPIDEMIA REFERENCES

Search Terms

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