Is there a recommended age to discontinue statins (risk vs benefits) in the geriatric population?

Statins or 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors are commonly used to treat dyslipidemia and have been shown to reduce the risk of atherosclerotic cardiovascular disease (ASCVD) and death.[1-5] Although the benefits of statins are well established in younger patients, their exact role in older patients has not been fully elucidated.[4,6-8] Due to age-related changes in pharmacokinetic and pharmacodynamic parameters, older patients may not benefit from use of statins and may be more likely to experience statin-related adverse events including myalgia, muscle weakness, or falls.[3,6,8-11] As such, a review of treatment guidelines and the medical literature was conducted to determine whether statins are appropriate in older patients and whether there is a recommended age in which to discontinue treatment.

Appendix 1 summarizes treatment guideline recommendations for management of dyslipidemia and use of statins in older patients. Appendix 2 summarizes selected studies which evaluate efficacy and safety of statins in elderly patients (which were not included in the meta-analyses reviewed below). Appendix 3 summarizes statin dosage recommendations for geriatric patients based on Food and Drug Administration (FDA)-approved product labeling.

In addition to the information reviewed in the Appendices, Teng et al conducted a meta-analysis and systematic review evaluating the efficacy and safety of statins for primary prevention of cardiovascular disease (CVD) in elderly patients.[6] The authors performed a search of PubMed and Cochrane Library databases identifying systematic reviews and randomized controlled trials (RCTs) between March 1, 2009 and August 31, 2014. Eligible studies were those that included patients aged ≥65 years without pre-existing CVD who had received a statin or placebo, and reported at least 1 outcome including a major cardiovascular event, all-cause mortality, elevated liver enzymes (>3x upper normal limit [UNL]), elevated creatine kinase (>10x UNL), myalgia, myopathy, rhabdomyolysis, and serious adverse events. Studies were excluded if results were not reported based on age stratification.

Teng et al included 8 trials in their meta-analysis.[6] These studies assessed both primary and secondary prevention; 2 trials directly evaluated elderly patients, while 6 trials involved subgroup analyses of elderly patients. A total of 25,592 patients were included; 49.9% received statin treatment and 50.1% received placebo/usual care. The mean age of the patients was 72.2 years and the mean length of follow-up was 3.5 years.

In terms of major cardiac adverse events (myocardial infarction [MI], stroke, coronary revascularization, sudden cardiac death, or angina), use of statins showed a significant reduction in these events compared to controls (relative risk [RR] 0.82; 95% confidence interval [CI] 0.74 to 0.92).[6] However, the authors noted significant heterogeneity (I^2=71.5%, p=0.002).

There was also a significant reduction in non-fatal MIs (RR 0.75; 95% CI 0.59 to 0.94) and total MIs (RR 0.74; 95% CI 0.61 to 0.90). For fatal MIs, no significant difference was observed between those who received statins versus controls (RR 0.43; 95% CI 0.09 to 2.01) with significant heterogeneity (I^2=76.6%, p=0.039). Additionally, for total strokes (fatal and nonfatal) (RR 0.85; 95% CI 0.68 to 1.06) and all-cause mortality (RR 0.96; 95% CI 0.88 to 1.04), no significant differences in risk were observed between statin-treated patients and controls; significant heterogeneity was not observed for either outcome. The authors noted a lack of data regarding adverse events such as myopathy, rhabdomyolysis, elevated liver enzymes, and cognitive impairment. The rate of treatment discontinuation due to adverse events also did not differ significantly between the 2 groups (RR 1.10; 95% CI 0.85 to 1.42).

Based on the results of the meta-analysis, the authors concluded that statin treatment significantly decreased major cardiac adverse events (MIs, stroke, coronary revascularization, sudden cardiac death) and non-fatal MIs compared to controls.[6] In terms of discontinuations due to adverse events, there was no significant difference between patients treated with statins and controls. Based upon these results, the authors asserted that elderly patients should not be excluded from receiving statin treatment, but should be carefully evaluated in light of patient-specific factors including life expectancy and risk for adverse events.

There were several limitations with the aforementioned meta-analysis.[6] First, of the included trials, 2 were open-label, which may increase the risk for bias. Additionally, the included trials were not originally designed to assess the effects of statins in elderly patients. The authors also noted that their analysis found significant heterogeneity for major cardiac events and fatal MIs and that the follow-up period of 3.5 years may not have been long enough to estimate the true benefits and risks of using statins in elderly patients.

Iwere et al conducted a meta-analysis which focused on the safety concerns relative to use of statins in elderly patients.[12] The authors conducted a search of CINAL, Cochrane Library, EMBASE, Medline, PSYCHINFO, and Scopus databases and the National Institutes of Health Clinical Trials website identifying RCTs between 1987 and July 2014. Eligible studies were those that included patients aged ≥65 years in which muscle adverse events were compared between statin treatment and placebo. The primary outcomes included the occurrence of myalgia, myopathy, and rhabdomyolysis as defined by the American College of Cardiology (ACC)/American Heart Association (AHA)/National Heart Lung and Blood Institute (NHLBI). Secondary outcomes included the number of patients who withdrew from clinical trials or discontinued treatment due to adverse events or experienced mortality due to a myopathy-related cause.

Iwere et al included 8 trials in their meta-analysis.[12] These studies assessed both primary and secondary prevention; 1 trial randomized patients >65 years of age, while 7 studies performed subgroup or post-hoc analyses in older patients. A total of 18,845 elderly patients were included with a mean follow-up of 2.9 years. In terms of the primary outcomes, 4 trials

reported myalgia; of patients treated with statins and placebo, 0.08% and 0.07% developed myalgia, respectively. After pooling the data, no significant difference was observed between the 2 groups (odds ratio [OR] 1.03; 95% CI 0.90 to 1.17; p=0.66; I^2=0%). For myopathy, 8 trials reported occurrence; of patients treated with statins and placebo, 0.06% and 0.06% developed myopathy, respectively. After pooling the data, no significant difference was observed between the 2 groups (OR 1.03; 95% CI 0.91 to 1.18; p=0.61; I^2=0%). For the last primary outcome, rhabdomyolysis, 8 trials reported occurrence. Pooled analyses showed that there was no increased risk in patients treated with statins (OR 2.93; 95% CI 0.30 to 28.18; p=0.35; I^2=0.0%).

For the secondary outcomes, 3 trials reported patients who discontinued treatment due to an adverse event; 0.05% and 0.04% withdrew from the statin and placebo groups, respectively.[12] After pooling the data, no significant difference was observed between the 2 groups (OR 1.08; 95% CI 0.80 to 1.46; p=0.62). The authors noted significant heterogeneity (I^2=79%), which did not change after reanalysis using the random-effects model. After excluding a trial which showed notable increases in myopathy in patients treated with statins, no heterogeneity was observed (OR 0.74; 95% CI 0.50 to 1.09; p=0.13; I^2=0.0%). Finally, no patients in any of the trials experienced mortality due to a myopathy-related cause.

Based on the results of the meta-analysis, the authors concluded that statin treatment did not cause an increased risk for myalgia, myopathy, and rhabdomyolysis in elderly patients.[12] As such, elderly patients who require treatment with a statin should receive these agents. There were several limitations that should be noted. Many of the analyses were based on subgroup data which should be interpreted cautiously due to the risk for reduced power and erroneous results. As noted earlier, these trials were not originally designed to assess the effects of statins in elderly patients. The authors also stated that the short follow-up period in the trials may not have been long enough to detect adverse events, which may be concerning given that rhabdomyolysis is a rare event.

Treatment guidelines for treatment of dyslipidemia are not consistent as to whether statins should be used in elderly patients (see Appendix 1).[1,3-5] They provide different age thresholds and recommendations. The American Academy of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) recommend that selected elderly patients ≥65 years receive aggressive statin treatment, but do not clearly define which patients should be treated.[5] The ACC/AHA recommend that treatment be individualized in patients aged >75 years with clinical ASCVD and that prescribers should evaluate the potential benefits against the risks for adverse events/drug-drug interactions, as well as patient preferences.[1] Further, they assert that it is appropriate to continue statins in this group of patients, as well as recommending initiation of a moderate-intensity statin in those not currently receiving treatment.

The National Lipid Association (NLA) recommends that patients aged 65 – 80 years with ASCVD or diabetes mellitus receive a moderate- or high-intensity statin, with the caveat that the risks/benefits of treatment require careful evaluation.[3] For secondary prevention, NLA

recommends that patients aged ≥80 years receive moderate-intensity statin treatment. Again, they cautioned for the need to evaluate the risks/benefits of treatment, as well as drug-drug interactions, potential for polypharmacy, current medical conditions (frailty), cost, and patient preferences. Finally, the United States Preventative Services Task Force (USPSTF) asserts that there is insufficient evidence to initiate a statin in a patient ≥76 years without a history of MI or stroke for primary prevention of CVD and death.[4] Patients in this age group were not included in clinical trials assessing primary prevention of CVD. Younger patients aged 65 – 75 years may meet the recommended risk threshold for statin treatment despite not having risk factors; however, USPSTF asserts that data are lacking in these patients and that initiation of a statin should only occur after careful consideration of the benefits/harms. Additionally, they note there may be a potential association between very low cholesterol levels and an increased risk of death in patients who are at an "advanced age." As such, additional research is needed to evaluate the benefits/harms when starting a statin in patients aged ≥76 years for the primary prevention of cardiovascular events.

Similar to the guidelines, studies published after the reviewed meta-analyses are not consistent in their findings (See Appendix 2). In a retrospective analysis, Ble et al found that statins were effective in reducing recurrent MIs in patients aged 60 – 79 years; however, statins did not reduce recurrent MIs patients in ≥80 years and increased the risk for falls and fractures in this age group.[11] Han et al performed a secondary post-hoc analysis of the ALLHAT-LLT trial and found that pravastatin was ineffective at reducing all-cause mortality and coronary heart disease (CHD) in patients aged ≥65 years.[13] Another study by Kutner et al examined the use of statins in patients in palliative care; they found that discontinuation of statins is safe and may improve quality of life in terms of decreased pill burden and medication costs.[14] Lastly, Pilotto et al conducted a retrospective study in frail, elderly patients aged ≥65 years in Italy and found that statins were associated with a lower 3-year mortality rate.[15] It is important to note that these studies were not without limitations, which are discussed in Appendix 2.

In addition to guidelines and medical literature, the FDA-approved product labeling was consulted to determine statin dosage recommendations for geriatric patients (See Appendix 3).[16-24] Generally, the labeling notes that statins should be used cautiously in elderly patients (aged ≥65 years) due to increased risk for adverse events. Clinical trials were not consistent amongst the various statins as to whether elderly patients had elevated statin concentrations. Additionally, the labeling did not provide specific dosage recommendations.

To conclude, based on a review of dyslipidemia treatment guidelines, FDA-approved product labeling, and the medical literature, there is a lack of consensus regarding use of statins in elderly patients.[1,3-6,11-24] Guidelines provide different age thresholds and recommendations, while labeling recommends using caution in elderly patients ≥65 years. The meta-analysis by Teng et al, which evaluated statins for primary prevention of CVD in elderly patients, concluded that statins significantly decrease major cardiac adverse events (MIs, stroke, coronary revascularization, sudden cardiac death) and non-fatal MIs compared to controls without any

differences in adverse events.[6] Based on their analysis, the authors assert that elderly patients should not be excluded from receiving statin treatment, but should be carefully evaluated in light of patient-specific factors and risk for adverse events. The second meta-analysis by Iwere et al focused on safety concerns.[12] They concluded that statins did not increase the risk for myalgia, myopathy, and rhabdomyolysis in elderly patients, and therefore should be used if treatment is warranted.[12] As noted earlier, additional clinical trials published after the meta-analyses found conflicting results regarding the efficacy and safety of using statins in older patients.[11,13-15] Therefore, based on this review, additional research is needed to more fully determine whether statins should be used in elderly patients and whether there is a recommended age in which to discontinue treatment. In the meantime, prescribers should carefully evaluate whether statin treatment is appropriate for each patient, while considering patient-specific factors and the potential for increased adverse events in geriatric patients.

Appendix 1: Summary of guideline recommendations regarding use of statins in older patients.

Guideline	Recommendations
AACE/ACE (2017)[5]	-Defines older adults as ≥65y -Recommends that aggressive statin therapy may offer benefit in select patients based on similar efficacy and safety results between younger and older patients in clinical trials and a meta-analysis (does not specify type of patients)[25-29] <u>Briefly reviewed the following trials</u>: -TNT trial: patients ≥65y, compared to low-dose, high-dose statins had significantly greater reductions in CV events and deaths; older patients experienced more ADRs but did not differ significantly from the entire cohort; older patients had a small increase in all-cause mortality leading investigators to recommend caution with older patients[30] -PROSPER trial: patients >70y showed a secondary prevention of ASCVD events when treated with pravastatin 40 mg daily compared to placebo[31] -4S trial: patients ≥60y showed significantly reduced rates of death and major coronary events when treated with simvastatin 40 mg daily compared to placebo[32]
ACC/AHA (2013)[1]	-Recommends that treatment be individualized in patients >75y with clinical ASCVD; should evaluate potential benefits, risk for adverse events/drug-drug interactions, and patient preferences -Appropriate to continue statins in patients >75y with clinical ASCVD who tolerate treatment -Recommends that patients >75y with clinical ASCVD and not receiving statin treatment receive a moderate intensity statin (after assessment of ALT, CK, and FLP)
NLA (2015)[3]	-Recommends that patients aged 65y – 80y with ASCVD or DM receive a moderate- or high-intensity statin; need to evaluate the risks/benefits of treatment -For secondary prevention, recommends that patients aged ≥80y receive a moderate-intensity statin; need to evaluate the risks/benefits of treatment, drug-drug interactions, potential for polypharmacy, current medical conditions (frailty), cost, and patient preferences
USPSTF (2016)[4]	-States that there is insufficient evidence to start a statin in a patient ≥76y without a history of MI or stroke for primary prevention of CVD and death -Patients aged 65y – 75y may meet the recommended risk threshold for statin treatment and not have a history of DM, dyslipidemia, HTN, or smoking; notes data are lacking in this age group who lack CVD risk factors; whether to start a statin in this age group should involve careful consideration of the benefits/harms

Guideline	Recommendations
	-Notes that patients aged ≥76y were not included in the statin trials for primary prevention of CVD; therefore, the potential benefits/harms are unknown -Notes observational data for patients at an advanced age regarding a potential association between very low cholesterol levels and an increased risk of death -Additional research needed to evaluate the benefits/harm when starting a statin in patients aged ≥76y for the primary prevention of cardiovascular events

AACE=American Association of Clinical Endocrinologists; ACC=American College of Cardiology; ACE=American College of Endocrinology; ADRs=adverse drug reactions; AHA=American Heart Association; ALT=alanine aminotransferase; ASCVD=atherosclerotic cardiovascular disease; CK=creatine kinase; CVD=cardiovascular disease; DM=diabetes mellitus; FLP=fasting lipid profile; HTN=hypertension; NLA=National Lipid Association; PROSPER=Prospective Study of Pravastatin in the Elderly at Risk; 4S=Scandinavian Simvastatin Survival Study; TNT=Treating to New Targets; USPSTF=United States Preventative Services Task Force; y=years.

Appendix 2: Selected studies evaluating efficacy and safety of statins in elderly patients.

Reference	Design/patient population	Intervention	Major outcome(s)	Results	Conclusions/ Limitations
Ble[11]	Retrospective parallel cohort study assessed safety and efficacy of statins* in older patients Used electronic medical records from UK CPRD with propensity score matching (1:1 ratio) Patients hospitalized for 1st MI between April 1, 1997 – March 31, 2014, aged ≥60y; followed for up to 10y Excluded patients who died within 4 weeks of having a MI	Treatment group: statin-naïve patients who received a statin prescription within 56 days of having a MI Control group: statin-naïve patients who did not receive a statin prescription within 56 days of having a MI	Primary: composite of fatal (within 28 days of MI) and non-fatal MI Secondary: stroke, severe falls (requiring hospitalization), fractures, dementia, all-cause mortality	Included 12,156 patients; mean age of 76.5±9.2y; 54.5% were male Primary outcome: -Statins were not associated with a significant decrease in MI recurrence (SHR 0.84; 95% CI 0.69 to 1.02; p=0.073) -Statins significantly reduced recurrent MI in patients aged 60-79y (SHR 0.73; 95% CI 0.57 to 0.94; p=0.013) -Statins did not significantly reduce recurrent MI in patients aged ≥80y (SHR 1.06; 95% CI 0.78 to 1.44; p=0.69) Secondary outcomes: -Statins did not significantly reduce the risk for stroke (SHR 0.92; p=0.652; 95% CIs not reported) or dementia (SHR 0.94; p=0.597; 95% CIs not reported) -For all patients: statins increased the risk for falls (SHR 1.36; 95% CI 1.17 to 1.60; p<0.001) and fractures (SHR 1.33; 95% CI 1.04 to 1.69; p=0.019), especially in the 1st 2y of treatment -For patients aged ≥80y: risk of falls (SHR 1.82; 95% CI 1.45 to 2.30; p<0.001) and fractures (SHR 1.91; 95% CI 1.36 to 2.67; p<0.001) was greater than younger patients -All patients treated with statins had a lower risk for all-cause mortality (HR 0.62; 95% CI 0.57 to 0.68; p<0.001)	-Statins were effective at reducing recurrent MIs in patients aged 60-79y -Statins were not found to reduce recurrent MIs and increased the risk for falls and fractures in patients aged ≥80y Limitations: -Retrospective design -Use of electronic medical records may result in incomplete data

Reference	Design/patient population	Intervention	Major outcome(s)	Results	Conclusions/ Limitations
Han[13]	Post-hoc secondary analysis of ALLHAT-LLT RCT assessed safety of pravastatin in older patients Patients were ≥65y without evidence of ASCVD, had stage 1 or 2 HTN with at least 1 CHD risk factor; those without CHD required to have an LDL-C of 120-189 mg/dL and TG<350 mg/dL Excluded patients already taking LLT, intolerant of statins, severe renal/ hepatic disease, or secondary causes of hyperlipidemia Patients were followed for up to 6y	Treatment groups: pravastatin 40 mg daily vs. usual care	Primary: all-cause mortality Secondary: cause-specific mortality, non-fatal MI, fatal CHD	Of the 10,355 patients in ALLHAT-LLT, this post-hoc analysis included 2867 adults ≥65y (1467 received statins, 1400 received usual care Primary outcomes: -Patients aged 65-74y: more deaths in pravastatin (n=141) group vs usual care (n=130), but not statistically significant (HR 1.08; 95% CI 0.85 to 1.37; p=0.55) -Patients ≥75y: more deaths in pravastatin (n=92) group vs usual care (n=65), but not statistically significant (HR 1.34; 95% CI 0.98 to 1.84; p=0.07) -After multivariate Cox proportional hazards regression: • Patients aged 65-74y: adjusted HR (pravastatin vs. usual care) was 1.05 (95% CI 0.82 to 1.33; p=0.24 for interaction) • Patients aged ≥75y: adjusted HR (pravastatin vs. usual care) was 1.36 (95% CI 0.98 to 1.89; p=0.24 for interaction) Secondary outcomes: -No significant differences were observed for deaths due to CVD, CHD, stroke, non-CVD, or unknown causes for pravastatin vs. usual care -No significant differences were observed for non-fatal MI or fatal CHD for pravastatin vs. usual care	Pravastatin was not effective at reducing all-cause mortality and CHD events in patients aged ≥65y who received pravastatin Limitations: -Use of a post-hoc analysis, open-label design (increased risk for bias) -ALLHAT-LLT required use of LLT (risk/benefit may differ for patients starting statins at a younger age vs. patients ≥75y)
Kutner[14]	MC, PG, unblinded, pragmatic study assessed benefit and safety of statin discontinuation in	Patients were randomized to 2 groups: 1) statin continuation group, or 2) statin	Primary: death within 60 days Secondary: survival and time to first	Included 381 patients: 189 and 192 patients in the discontinuation and continuation groups, respectively	-Discontinuation of statins is safe in patients in palliative care with advanced illness

Reference	Design/patient population	Intervention	Major outcome(s)	Results	Conclusions/ Limitations
	patients receiving palliative care Patients (≥18y) had an estimated life expectancy of 1 month – 1y, had been on a statin for ≥3 months, had recent worsening of functional status, and diagnosis of severe, life-limiting disease Excluded patients with active CVD, myositis, elevated LFTs and CK Patients were followed up to 1y	discontinuation group (if eligible)	cardiac-related event, performance status, QOL, symptoms, statin adverse events	Mean age of 74.1±11.6y; 48.8% had cancer; 58% had CVD; the 2 groups were similar except more patients in the discontinuation group had cognitive dysfunction Primary outcome: -The number of patients who died within 60 days did not differ significantly between the discontinuation and continuation groups (23.8% vs. 20.3%; 90% CI -3.5% to 10.5%; p=0.36) Secondary outcomes: -Survival did not differ between the discontinuation and continuation groups (229 vs. 190 days, respectively; p=0.60) -Time to first cardiac-related event did not differ between the discontinuation and continuation groups (13 vs. 11 events, respectively; p=0.64) -Patients who discontinued statins reported better QOL vs. those who continued (p=0.04) -Effect of discontinuation did not have a significant effect on symptoms (physical, performance status) (p=0.13) -Statin adverse events did not differ significantly between the discontinuation and continuation groups (p=0.71)	-Discontinuation may improve QOL Limitations: -Included patients ≥18y; did not stratify results based on age (although the mean age was 74.1±11.6y) -Changed primary endpoint and required sample size in the middle of the trial -Study was not blinded
Pilotto[15]	Retrospective, observational study assessed whether statins reduced mortality in frail, community-dwelling, elderly patients in Italy	Patients were classified as mild, moderate, or high baseline mortality risk based on the SVaMA (high score indicated high risk)	Primary: assessed 3y mortality rate (used MPI-SVaMA) based on statin treatment and baseline mortality risk	Included 2597 patients; 55.5% were females; mean age of 83.9±7.35y; 41% were using statins (n=1065) Baseline MPI-SVaMA mortality risk: 30.2% (n=785), 42.2% (n=1,096), and 27.6% (n=716) had mild (MPI-SVaMA-1), moderate (MPI-SVaMA-2), and severe risk of mortality (MPI-SVaMA-3), respectively	Statins were associated with a lower 3y mortality rate in frail, elderly patients ≥65y, which was not affected by age

Reference	Design/patient population	Intervention	Major outcome(s)	Results	Conclusions/ Limitations
	Patients were ≥65y with a previous hospitalization for CAD and had completed a CGA-based assessment using the SVaMA between January 1, 2005 – December 31, 2013, which assessed mortality risk Patients were followed up to 3y	Patients were also stratified based on statin use		Primary outcomes: -Statin users were more likely to have a low mortality risk vs non-users (based on MPI-SVaMA) (35.6% vs. 26.5%, respectively; p<0.001) -Higher MPI-SVaMA scores: associated with a lower rate of statin treatment and higher 3yr mortality rate (MPI-SVaMA: 23.4%, 39.1%, and 76.2% for mild, moderate, and severe risk groups, respectively, [p<0.001]) -Statin use was associated with lower mortality risk within each risk group (HR 0.45; 95% CI 0.37 to 0.55 for MPI-SVaMA-1), (HR 0.44; 95% CI 0.36 to 0.53 for MPI-SVaMA-2), (HR 0.28; 95% CI 0.21 to 0.39 for MPI-SVaMA-3) -Multivariate adjustment for age, gender, etc.: statins were associated with a lower 3y mortality risk compared to non-users (regardless of MPI-SVaMA score) (p<0.001) -Subgroup analyses: statins showed benefit regardless of age (HR 0.38; 95% CI 0.27 to 0.53 for ages 65 – 74y), (HR 0.45; 95% CI 0.38 to 0.54 for ages 75 – 84y), (HR 0.44; 95% CI 0.37 to 0.54 for ages ≥85y) [interaction test p=0.597]	Limitations: -Retrospective design -Results may not apply to patients living outside Italy

ALLHAT-LLT=Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack-Lipid-Lowering Therapy; ASCVD=atherosclerotic cardiovascular disease; CAD=coronary artery disease; CGA=Comprehensive Geriatric Assessment; CHD=coronary heart disease; CI=confidence interval; CPRD=Clinical Practice Research Datalink; CK=creatine kinase; CVD=cardiovascular disease; HR=hazard ratio; HTN=hypertension; LDL-C=low-density lipoprotein cholesterol; LFTs=liver function tests; LLT=lipid-lowering therapy; MC=multicenter; MI=myocardial infarction; MPI=Multidimensional Prognostic Index; PG=parallel group; QOL=quality of life; RCT=randomized controlled trial; SHR=subhazard ratio; SVaMA=Standardized Multidimensional Assessment Schedule for Adults and Aged Persons; TG=triglycerides; UK=United Kingdom; y=years
*Included atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin.

Appendix 3: Summary of PI recommendations for older patients

Statin	PI recommendations for older patients
Atorvastatin (Lipitor®)[16]	-No overall differences in safety or efficacy were observed between older (aged ≥65y) and younger patients in trials; clinical reports have not identified differences, but older adults may have greater sensitivity -Notes advanced age (≥65y) as a predisposing factor for myopathy; use caution in elderly -Plasma levels are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly (aged ≥65y) vs. younger patients; data suggest greater LDL-lowering at any dose of drug in the elderly vs. younger patients
Fluvastatin (Lescol®, Lescol® XL)[17,22]	-Fluvastatin exposures not significantly different between the elderly (aged ≥65y) and younger patients -Notes advanced age (≥65y) as a predisposing factor for myopathy; use caution in elderly -Plasma levels not significantly different in patients aged >65y compared to patients age 21y – 49y
Lovastatin (Mevacor®, Altoprev®)[18,24]	-1 small PK trial reported increased levels of ~45% in elderly (aged 70y – 78y) compared to younger patients when using lovastatin 80 mg/day; dosage adjustment in elderly patients not required, however -2 large trials reported similar lipid-lowering in elderly vs. younger patients; no safety differences reported for any of the doses -Notes that elderly patients (aged ≥65y) have increased risk for myopathy; use caution in elderly
Pitavastatin (Livalo®)[19]	-Use caution in elderly patients (aged ≥65y) due to increased risk for myopathy and sensitivity -Clinical trials reported no differences in efficacy or safety for elderly vs. younger patients -1 PK trial reported that the C_{max} and AUC were 10% and 30% higher, respectively, in elderly vs. younger patients; no differences in efficacy or safety were reported for elderly patients
Pravastatin (Pravachol®)[20]	-Clinical trials reported increased AUCs (25% to 50% higher) in elderly vs. younger patients. C_{max}, T_{max}, half-life were similar in both groups and substantial accumulation of pravastatin would not be expected in the elderly –Notes advanced age (≥65y) as a risk factor for myopathy; use caution in elderly
Rosuvastatin (Crestor®)[21]	-In clinical trials no differences in safety or efficacy were observed between elderly (≥65 y) and younger patients -No differences in rosuvastatin concentrations were observed between elderly and younger patients

Statin	PI recommendations for older patients
	-Elderly patients may have greater sensitivity and are at higher risk of myopathy; use caution in elderly patients
Simvastatin (Zocor®)[23]	-In clinical trials, no differences in safety or efficacy were observed between elderly and younger patients -Notes that elderly patients may have greater sensitivity and that advanced age (≥65y) is a risk factor for myopathy; use caution in elderly patients -1 PK study reported that the mean plasma level was ~45% higher in elderly patients (aged 70 – 78y) vs. younger patients -1 trial reported 2 cases of myopathy/rhabdomyolysis in patients aged 67 – 73y; there were 4 cases in patients aged ≥65y -1 trial which included 16 elderly patients (aged 70 – 78y) on simvastatin 40 mg/day, reported increased simvastatin plasma levels by ~45% compared to younger patients

AUC=area under the curve; C_{max}=mean maximum plasma concentration; PI=prescribing information; PK=pharmacokinetic; T_{max}=time to maximum plasma concentration; y=years

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