Care of the Aging Patient: From Evidence to Action

Evaluation and Treatment of Older Patients With Hypercholesterolemia
A Clinical Review

Timo E. Strandberg, MD, PhD; Laura Kolehmainen, MD, PhD; Alpo Vuorio, MD, PhD

IMPORTANCE Hypercholesterolemia is common among people older than 80 years. Substantial functional heterogeneity exists among older patients, and decision making for statin use differs in older patients relative to younger ones.

OBJECTIVE To discuss the presentation, modifying factors, and treatment of hypercholesterolemia (usually with statins) among persons older than 80 years.

EVIDENCE REVIEW MEDLINE and other sources were searched from January 1990 to June 2014. Personal libraries and a hand search of reference lists from guidelines and reviews from January 2000 to June 2014 were also used.

FINDINGS No randomized clinical trials (RCTs) of statin or any other hypocholesterolemic medication included persons older than 80 years at baseline. Findings from 75- to 80-year-old patients enrolled in RCTs and information from observational studies support statin treatment for secondary prevention of atherosclerotic cardiovascular disease (ASCVD) and probably in patients with diabetes without ASCVD. Harms from statin drugs are not increased in older patients, so the use of these agents for primary prevention is possible. Because people older than 80 years are biologically heterogeneous with varying life expectancy, may have frailty or comorbid conditions, and may take multiple medications, the decision to treat with statins must be individualized.

CONCLUSIONS AND RELEVANCE Ideally, treatment of hypercholesterolemia for patients at risk of ASCVD should start before they turn 80 years old. No RCT evidence exists to guide statin initiation after age 80 years. Decisions to use statins in older individuals are made individually and are not supported by high-quality evidence.

JAMA. 2014;312(11):1136-1144. doi:10.1001/jama.2014.10924

Supplemental content at jama.com

CME Quiz at jamanetworkcme.com and **CME Questions** page 1149

Author Affiliations: Geriatric Clinic, Department of Medicine, University of Helsinki, Helsinki, Finland (Strandberg); Institute of Health Sciences/Geriatrics, University and University Hospital of Oulu, Oulu, Finland (Strandberg); Helsinki University Central Hospital, Helsinki, Finland (Strandberg); Unit of Internal Medicine, North Karelia Central Hospital, Joensuu, Finland (Kolehmainen); Mehiläinen Airport Health Centre, Vantaa, Finland (Vuorio); Finnish Institute of Occupational Health, Lappeenranta, Finland (Vuorio).

Corresponding Author: Timo E. Strandberg, MD, PhD, Geriatric Clinic, Department of Medicine, University of Helsinki, Stenbäckinkatu 9 A, PO Box 22, FIN-00014 Helsinki, Finland (timo.strandberg@oulu.fi).

Section Editor: Edward H. Livingston, MD, Deputy Editor, *JAMA*.

Decision making for administration of statins to older patients is complex, with little evidence to support or refute benefit. We present 3 case scenarios of older patients to illustrate this situation.

An Older Patient Not Taking Statins Who Develops Cardiac Problems

Mr S was an 89-year-old white man who lived independently and had hypertension and coronary artery disease (CAD). An acute myocardial infarction occurred at age 70 years. During the past 2 years he experienced chest pain on exertion that worsened with time. His medications included typical CAD medications (aspirin [100 mg], dipyridamole [150 mg], metoprolol [47.5 mg], isosorbide dinitrate [20 mg], furosemide [40 mg], and sublingual nitrate as needed), but he had not been prescribed a statin.

On a recent visit to his general practitioner for an annual checkup, Mr S was found to have a low-density lipoprotein cholesterol (LDL-C) concentration of 104 mg/dL (2.7 mmol/L). Although this level was not considered elevated (reference, <115 mg/dL [3.0 mmol/L]), the value was higher than 100 mg/L (2.5 mmol/L), which is the recommended threshold for initiating treatment in the Finnish guideline for secondary prevention. The patient's physician believed that the LDL-C level was somewhat elevated for a patient with CAD, but because of the patient's old age, he did not recommend statin therapy.

Two months after this visit, the patient was taken to the emergency department for chest pain and dyspnea. A diagnosis of acute myocardial infarction and heart failure was made, and a coronary angiogram revealed extensive 3-vessel CAD. Because intervention for the CAD was considered too high risk, conservative treatment was administered. The patient received systemic levosimendan, pleural effusions were drained, and diuretics and angiotensin-converting enzyme inhibitors were administered, without improvement in his symptoms. The patient died 2 months later.

An Older Patient Receiving Statins Who Has Good Physical and Cognitive Function

Mr J is 92-year-old white man who also lives independently, has a history of hypercholesterolemia, and smoked when he was younger.

About 30 years ago, he developed clinically significant CAD and underwent a multivessel coronary artery bypass graft procedure at age 69 years. A statin was started after the bypass. At 92 Mr J lives an active, independent life with his 90-year-old spouse (who also uses a statin), drives his car, and goes bowling weekly at a local club. His only current medications are atorvastatin (10 mg), ramipril (10 mg), and aspirin (100 mg).

An Older Patient Receiving Statins Who Has Poor Physical or Cognitive Function

Ms P is an unmarried 86-year-old white woman who has a history of hypertension, hypercholesterolemia, and type 2 diabetes. Ultrasound examination had revealed atherosclerosis in the carotid arteries, and Alzheimer disease was diagnosed 3 years ago. She lived independently at home but because of gradually worsening neuropsychiatric symptoms was admitted to a nursing home. Her latest Mini-Mental State Examination score was 11 of 30. For many years she has taken simvastatin (20 mg) daily in addition to aspirin (100 mg), bisoprolol (5 mg), and felonidipine (5 mg) for hypertension. She also takes galantamine (24 mg) and memantine (20 mg) for Alzheimer disease, as well as quetiapine (75 mg), mirtazapine (15 mg), and lorazepam (1 mg) for neuropsychiatric symptoms, pantoprazole (20 mg) for gastroprotection, a calcium–vitamin D combination, and analgesics as needed. In total, she takes 12 different medications.

Although she resides in a nursing home, her overall clinical condition is stable. Her memory is failing, but she is otherwise alert and physically active, without specific symptoms. Her physician, an experienced geriatrician, has no plan to change her cardiovascular medications.

Features of Old Age

The 3 clinical scenarios summarized above are increasingly common in societies in which numbers of the oldest-old, ie, people older than 80 years, are rapidly increasing. The life expectancy of such persons is often underestimated. According to Organization for Economic Co-operation and Development 2010 health data,[1] the mean life expectancy for an 80-year-old man in various European countries varied from 6.3 years (Hungary) to 8.7 years (Greece). For an 80-year-old woman, the range is from 6.9 years (Slovak Republic) to 10.6 years (Spain, Switzerland). In the United States, an 80-year-old man can expect to live another 8.1 years and a woman 9.7 years.[2] Paralleling increased life expectancy is improved function and quality of life for the very elderly. A recent study comparing cohorts of people born in 1905 and in 1915 when they were 93 and 95 years old found that the 1915 cohort scored significantly better on the Mini-Mental State Examination and had significantly better activities of daily living scores than did the 1905 cohort.[3]

Death attributable to atherosclerotic cardiovascular disease (ASCVD) is less common among younger people now than in the past, resulting in a larger population of older individuals with chronic ASCVD. Although the process of atherosclerosis starts early, clinical complications of the disease are experienced in later life. Because of underreporting[4] and prevalent subclinical disease, the incidence of ASCVD events may be underestimated for people older than 80 years. Aside from discrete ASCVD-related events such as myocardial infarction or stroke, common geriatric conditions, including dementia and frailty, may be caused by atherosclerotic disease.[5] A new challenge of arterial aging[6] (arterial changes may affect health status without "traditional" clinical manifestations such as infarcts) also broadens the scope of prevention and treatment of ASCVD risk factors such as hypercholesterolemia.

Box. Distinguishing Features of Individuals Older Than 80 Years When Considering Preventive Therapies

1. Shorter life expectancy than younger individuals
2. Chronological age often given greater weight than physiological age
3. Substantial variation in physiological age between individuals attributable to frailty, comorbid diseases, and cognitive decline
4. Risk factors for atherosclerotic cardiovascular disease do not predict outcomes as well as they do for younger individuals
5. Competing causes of mortality mask the potential benefits of some therapies
6. Frailty may exacerbate adverse effects of therapy
7. Polypharmacy may result in drug interactions
8. Musculoskeletal function, pain, and cognition adverse effects of therapies (not restricted to statins) are more severe in older individuals because these factors predispose to reduced physical activity, sarcopenia, and falls

Individuals older than 80 years are physiologically heterogeneous, ranging from incapacitated nursing home residents to marathon runners. This heterogeneity (**Box**) must be taken into account when preventive therapies for chronic diseases are considered. Cardiovascular prevention may be ineffective if it is started too late or if initiated in low-risk patients when the benefits of treatment may be overshadowed by adverse effects. Age is an important risk factor for ASCVD because of accumulated cellular damage often combined with failure of compensatory cardiovascular homeostatic mechanisms. However, the predictive value of traditional ASCVD risk factors—eg, hypercholesterolemia, hypertension, and obesity—may be reversed in old age.[7] Therefore, it is difficult to predict which older patients will benefit from primary prevention. The utility of coronary calcium score, carotid intima-media thickness, and genetic markers as indicators for determining who of the oldest-old might benefit from primary prevention is not established. There is some evidence that plasma homocysteine level may correlate well with ASCVD risk in the oldest-old. In the randomized Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) comparing placebo and pravastatin in persons aged 70 to 82 years at baseline, the number needed to treat to prevent 1 coronary event during 3.2 years was 14.8 (95% CI, 9.3-36.6) for patients with high homocysteine levels but 64.5 (95% CI, 21.4-∞) for patients with low homocysteine levels.[8] When assessing older patients for primary prevention, life expectancy and a patient's overall health status must be considered in addition to ASCVD risk.[9-11]

Literature Search: Methods and Results

We reviewed the role of statins in prevention of ASCVD in the clinical context of Mr S, Mr J, and Ms P. A literature search was conducted incorporating publications from January 1990 to June 17, 2014. We updated 2 earlier reviews on this topic[12,13] using the same keywords (*cholesterol*, *mortality*) and the age limit 80 years or older.

We included reports having more than 500 participants and that reported data on clinically meaningful end points such as mortality, ASCVD, and physical function. Because few publications include patients 80 or older, we also evaluated research findings from populations with patients older than 65 years. The search yielded 26 articles on statin therapy. Mortality or ASCVD events were the end point for 15 studies and physical function the end point for 11 studies. For details and keywords see the eFigure in the Supplement.

Our discussion of secondary prevention is based on the recent American College of Cardiology (ACC)/American Heart Association (AHA) guideline on the treatment of blood cholesterol.[14] This guideline includes recommendations for patients older than 75 years.

Hypercholesterolemia

Effect on ASCVD

There is an established and graded association between serum cholesterol levels and ASCVD risk.[15] Hypercholesterolemia is present when total cholesterol level exceeds 200 mg/dL (5.2 mmol/L), corresponding to an LDL- C level of 115 mg/dL (3.0 mmol/L), but many clinicians target for LDL-C levels less than 100 mg/dL (2.5 mmol/L) or less than 70 mg/dL (1.8 mmol/L) for secondary prevention.[14] Although low levels of high-density lipoprotein cholesterol and elevated triglyceride levels are associated with ASCVD risk in both younger and older patients, they are not targets of drug therapy. LDL-C is the main driver ("predisposing" factor) of the atherosclerotic process in the arterial wall. Statins induce atherosclerotic plaque regression when LDL-C levels are lowered to less than 100 mg/dL (2.5 mmol/L).[16] There is no evidence that any current treatment can reduce LDL-C too much. Combination of a statin with new antiproprotein convertase subtilisin/kexin type 9 (PCSK9) antibodies such as evolocumab, alirocumab, and bococicumab may lower LDL-C levels by up to 84%, resulting in levels less than 50 mg/dL (1.3 mmol/L). During studies lasting up to 12 months, these very low LDL-C levels have not been associated with any specific harms.[17,18]

In addition to being influenced by LDL-C, ASCVD events such as acute myocardial infarction and stroke are influenced by other risk factors such as smoking, hypertension, and diabetes. Consequently, prevention must address total ASCVD risk in addition to treating hypercholesterolemia.[14]

The Cholesterol Paradox in Old Age

In general, higher serum cholesterol level is associated with increased ASCVD risk (especially for CAD) in middle-aged and early old age patients. This association is attenuated in old age and can be reversed.[7] Cholesterol levels may decrease in old age because of the development of frailty[19] or as a result of the presence of comorbid conditions such as cancer. An apparent increase in mortality associated with low cholesterol level in older people may be related to several factors, such as changes in cholesterol metabolism, malnutrition, frailty, and chronic diseases leading to multidimensional (biological, functional, psychological, and social) impairments,[20,21] which simultaneously decrease cholesterol level and increase mortality risk. After adjusting for chronic disease states, the positive association between serum cholesterol levels and increased risk of death from CAD in men and women with a mean age of 79.2 years during a 5-year follow-up was restored.[22] Although the relative differences in risk related to cholesterol level decrease with age, in comparison with younger age the absolute effects of cholesterol level on CAD mortality rates are much greater when people get older. The association between elevated cholesterol levels and mortality was also demonstrated in a meta-analysis of 61 observational studies consisting of 892 337 individuals without a history of vascular disease and with a mean follow-up of 13 years.[15] Among 80- to 89-year old individuals, the annual CAD mortality rate increased 10-fold more for elderly patients compared with 40- to 49-year-olds for each 38.6-mg/dL (1-mmol/L) increase in total cholesterol levels.

The confusing relationship between the association between cholesterol levels and mortality for the very old results in uncertainty regarding the benefits of hypercholesterolemia drug treatment for healthy, very old patients. A large 5-year primary prevention randomized clinical trial (RCT) (n = 12 000) comparing atorvastatin (40 mg) with placebo in healthy people older than 70 years (Statins for Reducing Events in the Elderly [STAREE]) has been registered, with primary end points of total mortality or institutionalization.[23] Until the results of that trial are known, treatment decisions regarding administration of cholesterol-lowering agents for very old patients must be based on observational studies and extrapolations from the RCTs in younger people.

Treating Hypercholesterolemia in the Very Old—Evidence From Statin Trials

Statin use for primary prevention is also increasing among people older than 80 years, as shown in recent population-based surveys. In a large US survey, the prevalence of use was 29% in persons aged 80 to 84 years, 24% in those aged 85 to 89 years, and 14% in those older than 90 years.[24] Although treatment is often started late, the oldest patients using statins will have had a long-term, probably irreversible "cholesterol burden" in their arteries; this should be considered when the mortality and cardiovascular disease risks for older patients using statins are compared with those for patients not using statins.

Because there are no RCTs of statins started in patients older than 80 years, outcomes for this may be estimated from outcomes from younger groups. Evidence of the benefit of treating hypercholesterolemia is derived from large RCTs with mainly (but not exclusively) statins, which can reduce LDL-C levels between 33% and 58%. A large meta-analysis reported than LDL-C reduction is associated with a major decrease in the ASCVD event rate[25]: each 38.6-mg/dL (1-mmol/L) reduction in LDL-C level decreases the annual rate of major ASCVD events by just more than one-fifth and all-cause mortality by 10%. The relative reduction of ASCVD has been similar at all pretreatment LDL-C levels and observed in all relevant subgroups, eg, men and women, younger and older persons, and those with and without diabetes. The RCTs have included subgroups with ages ranging from 75 to 80 years at baseline; in the PROSPER trial, all participants were aged 70 to 82 years at baseline.[8] Because ASCVD events were also reduced in 75- to 80-year-old patients in RCTs, the ACC/AHA guideline supports continuing statin use beyond 75 years in persons already taking and tolerating a statin.[14] Based on same evidence, the guideline also supports starting moderate-intensity statin treatment (in alphabetical order: atorvastatin [10-20 mg], fluvastatin [80 mg], lovastatin [40 mg], pitavastatin [2-4 mg], pravastatin [40 mg], rosuvastatin [5-10 mg], simvastatin [20-40 mg]) in patients aged 75 to 82 years with clinical ASCVD. Listed doses have been approved by the US Food and Drug Administration, but all statins

Table 1. Observational Studies and Randomized Clinical Trials of Statins in Older People With or Without ASCVD

Source	No. of Participants	Age, y	Mean Follow-up, y	Patient Characteristics	Mortality and ASCVD Findings in Statin Users vs Nonusers
Observational					
Gränsbo et al,[26] 2010	14 907	>80	Up to 5 (median, 0.8)	Post AMI	Users: total mortality, 237.3 per 1000 patient-years; nonusers: 552.7 per 1000 patient-years (propensity score-adjusted HR, 0.55 [95% CI, 0.51-0.59])
Foody et al,[27] 2006	8432	≥80	3.0	Medicare beneficiaries discharged with AMI	Statin at discharge: total mortality, 460 (35.1%); no statin at discharge: 3690 (51.7%) (propensity score-adjusted HR, 0.97 [0.87-1.09])
Olafsdottir et al,[28] 2011	5152	66-96 (mean, 77)	5.3	Population-based, 12.5% had diabetes	Users with diabetes: total mortality, 42 (18.8%); nonusers with diabetes: total mortality, 136 (32.7%) (adjusted HR, 0.47 [95% CI, 0.32-0.71])
Cooke et al,[29] 2009	4232	66-101 (mean, 77.5)	2.3	Population-based, discharged from hospital with CAD	Statin at discharge: total mortality, 186 (11.4%); no statin at discharge: 934 (35.9%) (propensity score-adjusted HR, 0.74 [0.63-0.88] without age interaction)
Shah et al,[30] 2008	3779	>85	3.0	HFpEF	Higher survival probability (log-rank $P < .001$) among those with statin at discharge (adjusted HR, 0.73 [95% CI, 0.62-0.88])
Eaton et al,[31] 2002	2626	>65 (935 >85)	1.0	Nursing home	Users: total mortality, 265 (20.2%); nonusers: 424 (32.3%) (adjusted HR, 0.69 [95% CI, 0.58-0.81]): significant benefit in men and women and age groups 75 to 84 and ≥85
Gnjidic et al,[32] 2013	1665	481 men ≥80	Up to 6.8 (mean, 4.0)	Population-based	Nonsignificant reduction in total mortality (HR, 0.88 [0.66-1.18]); no significant interaction ($P = .73$) between statin use and frailty
Galindo-Ocana et al,[33] 2012	1260	Median, 80 (29% >84)	1.0	Multiple comorbidities (mean comorbidities, 3.2)	Total mortality between users vs nonusers (adjusted HR, 0.67 [95% CI, 0.53-0.84])
Aronow and Ahn,[34] 2002	770	>80	3.0	Post AMI	Reduction in new coronary events in all age groups including those aged 91-100 y (users: 44 [56%]; nonusers: 78 [81%]; $P < .001$); total mortality not reported
Jacobs et al,[35] 2013	702	>85	85-90	Population-based	Better survival (log-rank $P = .01$) among users vs nonusers (adjusted HR, 0.61 [95% CI, 0.42-0.89])
Allen Maycock et al,[36] 2002	655	≥80	3.3	CAD	Total mortality, 9% in users and 29% in nonusers (adjusted HR, 0.50 [95% CI, 0.26-0.96])
Meta-analyses of Placebo-Controlled RCTs					
Savarese et al,[37] 2013 (primary prevention)	24 674 (8 trials [7 double-blind])	>65 (mean, 73)	3.5	No clinical CVD	No significant reduction by statin in total mortality (RR, 0.94 [95% CI, 0.86-1.04]), but reductions in MI (0.61 [95% CI, 0.43-0.85]) and stroke (0.76 [95% CI, 0.63-0.93])
Alifalo et al,[38] 2008 (secondary prevention)	19 569 (9 trials)	>65 (upper age limit 80 y in 4 trials)	3.7	Clinical ASCVD	Users: total mortality, 1531 (15.6%); placebo: 1827 (18.7%) (RR, 0.78 [95% CI, 0.65-0.89]); significant in all 4 trials with the upper age limit of 80 y
Yan et al,[39] 2013 (meta-analysis of RCTs of intensive vs nonintensive statin therapy)	11 132 (5 trials)	>65 (mean, 69.6-74.0)	3.0	CAD	No significant difference in total mortality between intensive and nonintensive statin treatment (HR, 0.97 [95% CI, 0.87-1.09]) but reductions in CVD events: nonfatal MI (RR, 0.78 [95% CI, 0.65-0.94]), stroke (0.72 [95% CI, 0.56-0.94]), and coronary revascularization (0.69 [95% CI, 0.52-0.90])
Kjekshus et al,[40] 2007 (placebo-controlled trial)	2064	>75	3.0	HFrEF	Users: total mortality, 728 (29.0%): placebo: 759 (30.4%) (HR, 0.95 [95% CI, 0.86-1.05])

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; AMI, acute myocardial infarction; CAD, coronary artery disease; CVD, cardiovascular disease; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; MI, myocardial infarction; RCT, randomized clinical trial; RR, relative risk.

and doses have not been tested in RCTs. Among individuals older than 75 years without clinical ASCVD, additional factors must be taken into account.

Observational studies in older people as well as the RCTs in which the upper age limit at baseline has been 82 years are shown in Table 1.[26-40] These studies demonstrate the benefits of statins in patients older than 80 years with ASCVD as secondary prevention. This probably applies to patients with diabetes, but the benefits of statins used for primary prevention in very old patients with diabetes is not well known and recommendations are based on some observational evidence,[28] expert opinion, and patient preference. In addition to considering a patient's personal preferences, it is also important to consider life expectancy, treatment lag time to benefit,[11] biological age (largely equivalent with the degree of frailty), cognitive decline, comorbid conditions (multimorbidity), concomitant use of multiple drugs (polypharmacy), and specific safety concerns regarding statin therapy in older individuals.

Effect of Frailty

Although lacking a universal definition, frailty is now considered a geriatric syndrome characterized by reduced physiological reserve and increased predisposition to even minor stressor events.[19] Clinically it can be defined phenotypically by a combination of weakness, slowness, exhaustion, inactivity, and shrinking or as a cumulative deficit model characterized by a frailty index. Frailty is a common condition; it can be recognized in 10% of people older than 70 years, with prevalence steadily increasing with age. Frail individuals are particularly susceptible to drug adverse effects, and frailty also may result in reduced treatment efficacy. For example, treating hypertension in healthy, robust patients older than 80 years re-

sulted in reduced mortality and cardiovascular disease end points, but the benefits were not seen if the older patients were frail.[41] In an observational study, frail men older than 70 years, of whom many did not have ASCVD, did not show reduced mortality or institutionalization with statin treatment.[32] These observations are similar, for example, to those from an RCT including patients with advanced heart failure not benefitting from statin therapy.[40] In contrast, some studies have shown beneficial effects of statins in frail individuals, such as nursing home residents, patients with many comorbid conditions, and very old patients.[31,33-35]

Adverse Effects of Statins in Older Patients

Potential adverse effects are important to consider. In general, based on RCT outcomes in adult patients younger than 80 years, statins are safe and well tolerated.[25] The same is true for intensive statin therapy in patients older than 65 years but younger than 80 years.[39] However, frail individuals with comorbidity and polypharmacy may be more prone to adverse effects and drug interactions. Because older persons with reduced hepatic or renal function and other significant comorbidities were usually excluded from the RCTs, the spectrum of statin adverse events for these patients is not known. Serious adverse events may also be more frequent in actual practice than those observed in controlled studies. RCTs of statins in vulnerable patients, such as those with advanced heart failure,[40] end-stage renal disease,[42] or dementia,[43] found few adverse effects of statins.

Well-documented, established adverse effects of statins include muscle toxicity, effects on liver enzyme levels, and the recently discovered risk of diabetes.[44-46] Cognitive and neurologic symptoms have been reported, but there is no consistent evidence supporting a cause-effect relationship between statin use and these disorders.[44,45]

For older patients, the muscle-related effects are particularly important. Muscle effects range from pain without elevated serum creatinine kinase levels to rhabdomyolysis. However, the occurrence of life-threatening toxicity is rare. Evidence from 26 randomized statin trials with 170 000 participants showed that the frequencies of myopathy (symptoms plus creatinine kinase levels >10 times the upper limit of normal) and rhabdomyolysis were 11 and 3.4 per 100 000 person-years, respectively.[25] Milder symptoms (myalgia and cramps without elevated creatinine kinase levels) are common, but a true cause-effect relationship is difficult to establish.[44,45] Age older than 75 to 80 years is often listed as a risk factor for adverse effects such as myopathy,[14] but actual evidence for this is inconsistent and possibly confounded in part because of the typically less physically active lifestyle of older people. Adverse muscle effects of statins and the increased overall vulnerability of older people have raised concerns that statin treatment could promote sarcopenia and predispose to frailty, falls, and morbidity, especially in nursing home residents.[47] These complications were not observed in retrospective studies of people with mean ages older than 70 years (**Table 2**).[31-33,48-54] However, most of the studies have not included people older than 80 years at baseline or the frailest individuals living in nursing homes, ie, those about whom the greatest concerns have been raised. Nevertheless, the general conclusion from the available evidence in community-living older people is that statin treatment has no general deteriorating effect on frailty or on physical function. At the individual level—and especially in patients already frail and with polypharmacy—it is important to provide close follow-up for possible adverse effects and also be vigilant to situations, such as drug interactions, dehydration, and comorbidity, in which risk of adverse effects increases.

Other considerations include elevations of hepatic transaminase levels, which usually resolve after dose reduction or discontinuation of the drug or may also normalize spontaneously. The clinical significance of statin-related diabetes is not known in older patients, who may not have time to develop microvascular complications.

There is a higher risk for drug interactions in older people because of polypharmacy. This risk may be higher with lipophilic statins (atorvastatin, lovastatin, pitavastatin, and simvastatin) metabolized by cytochrome P450 3A4 (CYP3A4), which require surveillance for adverse effects in this respect.[13]

Managing Hypercholesterolemia in People Older Than 80 Years

It is important to consider possible secondary causes for hypercholesterolemia, which in an older person may be associated with liver or kidney disease, hypothyroidism (most important in old age), or use of atypical antipsychotic drugs (clozapine, olanzapine, risperidone). Nonpharmacologic therapy should be considered to reduce total risk, including smoking cessation, sodium restriction, avoidance of obesity, and increasing physical activity. There may be caveats for dietary advice for hypercholesterolemia. Threats to quality of life and personal and cultural preferences must be recognized. In an older person, recommending eating less fat or red meat may lead to accelerated sarcopenia and frailty. A nutritionist should be involved when major changes in diet or intentional weight loss is planned. Plant stanol/sterol products (eg, Benecol, Promise Activ, Smart Balance HeartRight, Becel pro.Activ) reduce cholesterol absorption from the small intestine and may reduce serum cholesterol levels by 10% to 17%.[55] Their use may be combined with statin treatment, but no outcome studies are available.

Statins

After more than 25 years of clinical use, statins have been extensively studied and are inexpensive. Physicians can prescribe statins with differing potencies and with different pharmacokinetic properties (hydrophilic or lipophilic, metabolism, excretion, interactions). The ACC/AHA guideline recommends a moderate-intensity (but not a high-intensity) statin treatment for patients older than 75 years and with clinically evident ASCVD.[14] There is no recommendation for initiating statins for patients older than 75 years and without clinical ASCVD. In these cases, decision making is individualized (Box). It is best to choose a low- to moderate-intensity statin regimen, such as with atorvastatin (10 mg), fluvastatin (20-80 mg), lovastatin (20-40 mg), pitavastatin (1-4 mg), pravastatin (10-40 mg), rosuvastatin (5-10 mg), or simvastatin (10-40 mg). There are no age-specific monitoring recommendations, although the threshold for measuring levels of creatinine kinase and glucose can be low. Development of frailty (weight loss, physical inactivity) should be closely monitored in any older individual, irrespective of statin treatment.

There is research interest in potential "pleiotherapeutic" effects of statins—ie, effects not related to ASCVD. These include bet-

Table 2. Observational Studies of Statin Therapy and Functioning in Older People

Source	No. of Participants	Age, y	Proportion of Women, No. (%)	Follow-up, y	Findings in Statin Users
LaCroix et al,[48] 2008 (WHI-OS)	25 378	65-79	25 378 (100)	3.0	No overall association with development of frailty (adjusted OR, 1.00 [95% CI, 0.85-1.16]); longer use (at least 3 y) with low-potency statins (simvastatin, lovastatin, pravastatin, or fluvastatin) was associated with less development of frailty (OR, 0.55 [95% CI, 0.28-1.09]; P = .02 for trend)
Gray et al,[49] 2012 (WHI clinical trials)	5777	65-79	5777 (100)	6.0	No overall association with physical performance including walk speed, grip strength, and chair stands
Cooke et al,[29] 2009	4232	66-101 (mean, 77.5)	2196 (52)	Mean, 2.3	Despite a reduction in total mortality (Table 1), no difference in health service utilization (HR, 1.04 [95% CI, 0.97-1.12])
Lee et al,[50] 2014	4137	>65 (mean, 72.9)	0	Mean, 6.9	Modestly lower physical activity than among nonusers (difference in metabolic equivalents, −0.03 [95% CI, −0.04 to −0.02])
Lynch et al,[51] 2012	3422	Mean, 81	2053 (60)	Rehabilitation period (median, 36 d)	Various indications (eg, stroke, hip fracture, major surgery) for rehabilitation; greater adjusted improvement in the 20-point Barthel scores (4.30 vs 3.59 points, P < .001) during the rehabilitation period (similar scores at baseline)
Gray et al,[52] 2011 (Health Aging and Body Composition Study)	3055	70-79	1587 (52)	6.5	No effect on development of mobility disability (HR, 1.02 [95% CI, 0.87-1.17])
Eaton et al,[31] 2002	2626 (nursing home patients)	>65 (935 >85)	1897 (72)	1.0	Despite lower total mortality (Table 1), no difference in decline of physical function (HR, 0.89 [95% CI, 0.55-1.45]) in men; 0.96 [95% CI, 0.73-1.26] in women)
Gnjidic et al,[32] 2013	1665	>70 (mean, 77); 481 men ≥80	0	Up to 6.8	No significant interaction (P = .40) between statin use and frailty for institutionalization
Galindo-Ocana et al,[33] 2012	1260 (patients with multiple morbidities (polypathological)	Median, 80 (29% >84)	611 (48.5)	1.0	Less decline in Barthel index (HR, 0.48 [95% CI, 0.32-0.71]) among those with index 60 or higher at baseline; no significant difference among those with lower index at baseline (HR, 1.05 [95% CI, 0.71-1.57])
Agostini et al,[53] 2007	756	>65 (mean, 74)	7 (1)	Statin use 2 y before	Better timed chair stands (−0.5 s, P = .04) but overall modest differences between users and nonusers
Witham et al,[54] 2014	639	Mean, 65	318 (50)	Mean, 4.4	No significant difference in change of hand grip during follow-up between users and nonusers

Abbreviations: HR, hazard ratio; OR, odds ratio; WHI-OS, Women's Health Initiative Observational Study.

ter recovery from serious infections or trauma, reduced incidence (or better outcome) of certain cancers, and fewer complications with surgery.[56-58] No RCT evidence for patients of any age are available to support these claims.

Other Drugs

Nonstatin medications for hypercholesterolemia include ezetimibe, which inhibits cholesterol absorption, and resins, which inhibit bile acid reabsorption. These medications can be combined with statins or used alone, especially in statin-intolerant patients, to reduce LDL-C level. Fibrates and niacin, alone or combined with statins, can be used in select cases of combined hyperlipidemia and hypertriglyceridemia. There are no outcome studies in patients older than 80 years, and these drugs may have adverse effects that further limit their use.[59]

When to Discontinue Statin Therapy?

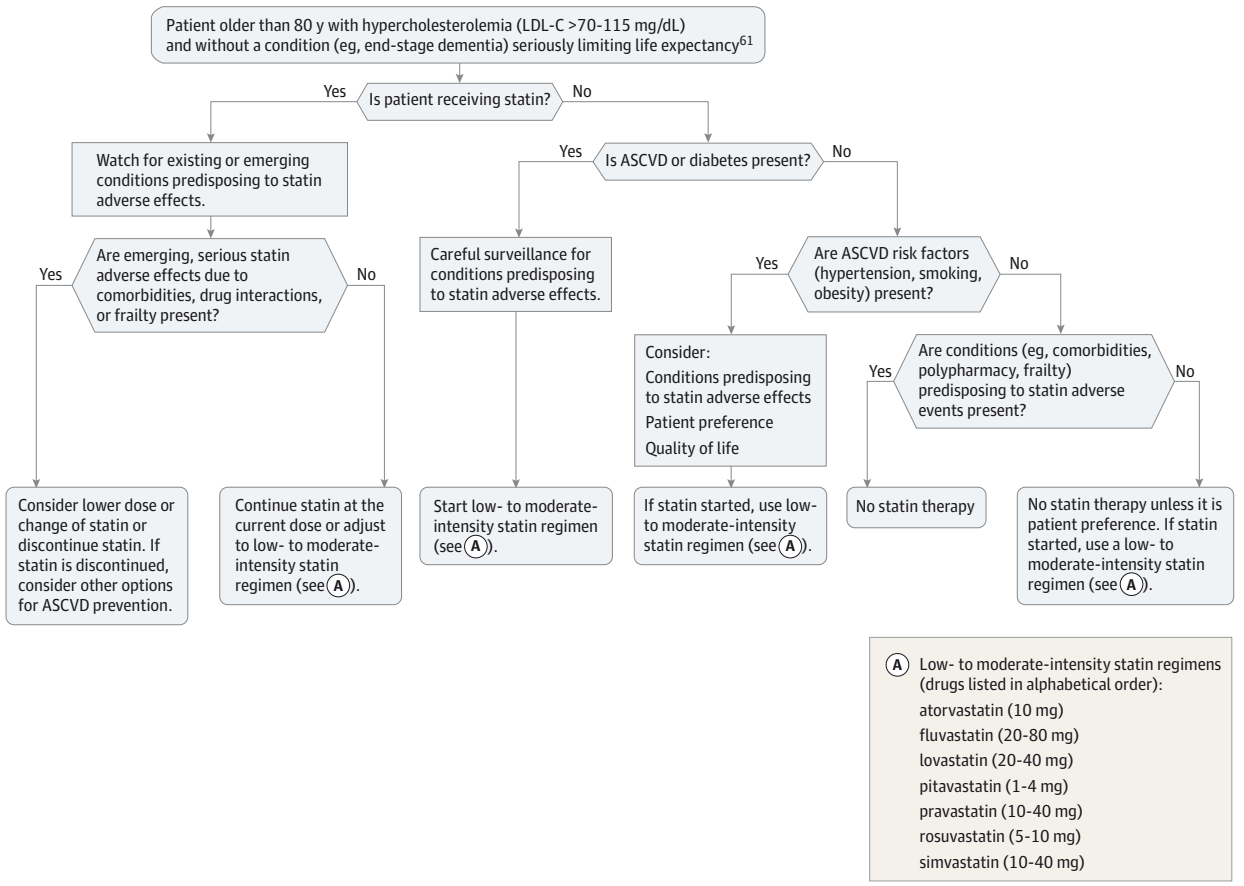
Adverse Effects Threatening Physical and Mental Function

It is mandatory to consider statin discontinuation if there are adverse effects impairing quality of life that cannot be managed by dose reduction or change of statin type. However, it is possible to successfully rechallenge patients older than 75 years after an adverse effect.[60] Conditions that predispose to serious adverse effects include drug interactions, extreme polypharmacy, frailty, and comorbidity. It is important to note that comorbidity and development of frailty are not indications for palliative care only; nor is treatment in a nursing home considered palliative care. Therefore, not using statin therapy for these reasons is not appropriate. Quality of life of even these most vulnerable patients can be better preserved if an ASCVD event is avoided with statin therapy.

Transition to End-of-Life Care

In the care of older patients, determination of life expectancy is important[9-11] but not always straightforward. Assessment may be facilitated by calculators[61] and predictive tools such as the Multidimensional Prognostic Index that have been validated in older persons having a variety of clinical conditions.[10] When recommending preventive treatments it is important to consider life expectancy, because it relates to the time in which benefits or harms are expected.[11,62] For statin treatment, the time to benefit may be less than 2 years[62]—well within the general life expectancy of men and women older than 80 years and also within the average life expectancy (4 to 12 years depending on comorbidities) of an individual with a new diagnosis of Alzheimer disease.[63] When a decision to pursue only palliative or symptomatic

Figure. Suggested Treatment Algorithm for Statin Treatment in Patients Older Than 80 Years With Hypercholesterolemia and Without a Condition Seriously Limiting Life Expectancy



This approach is used by the authors and is based on the best available evidence but does not represent treatments validated in clinical trials, because the clinical features of the patients considered in this article have not been studied in randomized clinical trials. ASCVD indicates atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

treatment of a terminal disease is made, ASCVD preventive treatments should be discontinued, irrespective of chronological age. Typical reasons for palliative treatment are incurable cancer, end-stage heart or kidney failure, and the final phase of Alzheimer disease, end-stage dementia, when an individual has lost the capability of responding to the environment, ability to speak, and finally to control movements, corresponding to the final, seventh phase of the Functional Assessment Stages scores.[64] A consensus panel of geriatricians in a US university center considered statins as never appropriate in such patients.[65] Interestingly, no consensus was reached on aspirin or vitamins for these patients.

Recommendations for Mr S, Mr J, and Ms P

What recommendations should be made for the 3 patients presented in this article? Treatment recommendations for persons older than 80 years who have hypercholesterolemia and a time to benefit of statin treatment exceeding life expectancy are presented in the **Figure**. This approach is used by the authors and is based on the best available evidence but does not represent treatments validated in clinical trials, because the clinical features of the patients considered in this article have not been studied in RCTs. It is important to distinguish patients already using a statin when they turn 80 years old (ie, they have started their treatment at an age where there is RCT evidence of benefit) from those with de novo initiation after that age. In secondary prevention, the benefits of statin therapy outweigh the risk of serious adverse events. In primary prevention, each patient's characteristics predisposing to adverse effects (frailty status, comorbidities, other medications) as well as quality of life should be considered in the decision to start treatment. Shared decision making is very important in old age. Among older people, personal preferences vary. Some value longevity and avoidance of infarction or stroke and may appreciate even a small probability of benefit; for others, avoidance of adverse effects of therapy is most important. It is also worth ensuring that the patient's assumptions are not based on unrealistic expectations of benefits (eg, "statins make me immortal") or misinformation about adverse effects (eg, "statins cause dementia").

Statin therapy for Mr S, the 89-year-old, should have been started 10 to 20 years earlier. It is not likely that initiation of statin therapy a few months earlier would have changed the patient's clini-

cal course. In this patient, ASCVD was far enough advanced that statin therapy would not be beneficial.

Mr J, the 92-year-old, should continue statin therapy unless unmanageable adverse effects occur or his clinical condition deteriorates sufficiently to require initiation of palliative treatment.

Ms P, the 86-year-old, is nearing the stage when the statin could be discontinued, but currently, despite her Alzheimer disease, her calculated 1-year mortality risk is only 3.6% (estimated using the Estimated Prognosis for Elders tool[61]), so it is reasonable to continue her statin therapy because the benefits for statin therapy are expected to continue within this time frame.

Clinical Bottom Line

- People older than 80 years comprise an increasing patient segment in whom hypercholesterolemia and risk of cardiovascular disease are prevalent.
- Ideally, treatment of hypercholesterolemia (usually with a statin) in high-risk individuals should be started before age 80 years.
- Older people are a heterogeneous group, both clinically and functionally.
- Decisions to start statins in older individuals should be made individually and are not supported by high-quality evidence.

ARTICLE INFORMATION

Author Contributions: Dr Strandberg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Obtained funding: Strandberg.
Administrative, technical, or material support: Strandberg.
Study supervision: Strandberg.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Strandberg reported receiving lecture or consultation fees from Amgen, Merck, NovoNordisk, Nutricia, Pfizer, Sanofi, and Takeda; holding stock from OrionPharma; participating in national and international treatment trials funded by pharmaceutical companies; and serving as president of the European Union Geriatric Medicine Society. Dr Kolehmainen reported receiving lecture fees from Novartis and Lilly and travel expenses from Abbott and sanofi-aventis. Dr Vuorio reported receiving lecture honoraria from Aegerion.

Funding/Support: Dr Strandberg reported that his research, not directly applicable to this review, has been supported by the University Central Hospitals of Helsinki and Oulu and by the Gustav V och Victoria Frimurarestiftelse.

Role of the Funders/Sponsors: The funders/sponsors had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Additional Contributions: We thank the patients, their relatives, and their physicians for sharing their stories and for providing permission to publish them. We thank Andy Langdon (Helsinki, Finland) for proofreading, Leena Lodenius, MSci (Finnish Medical Society Duodecim, Helsinki, Finland), for help in the literature search, and Petri T. Kovanen, MD, PhD (Wihuri Research Institute, Helsinki, Finland), for valuable comments on the first version of the manuscript. None of these individuals received any compensation for their contributions.

Care of the Aging Patient Series: Authors interested in contributing Care of the Aging Patient articles may contact the section editor Dr Livingston at edward.livingston@jamanetwork.org.

Care of the Aging Patient: From Evidence to Action is produced and edited at the University of California, San Francisco, by Kenneth Covinsky, MD, Louise Walter, MD, Louise Aronson, MD, MFA, and Anna Chang, MD; Amy J. Markowitz, JD, is managing editor.

REFERENCES

1. Organisation for Economic Co-operation and Development (OECD). OECD.StatExtracts. OECD website. http://stats.oecd.org/Index.aspx/DataSetCode=HEALTH_STAT. Accessed August 7, 2014.

2. Social Security Administration (SSA). Actuarial Life Table. SSA website. http://www.ssa.gov/oact/STATS/table4c6.html. Accessed August 7, 2014.

3. Christensen K, Thinggaard M, Oksuzyan A, et al. Physical and cognitive functioning of people older than 90 years: a comparison of two Danish cohorts born 10 years apart. *Lancet*. 2013;382(9903):1507-1513.

4. Andersen-Ranberg K, Fjederholt KT, Madzak A, Nybo M, Jeune B. Cardiovascular diseases are largely underreported in Danish centenarians. *Age Ageing*. 2013;42(2):249-253.

5. Strandberg TE, Pitkälä KH, Tilvis RS, O'Neill D, Erkinjuntti TJ. Geriatric syndromes—vascular disorders? *Ann Med*. 2013;45(3):265-273.

6. Scuteri A, Lakatta EG. Bringing prevention in geriatrics: evidences from cardiovascular medicine supporting the new challenge. *Exp Gerontol*. 2013;48(1):64-68.

7. Schatz IJ, Masaki K, Yano K, Chen R, Rodriguez BL, Curb JD. Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study. *Lancet*. 2001;358(9279):351-355.

8. Drewes YM, Poortvliet RKE, Blom JW, et al. Homocysteine levels and treatment effect in the PROspective Study of Pravastatin in the Elderly at Risk. *J Am Geriatr Soc*. 2014;62(2):213-221.

9. Gill TM. The central role of prognosis in clinical decision making. *JAMA*. 2012;307(2):199-200.

10. Pilotto A, Panza F, Ferrucci L. A multidimensional prognostic index in common conditions leading to death in older patients. *Arch Intern Med*. 2012;172(7):594-595.

11. Lee SJ, Leipzig RM, Walter LC. Incorporating lag time to benefit into prevention decisions for older adults. *JAMA*. 2013;310(24):2609-2610.

12. Petersen LK, Christensen K, Kragstrup J. Lipid-lowering treatment to the end? a review of observational studies and RCTs on cholesterol and mortality in 80+-year olds. *Age Ageing*. 2010;39(6):674-680.

13. Szadkowska I, Stanczyk A, Aronow WS, et al. Statin therapy in the elderly: a review. *Arch Gerontol Geriatr*. 2010;50(1):114-118.

14. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25)(suppl 2):S1-S45.

15. Lewington S, Whitlock G, Clarke R, et al; Prospective Studies Collaboration. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet*. 2007;370(9602):1829-1839.

16. Tian J, Gu X, Sun Y, et al. Effect of statin therapy on the progression of coronary atherosclerosis. *BMC Cardiovasc Disord*. 2012;12:70.

17. Marais AD, Kim JB, Wasserman SM, Lambert G. PCSK9 inhibition in LDL cholesterol reduction: genetics and therapeutic implications of very low plasma lipoprotein levels [published online July 18, 2014]. *Pharmacol Ther*. doi:10.1016/j.pharmthera.2014.07.004.

18. Stein EA, Raal FJ. Targeting LDL: is lower better and is it safe? *Best Pract Res Clin Endocrinol Metab*. 2014;28(3):309-324.

19. Afilalo J, Alexander KP, Mack MJ, et al. Frailty assessment in the cardiovascular care of older adults. *J Am Coll Cardiol*. 2014;63(8):747-762.

20. Fontana L, Addante F, Copetti M, et al. Identification of a metabolic signature for multidimensional impairment and mortality risk in hospitalized older patients. *Aging Cell*. 2013;12(3):459-466.

21. Tilvis RS, Valvanne JN, Strandberg TE, Miettinen TA. Prognostic significance of serum cholesterol, lathosterol, and sitosterol in old age; a 17-year population study. *Ann Med*. 2011;43(4):292-301.

22. Corti M-C, Guralnik JM, Salive ME, et al. Clarifying the direct relation between total cholesterol levels and death from coronary heart disease in older persons. *Ann Intern Med*. 1997;126(10):753-760.

23. STAREE Study Investigators. A Clinical Trial of STAtin Therapy for Reducing Events in the Elderly (STAREE). ClinicalTrials.gov website.

http://clinicaltrials.gov/show/NCT02099123. Accessed June 21, 2014.

24. Chokshi NP, Messerli FH, Sutin D, Supariwala AA, Shah NR. Appropriateness of statins in patients aged ≥80 years and comparison to other age groups. *Am J Cardiol*. 2012;110(10):1477-1481.

25. Baigent C, Blackwell L, Emberson J, et al; Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376(9753):1670-1681.

26. Gränsbo K, Melander O, Wallentin L, et al. Cardiovascular and cancer mortality in very elderly post-myocardial infarction patients receiving statin treatment. *J Am Coll Cardiol*. 2010;55(13):1362-1369.

27. Foody JM, Rathore SS, Galusha D, et al. Hydroxymethylglutaryl-CoA reductase inhibitors in older persons with acute myocardial infarction: evidence for an age-statin interaction. *J Am Geriatr Soc*. 2006;54(3):421-430.

28. Olafsdottir E, Aspelund T, Sigurdsson G, et al. Effects of statin medication on mortality risk associated with type 2 diabetes in older persons: the population-based AGES-Reykjavik Study. *BMJ Open*. 2011;1(1):e000132.

29. Cooke CA, Kirkland SA, Sketris IS, Cox J. The impact of statins on health services utilization and mortality in older adults discharged from hospital with ischemic heart disease: a cohort study. *BMC Health Serv Res*. 2009;9:198.

30. Shah R, Wang Y, Foody JM. Effect of statins, angiotensin-converting enzyme inhibitors, and beta blockers on survival in patients >or=65 years of age with heart failure and preserved left ventricular systolic function. *Am J Cardiol*. 2008;101(2):217-222.

31. Eaton CB, Lapane KL, Murphy JB, Hume AL. Effect of statin (HMG-Co-A-Reductase Inhibitor) use on 1-year mortality and hospitalization rates in older patients with cardiovascular disease living in nursing homes. *J Am Geriatr Soc*. 2002;50(8):1389-1395.

32. Gnjidic D, Le Couteur DG, Blyth FM, et al. Statin use and clinical outcomes in older men: a prospective population-based study. *BMJ Open*. 2013;3(3):e002333.

33. Galindo-Ocaña J, Bernabeu-Wittel M, Formiga F, et al; PROFUND Project Researchers. Effects of renin-angiotensin blockers/inhibitors and statins on mortality and functional impairment in polypathological patients. *Eur J Intern Med*. 2012;23(2):179-184.

34. Aronow WS, Ahn C. Incidence of new coronary events in older persons with prior myocardial infarction and serum low-density lipoprotein cholesterol > or = 125 mg/dl treated with statins versus no lipid-lowering drug. *Am J Cardiol*. 2002;89(1):67-69.

35. Jacobs JM, Cohen A, Ein-Mor E, Stessman J. Cholesterol, statins, and longevity from age 70 to 90 years. *J Am Med Dir Assoc*. 2013;14(12):883-888.

36. Allen Maycock CA, Muhlestein JB, Horne BD, et al; Intermountain Heart Collaborative Study. Statin therapy is associated with reduced mortality across all age groups of individuals with significant coronary disease, including very elderly patients. *J Am Coll Cardiol*. 2002;40(10):1777-1785.

37. Savarese G, Gotto AM Jr, Paolillo S, et al. Benefits of statins in elderly subjects without established cardiovascular disease: a meta-analysis. *J Am Coll Cardiol*. 2013;62(22):2090-2099.

38. Afilalo J, Duque G, Steele R, Jukema JW, de Craen AJ, Eisenberg MJ. Statins for secondary prevention in elderly patients: a hierarchical Bayesian meta-analysis. *J Am Coll Cardiol*. 2008;51(1):37-45.

39. Yan YL, Qiu B, Hu LJ, et al. Efficacy and safety evaluation of intensive statin therapy in older patients with coronary heart disease: a systematic review and meta-analysis. *Eur J Clin Pharmacol*. 2013;69(12):2001-2009.

40. Kjekshus J, Apetrei E, Barrios V, et al; CORONA Group. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med*. 2007;357(22):2248-2261.

41. Muller M, Smulders YM, de Leeuw PW, Stehouwer CD. Treatment of hypertension in the oldest old: a critical role for frailty? *Hypertension*. 2014;63(3):433-441.

42. Fellström BC, Jardine AG, Schmieder RE, et al; AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med*. 2009;360(14):1395-1407.

43. McGuinness B, O'Hare J, Craig D, Bullock R, Malouf R, Passmore P. Cochrane review on "Statins for the Treatment of Dementia." *Int J Geriatr Psychiatry*. 2013;28(2):119-126.

44. Jukema JW, Cannon CP, de Craen AJM, Westendorp RGJ, Trompet S. The controversies of statin therapy: weighing the evidence. *J Am Coll Cardiol*. 2012;60(10):875-881.

45. Macedo AF, Taylor FC, Casas JP, Adler A, Prieto-Merino D, Ebrahim S. Unintended effects of statins from observational studies in the general population: systematic review and meta-analysis. *BMC Med*. 2014;12(1):51.

46. Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients—the PRIMO study. *Cardiovasc Drugs Ther*. 2005;19(6):403-414.

47. Morley JE, Mahon G. Statins and the nursing home. *J Am Med Dir Assoc*. 2013;14(12):853-854.

48. LaCroix AZ, Gray SL, Aragaki A, et al; Women's Health Initiative. Statin use and incident frailty in women aged 65 years or older: prospective findings from the Women's Health Initiative Observational Study. *J Gerontol A Biol Sci Med Sci*. 2008;63(4):369-375.

49. Gray SL, Aragaki AK, LaMonte MJ, et al. Statins, angiotensin-converting enzyme inhibitors, and physical performance in older women. *J Am Geriatr Soc*. 2012;60(12):2206-2214.

50. Lee DSH, Markwardt S, Goeres L, et al. Statins and physical activity in older men: the osteoporotic fractures in men study. *JAMA Intern Med*. 2014;174(8):1263-1270.

51. Lynch JE, Henderson NR, Ramage L, McMurdo MET, Witham MD. Association between statin medication use and improved outcomes during inpatient rehabilitation in older people. *Age Ageing*. 2012;41(2):260-262.

52. Gray SL, Boudreau RM, Newman AB, et al. Angiotensin-converting enzyme inhibitor and statin medication use and incident mobility limitation in community older adults: the Health, Aging and Body Composition Study. *J Am Geriatr Soc*. 2011;59(12):2226-2232.

53. Agostini JV, Tinetti ME, Han L, McAvay G, Foody JM, Concato J. Effects of statin use on muscle strength, cognition, and depressive symptoms in older adults. *J Am Geriatr Soc*. 2007;55(3):420-425.

54. Witham MD, Syddall HE, Dennison E, Cooper C, McMurdo MET, Sayer AA. ACE inhibitors, statins and thiazides: no association with change in grip strength among community dwelling older men and women from the Hertfordshire Cohort Study [published online February 11, 2014]. *Age Ageing*. doi:10.1093/ageing/afu008.

55. Baumgartner S, Mensink RP, Plat J. Plant sterols and stanols in the treatment of dyslipidemia: new insights into targets and mechanisms related to cardiovascular risk. *Curr Pharm Des*. 2011;17(9):922-932.

56. Iannuzzi JC, Rickles AS, Kelly KN, et al. Perioperative pleiotropic statin effects in general surgery. *Surgery*. 2014;155(3):398-407.

57. Kozarov E, Padro T, Badimon L. View of statins as antimicrobials in cardiovascular risk modification. *Cardiovasc Res*. 2014;102(3):362-374.

58. Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. *N Engl J Med*. 2012;367(19):1792-1802.

59. Thomas JE, Tershakovec AM, Jones-Burton C, Sayeed RA, Foody JM. Lipid lowering for secondary prevention of cardiovascular disease in older adults. *Drugs Aging*. 2010;27(12):959-972.

60. Zhang H, Plutzky J, Turchin A. Discontinuation of statins in routine care settings. *Ann Intern Med*. 2013;159(1):75-76.

61. Estimating Prognosis for Elders. ePrognosis website. http://eprognosis.ucsf.edu. Accessed August 19, 2014.

62. Holmes HM, Min LC, Yee M, et al. Rationalizing prescribing for older patients with multimorbidity: considering time to benefit. *Drugs Aging*. 2013;30(9):655-666.

63. DuGoff EH, Canudas-Romo V, Buttorff C, Leff B, Anderson GF. Multiple chronic conditions and life expectancy: a life table analysis. *Med Care*. 2014;52(8):688-694.

64. American Geriatrics Society (AGS). A Guide to Dementia Diagnosis and Treatment. AGS website. http://dementia.americangeriatrics.org/. Accessed August 19, 2014.

65. Holmes HM, Sachs GA, Shega JW, Hougham GW, Cox Hayley D, Dale W. Integrating palliative medicine into the care of persons with advanced dementia: identifying appropriate medication use. *J Am Geriatr Soc*. 2008;56(7):1306-1311.