Drugs Aging (2015) 32:87–93
DOI 10.1007/s40266-014-0238-5

CURRENT OPINION

Statin Treatment for Older Adults: The Impact of the 2013 ACC/AHA Cholesterol Guidelines

Yitzchak Weinberger · Benjamin H. Han

Published online: 14 January 2015
© Springer International Publishing Switzerland 2015

Abstract The 2013 American College of Cardiology (ACC) and American Heart Association (AHA) practice guidelines for the treatment of blood cholesterol significantly changed the paradigm of how providers should prescribe statin therapy, especially for older adults. While the evidence supports statin therapy for older adults with cardiovascular disease for secondary prevention and with high cardiovascular risk for primary prevention, the evidence is lacking for older adults without major cardiovascular risk aside from age. The unclear evidence base for older adults must be considered along with the potential harms of statin therapy when incorporating the 2013 ACC/AHA practice guidelines for considering statin treatment, particularly for primary prevention for older adults.

Key Points

The 2013 ACC/AHA statin prescribing guidelines represent a fundamental shift in how statins will be prescribed in primary prevention.

Older age groups are particularly impacted by the new guidelines, as age appears to be the major determining factor in initiating a statin for primary prevention.

A study is needed to justify initiating statins in older adults with low normal cholesterol levels and no clinical atherosclerotic cardiovascular disease risk factors.

1 Introduction

In the last century, there has been an increase in the population aging. Advanced life-saving procedures, new medications, and our evolving medical knowledge are key factors in increased longevity. The focus on prevention has contributed to the growing numbers of older people. Cardiovascular disease (CVD) remains the number one cause of death, and the application of measures to prevent it has undoubtedly contributed to the increase of the older population. Age is one of the most recognized non-modifiable risk factors for CVD. Other modifiable risk factors such as hypertension, diabetes mellitus, dyslipidemia, and obesity may be increased with older age [1]. Therefore, primary and secondary prevention for CVD is of importance for older adults who possess the inherent risk for developing CVD.

Y. Weinberger
Department of Medicine, Brookdale Hospital Medical Center, Brookdale Plaza, Brooklyn, NY 11212, USA
e-mail: YWeinber@bhmcny.org

B. H. Han (✉)
Division of Geriatric Medicine and Palliative Care, Department of Medicine, New York University School of Medicine, 550 1st Ave., New York, NY 10016, USA
e-mail: Benjamin.Han@nyumc.org

Statins are very effective in lowering low-density lipoprotein (LDL) cholesterol [2] and shown to be cardioprotective through their anti-inflammatory and oxidative properties [3]. This has been associated with a decrease in cardiovascular disease outcomes [2], but for only for specific patient populations. Unfortunately, many clinical research trials have excluded older adults [4], and the evidence base for many treatments for older patients is lacking. The 2013 American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines for cholesterol treatment have the greatest implications for older age groups; however, the evidence especially for primary prevention is unclear.

2 ACC/AHA Blood Cholesterol Guidelines

The new paradigm shift for which populations should be considered for statin treatment comes from new recommendations and prescribing guidelines issued in 2013 by the ACC/AHA [5]. The guidelines identified four groups of patients who should be considered for statin treatment. These groups are adults with: (1) clinical atherosclerotic cardiovascular disease (ASCVD) defined as coronary artery disease, cerebrovascular disease, and peripheral arterial disease, (2) LDL levels >190 mg/dL, (3) patients with diabetes mellitus aged 40–75 years with LDL levels >70 mg/dL, (4) LDL >70mg/dL and a 10-year risk of ASCVD of at least 7.5 %. New pooled cohort equations and a risk-calculator were developed to estimate the 10-year risk of developing ASCVD outcomes for the purposes of primary prevention [6]. The guidelines specify to calculate ASCVD risk using the calculator for adults up to the age of 79 years, and do not mention considerations to stop statin therapy for adults aged over 79 years.

These guidelines were met with much criticism. The majority expressed concern with regard to the great increase in the number of patients subject to statin therapy [7–9]. A recent study concluded that under the new guidelines, an increase in the net number of new statins prescriptions would exceed 10 million [9]. This expansion would be mostly in older adults between the ages of 60 and 75 years. The guidelines themselves indicate that age would be a major deciding factor in initiating statins. Using the 10-year ASCVD risk calculator [6] with its stated optimal values for total cholesterol of 170 mg/dL, high-density lipoprotein (HDL) of 50 mg/dL, systolic blood pressure of 110 mm Hg, not taking medications for hypertension, not having diabetes mellitus, and not a smoker: all white men aged between 63 and 75 years, all white women aged between 71 and 75 years, all African American men aged between 66 and 75 years, and all African American women aged between 70 and 75 years would be determined to be statin candidates for primary prevention. A new condition, "statinopause" or "statin deficiency", was coined to describe this [10].

3 Evidence for Primary Prevention for Older Adults

The 2013 ACC/AHA cholesterol guidelines do recommend statin treatment as primary prevention for older adults, and careful review of the evidence used for the guidelines is warranted for the basis of these practice recommendations.

A 2009 meta-analysis on the effect of statins in subjects without CVD disease that included more than 70,000 participants, found a decrease in mortality and reduction in coronary and cerebrovascular events [11].This analysis, however, was not focused on the older population; in a subgroup analysis of those aged older than 65 years the same benefit was found. However, the benefits in the older sub-group did not reach statistical significance. The confidence interval for all-cause mortality and cerebrovascular events in the subgroup of patients aged >65 years crossed the identity line pointing towards no definitive evidence of benefit.

A more recent meta-analysis that focused only on older patients aged ≥65 years did find statins to significantly reduce the incidence of myocardial infarction (MI) and stroke, but not significantly reduce all-cause death or cardiovascular death [12]. Again, careful examination of the eight studies selected for this meta-analysis shows that all of the studies involved patients with high cardiovascular risk ranging from hypercholesterolemia to diabetes mellitus. Therefore, this meta-analysis only shows benefit for a subpopulation of older adults, and is not generalizable to older adults without high cardiovascular risk.

The first statin trial to include a cohort of older individuals was the AFCAPS/TexCAPS study [13]. This trial included over 6,000 participants of whom roughly 20 % were aged ≥65 years. The entry lipid parameters were hypercholesterolemia and/or low HDL levels with the benefits of lovastatin vs the placebo being studied. Treatment with lovastatin resulted in a 37 % reduction ($p < 0.001$) in the risk of an acute major coronary event. Thus, this trial demonstrated the efficacy of a statin in primary prevention among specifically older adults with hypercholesterolemia and/or low HDL.

Following the AFCAPS/TexCAPS trial, the ALLHAT-LLA [14] trial evaluated pravastatin vs placebo in subjects aged ≥55 years who were also enrolled in its portion of the blood pressure-lowering trial (ALLHAT). Subjects aged ≥65 years comprised 55 % of the trial participants. All participants had hypertension, as it was a lipid study within a hypertensive study. A large number of participants also had diabetes mellitus (35 %), and a smaller yet significant

percent had history of cardiovascular heart disease (CHD) (15 %). This trial did not find significant reduction in total mortality, CHD, or stroke in the statin group.

Like the ALLHAT-LLA, the ASCOT-LLA [15], was a statin trial within a larger hypertensive trial (ASCOT). The entry criterion was high-risk individuals with at least three cardiovascular risk factors. Participants aged ≥60 years comprised 64 % of the study population. Atorvastatin vs placebo was studied. The treatment group across all ages had a significant reduction in primary endpoints of myocardial infarction and fatal CHD events (36 % reduction). This trial supported the use of statins for primary prevention specifically for high-risk older adults.

The HPS [16] and PROSPER [17] were also clinical trials investigating statins in high-risk individuals, but also included a cohort for secondary prevention. HPS studied simvastatin vs placebo in individuals aged 40–80 years. Although the percentage of patients aged older than 65 years were not reported in the primary prevention group, overall, more than half of the trial participants were aged older than 65 years. The treatment group had a significant 25 % reduction in the primary endpoint of first major coronary artery disease event. This reduction was regardless of age.

The PROSPER [17] trial is the only trial specifically designed to study statins in older adults aged 70 years and older. It enrolled high-risk participants as well as those with established vascular disease to study the effect of pravastatin vs placebo. Of the study population, 55.8 % were considered primary prevention, although with high risk for cardiovascular disease, and the remainder with established vascular disease. The primary outcome included the composite of CHD death, non-fatal MI, and fatal or non-fatal stroke. The primary endpoint was reduced by 15 % ($p = 0.014$) and included a 24 % reduction in CHD death and a 19 % reduction in combined CHD death and non-fatal MI. However the study did not reach statistical significance for statin benefit in stroke prevention and reduction of all-cause mortality. The long-term follow-up of the PROSPER trial also did not reach a significant reduction of all-cause mortality in the pravastatin group [18].

The CARDS [19] trial examined atorvastatin vs placebo in patients with diabetes mellitus. More than 50 % of the patient population were aged older than 60 years, with 12 %aged older than 70 years. The study was terminated early because of a significant decrease in events in the atorvastatin group, indicating a statin benefit in adults with diabetes mellitus.

In a sub-study analysis of the more recent JUPITER [20] study, which included 5,695 participants aged over 70 years, a significant reduction in major cardiovascular events was found in the statin group. The number needed to treat to prevent a cardiovascular event in 4 years was in fact smaller in the older cohort compared with the younger cohort studied in the parent trial, JUPITER. In addition, the entry criteria for the JUPITER study required a high-sensitivity C-reactive Protein (hsCRP) level of ≥2 mg/dL. In clinical practice, it is unclear how to interpret older adults with an hsCRP of ≥2 mg/dL, and whether this population is generalizable to older adults without significant cardiovascular disease risk factors.

There is a lack of data for primary prevention in older patients. Although these individuals may benefit most from statins owing to their age being a significant risk factor, it is difficult to justify initiating statin therapy to all older adults especially those without risk factors aside from age. The few clinical trials done for this age group focused specifically on a subset of older adults with high cardiovascular risk. A review of all the randomized controlled trials of statin therapy for primary prevention that included older individuals can be found in Table 1.

4 Evidence for Secondary Prevention for Older Adults

The evidence is more robust for statin therapy in older adults with established clinical ASCVD (secondary prevention), and summarized in Table 2. The ACC/AHA guidelines when discussing statins for secondary prevention in older adults support moderate intensity statin therapy over high intensity for those aged older than 75 years [5]. There is insufficient evidence from randomized controlled studies to support high-intensity therapy for individuals aged older than 75 years. In addition, the guidelines of the Expert Panel consider it reasonable to continue statin therapy in persons aged >75 years who have clinical ASCVD and are tolerating statin therapy.

The first major secondary prevention trial was the 1994 4S study [21]. Of the 4,444 participants, 2,282 were aged ≥60 years (51.3 %). Simvastatin vs placebo was studied in patients with known cardiovascular heart disease. Simvastatin significantly reduced the primary outcome measure of all-cause mortality in the older age group, as it did in the younger group. A subgroup analysis of patients aged over 65 years found the absolute risk reduction of all-cause mortality to be greater in the older subjects than in the younger subjects [22]. This is most likely because of the higher cardiovascular disease event rate in the older population.

A 2008 secondary prevention meta-analysis found benefits in starting statin therapy for individuals aged 65–82 years [23]. This analysis included nine trials with 19,569 patients with an age range of 65–82 years. One of the trials included in the meta-analysis was the PROSPER study with access to its unpublished data. The published

Table 1 Primary prevention trials with older adults

Trial	Total patients	Older participants	CAD risk factors	Intervention	Primary endpoint	Outcome Intervention vs placebo	Absolute risk reduction (%)	Relative risk reduction for primary outcome
AFCAPS/ TexCAPS	6,605 patients: men aged 45–73 years; women post-menopausal 55–73	1,416 (21 %) aged ≥65 years (1,064 men; 352 women)	Hypercholesterolemia	Lovastatin (20–40 mg) vs placebo in addition to a low-saturated fat, low-cholesterol diet	Reduction in rate of first acute major coronary event	3.5 vs 5.5 % first major coronary events (37 % rate reduction, $p < 0.001$)	2.00	37 % (NNT = 51)
ALLHAT-LLA	10,355 patients: men and women, ages 55 years and older	5,707 men and women aged ≥65 years (55 %)	All participants with HTN, 14 % of patients with CAD and 35 % with type 2 DM	Pravastatin 40 mg vs usual care	Reduction in all-cause mortality	12.2 vs 12.3 % deaths (no significant reduction in all-cause mortality, $p = 0.88$)	1.10	10.6 % (NNT = 91)
ASCOT-LLA	10,305 patients men and women, ages 40–79 years	6,570 men and women aged >60 years (64 %)	All participants with HTN and three cardiovascular risk factors (DM, PAD, CVA, smoker, or low HDL)	Atorvastatin 10 mg vs placebo	Reduction of non-fatal MI and fatal CAD	1.9 vs 3.0 % events (36 % reduction, $p < 0.0005$)	1.10	36 % (NNT = 94)
CARDS	2,838 patients: men and women, ages 40–75 years	1,411 men and women aged 60–70 years (50 %) 240 men and women aged >70 years (8 %)	All participants with type 2 DM and one of the following: HTN, retinopathy, micro/ macro-albuminuria smoker	Atorvastatin 10 mg vs placebo	Reduction in rate of first major cardiovascular event	5.8 vs 9.0 % first major coronary event (37 % rate reduction, $p = 0.001$)	3.20	35 % (NNT=31)
JUPITER (secondary analysis)	5,695 patients: men and women, ages 70–97 years	All participants older than 70 years	hsCRP ≥2 mg/dL	Rosuvastatin 20 mg vs placebo	Occurrence of first cardiovascular event	2.6 vs 4.2 % occurrences of first cardiovascular event (44 % rate reduction, $p < 0.001$)	4	44 % (NNT = 24)
HPS*	20, 536 patients: men and women, ages 40–80 years	5,806 men and women aged ≥70 years (28 %)	At least one of: (1) CAD; (2) occlusive disease of non-coronary arteries (3) DM; (4) Male individual aged ≥65 years with treated HTN	Simvastatin 40 mg vs placebo	All-cause mortality (vascular and non-vascular)	12.9 vs. 14.7 % deaths (17 % rate reduction, $p = 0.0003$)	1.80	27 % (NNT = 33)
PROSPER*	5,804 patients: men and women, ages 70–82 years	All participants aged older than 70 years	Pre-existing vascular disease or high risk for vascular disease	Pravastatin 40 mg vs placebo	Combined endpoint of coronary death, non-fatal MI, fatal and non-fatal stroke	14.1 vs 16.2 % ($p = 0.014$)	2.10	15 % (NNT=48)

CVA cerebrovascular accident, *CAD* coronary artery disease, *DM* diabetes, *HDL* high-density lipoprotein, *hsCRP* high-sensitivity C-reactive protein, *HTN* hypertension, *MI* myocardial infarction, *NNT* number needed to treat, *PAD* peripheral arterial disease

*Also enrolled secondary prevention participants

Table 2 Secondary prevention trials with older adults

Trial	Patients	Older subjects (male and female)	CAD risk factors	Intervention	Primary endpoint	Outcome: intervention vs placebo	Absolute risk reduction (%)	Relative risk reduction for primary outcome
4S	4,444 patients: men and women, ages 35–70 years	2,282 aged ≥60 years (51.3 %)	Established CAD (MI or AP)	Simvastatin 20 or 40 mg vs placebo	All-cause mortality	8.2 vs. 11.5 % deaths ($p = 0.0003$)	3.3	30 % (NNT = 15)
CARE	4,159 patients: men and women, ages 21–75 years	2,129 aged >60 years (51 %)	MI	Pravastatin 40 mg vs placebo	Fatal coronary event or a nonfatal MI	10.2 vs 13.2 % fatal coronary event or MI ($p = 0.003$)	3.0	24 % (NNT = 35)
LIPID	9,014 patients: men and women, ages 31–75 years	2,168 (24 %) aged 65–69 years; 1,246 (15 %) aged ≥70 years	Acute MI or recently documented UA	Pravastatin 40 mg vs placebo	Mortality from CAD	6.4 vs. 8.3 % deaths from CAD ($p < 0.001$)	1.8	24 % (NNT = 34)

AP angina pectoris, *CAD* coronary artery disease, *MI* myocardial infarction, *NNT* numbers needed to treat, *UA* unstable angina

PROSPER results (which did not show significant effects of statin therapy in older adults) had not stratified the primary and secondary prevention cohorts. The unpublished data, however, showed that the secondary prevention cohort had indeed derived a significant benefit in all-cause mortality with statin therapy.

The CARE [24] and LIPID [25] trials are two more trials that investigated statins in secondary prevention and both enrolled close to 50 % of participants aged older than 60 years. In both trials, statins were shown to significantly reduce all-cause mortality and cardiovascular heart disease deaths in all age groups. As with the 4S trial, subgroup analysis of older adults in the CARE trial, demonstrated an increased absolute risk reduction in the older over the younger age group [26].

5 Implications for Older Adults

These clinical trials demonstrate the benefit of statins in older adults, and are the evidence base for the 2013 ACC/AHA cholesterol guidelines. However, as critics point out, none of these trials deal with age as a risk factor alone. Older subjects in these trials had additional risk factors besides age. To date, no studies have been conducted to assess statins for primary prevention in the low-risk older population, it also may not be clear if LDL still predicts coronary heart disease and mortality as one ages [27]. A recent study of older participants aged 85 years and older found that higher total cholesterol levels were associated with lower mortality, including cardiovascular and non-cardiovascular mortality [28]. This has been explained conceptually as "reverse epidemiology", where higher cholesterol may be a reflection of a more "robust" aging with better nutritional status, fewer comorbidities, and less frailty. This results in a dilemma for providers caring for older adults who have to weigh the risks and benefits of statin therapy with an incomplete evidence base for patients often with multiple competing health and social concerns.

From a geriatric provider perspective, there are risks and downsides to statin therapy for older adults, particularly for those with multiple chronic conditions and frailty. Statins are known to cause myopathy and have been associated with liver dysfunction and cataracts in observational studies [29], and exertional fatigue [30]. The most common adverse event of statin therapy is myopathy. The ACC/AHA in their clinical advisory estimated that severe myopathy occurs at a rate of 0.08 % with lovastatin and simvastatin [31]. The advisory paper concluded that the risk of myopathy is particularly increased in those aged 80 years or older, although comparative rates between and older and younger subjects were not reported. In a retrospective study on statin monotherapy, patients aged 65 years and older were more likely to be hospitalized with rhabdomyolysis compared with those aged younger than 65 years (relative risk, 5.4; 95 % confidence interval 1.3–21.6) [32]. A possible reason for this increase has been suggested to be related to drug–drug interactions. Statin-induced myopathy is dose dependent, and many drugs interact with statins to raise the plasma-statin concentration. As older adults often have multiple chronic conditions that result in having to take several medications, their risk for myopathy is greater.

More recently, concern has been raised that statins may be associated with cognitive impairment. In 2012, the US Food and Drug Administration stated that "ill-defined memory loss" and "confusion" were noted among statin

users [33]. The cognitive impairment was not related to fixed dementias such as Alzheimer's dementia, but rather thought to be reversible with cessation of the statin drug. However, two large meta-analysis studies that included 38 trials did not find an association between statins and cognitive impairment. To the contrary, a possible protective effect of statins on long-term cognition was noted [34].

The association between statins and diabetes mellitus has been suggested by the JUPITER trial [3]. There is controversy as to whether this risk differs with the different statin drugs. It seems, however, that the higher intensity statins are associated with a higher risk of diabetes mellitus than the moderate intensity statins [35]. Age also seems to be a risk factor for developing diabetes mellitus for those taking statins, as this association is found primarily in trials with older patients [36]. A recent study by Swerdlow et al. [37] used an updated meta-analysis of 20 randomized controlled studies to show that statin therapy increases the risk of incident type 2 diabetes mellitus, with an odds ratio of 1.12 (95 % confidence interval 1.06—1.18). The study further showed using the technique of "Mendelian randomization", that the gene encoding the HMG-coenzyme A (HMGCoA) reductase protein, when suppressed, causes a slight increase in the incidence of type 2 diabetes mellitus, suggesting that the diabetogenic effect of statins is inherent in the inhibition of HMGCoA.

These possible harm scan complicate the care of older adults and may contribute to geriatric conditions [38] and a decline in function. This underscores the importance of carefully weighing the benefits vs the risks prior to initiating statin treatment. The addition of any new long-term medication to an older adult's drug regimen is never taken lightly given possible drug–drug interactions, adverse drug reactions, and difficulties with medication adherence [39], particularly those with multiple chronic conditions. Further, there is no guidance, given the lack of data, for adults over the age of 80 years in regard to when to stop statin therapy if it had been indicated for primary prevention.

6 Conclusion

The 2013 ACC/AHA guidelines will have a profound impact on the way statin drugs will be prescribed for older adults. Many more adults, who previously were not recommended for statins, will now become candidates for starting statin therapy. Older age groups are particularly impacted by the new guidelines, as age appears to be the major determining factor in initiating a statin for primary prevention. The evidence for statins in secondary prevention and primary prevention in higher risk older patients exists and its benefits may outweigh its risks. However, there is currently no evidence to support giving statin therapy to low-risk older adults for primary prevention, which the 2013 ACC/AHA guidelines recommend. More studies are needed to better characterize, estimate, and stratify risk of cardiovascular outcomes for older adults without clinical evidence of ASCVD or with established high-risk factors. The decision to endorse statin treatment for older adults should involve consideration of possible benefits, risks, and competing interests and include a shared provider-patient decision-making discussion.

Acknowledgments No external funding was used in the preparation of this review and the authors have no potential conflicts of interest that are relevant to the content of this manuscript.

References

1. Ducharme N, Radhamma R. Hyperlipidemia in the elderly. Clin Geriatr Med. 2008;24(3):471–87.
2. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet. 2005;366:1267–78.
3. Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359:2195–207.
4. Zulman DM, Sussman JB, Chen X, et al. Examining the evidence: a systematic review of the inclusion and analysis of older adults in randomized controlled trials. J Gen Intern Med. 2011;26:783–90.
5. Stone NJ, Robinson J, 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. http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437741.48606.98.long. Accessed 1 Aug 2014.
6. 10-year CVD Risk Calculator. http://cvdrisk.nhlbi.nih.gov/calculator.asp. Accessed 1 July 2014.
7. Ridker PM, Cook NR. Statins: new American guidelines for prevention of cardiovascular disease. Lancet. 2013;382(9907):1762–5.
8. Ioannidis JP. More than a billion people taking statins? Potential implications of the new cardiovascular guidelines. JAMA. 2014;311(5):463–4.
9. Pencina MJ, Navar-Boggan AM, D'Agostino RB, et al. Application of new cholesterol guidelines to a population-based sample. N Engl J Med. 2014;370:1422–31.
10. Han BH, Weinberger Y, Sutin D. Statinopause. J Gen Intern Med. 2014;29(12):1702–6.
11. Brugts JJ, Yetgin T, Hoeks SE, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. BMJ. 2009;338:b2376.
12. 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):2090–9.
13. Downs J, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA. 1998;279:1615–22.
14. ALLHAT Officers and Coordinators for the ALLHAT Collaborative. Research group. The Antihypertensive and Lipid-

Lowering Treatment to Prevent Heart Attack Trial: Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA. 2002;288:2998–3007.
15. Sever PS, Dahlöf BB, Poulter NR, et al., on behalf of the ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicenter randomised controlled trial. Lancet 2003;361:1149–1158.
16. Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360:7–22.
17. Shepherd J, Blauw GJ, Murphy MB, et al. Prospective study of pravastatin in the elderly at risk. pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. Lancet. 2002;360:1623–30.
18. Lloyd SM, Stott DJ, de Craen AJ, et al. Long-term effects of statin treatment in elderly people: extended follow-up of the Prospective study of pravastatin in the elderly at risk (PROSPER). PLoS One. 2013;8(9):e72642.
19. CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomized placebo-controlled trial. Lancet. 2004;364:685–96.
20. Glynn RJ, et al. Rosuvastatin for primary prevention in older persons with elevated C-reactive protein and low to average low-density lipoprotein cholesterol levels: exploratory analysis of a randomized trial. Ann Intern Med. 2010;152:488.
21. Randomised trial of cholesterol lowering in. 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344(8934):1383–9.
22. Miettinen TA, Pyörälä K, Olsson AG, et al. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris: findings from the Scandinavian Simvastatin Survival Study (4S). Circulation. 1997;96(12):4211–8.
23. Afilalo J, Duque G, Steele R, et al. Statins for secondary prevention in elderly patients: a hierarchical bayesian meta-analysis. J Am Coll Cardiol. 2008;51(1):37–45.
24. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels: cholesterol and recurrent events trial investigators. N Engl J Med. 1996;335(14):1001–9.
25. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels: the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. N Engl J Med. 1998;339(19):1349–57.
26. Lewis SJ, Moye LA, Sacks FM, et al., for the CARE investigators. Effect of pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the average range. Ann Intern Med. 1998;129:681–9.
27. Kronmal RA, Cain KC, Ye Z, Omenn GS. Total serum cholesterol levels and mortality risk as a function of age: a report based on the Framingham data. Arch Int Med. 1993;153(9):1065–73.
28. Newson RS, Felix JF, Heeringa J, et al. Association between serum cholesterol and noncardiovascular mortality in older age. J Am Geriatr Soc. 2011;59:1779–85.
29. Hippisley-Cox H, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. BMJ. 2010;340:c2197.
30. Golomb BA, Evans MA, Dimsdale JE, White HL. Effects of statins on energy and fatigue with exertion: results from a randomized controlled trial [letter]. Arch Intern Med. 2012;172:1180–2.
31. Pasternak RC, Smith SC Jr, Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. Circulation. 2002;106(8):1024–8.
32. Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA. 2004;292:2585–90.
33. FDA Drug Safety Communication: important safety label changes to cholesterol-lowering statin drugs. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm. Accessed 31 August 2014.
34. Richardson K, Schoen M, French B, et al. Statins and cognitive function: a systematic review. Ann Intern Med. 2013;159(10):688–97.
35. Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA. 2011;305(24):2556–64.
36. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet. 2010;375(9716):735–42.
37. Swerdlow DL, Preiss D, Kuchenbaecker KB, et al. HMG-coenzyme a reductase inhibition, type 2 diabetes, andbody-weight:evidencefromgeneticanalysisandrandomisedtrials. Lancet. 2014; pii:S0140-6736(14)61183-1. [Epub ahead of print].
38. Cigolle CT, Langa KM, Kabeto MU, Tian Z, Blaum CS. Geriatric conditions and disability: the health and retirement study. Ann Intern Med. 2007;147(3):156–64.
39. American Geriatrics Society. 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2012;60(4):616–31.