Statins for Primary Prevention of Cardiovascular Events and Mortality in Older Men

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BACKGROUND/OBJECTIVES: We sought to determine whether statin use for primary prevention is associated with a lower risk of cardiovascular events or mortality in older men.

DESIGN: Prospective cohort study.

SETTING: Physicians' Health Study participants.

PARTICIPANTS: 7,213 male physicians ≥70 years without a history of cardiovascular disease (CVD).

MEASUREMENTS: Multivariable propensity score for statin use with greedy matching (1:1) to minimize confounding by indication.

RESULTS: Median baseline age was 77 (70–102), median follow-up was 7 years. Non-users were matched to 1,130 statin users. Statin use was associated with an 18% lower risk of all-cause mortality, HR 0.82 (95% CI 0.69–0.98) and non-significant lower risk of CVD events, HR 0.86 (95% CI 0.70–1.06) and stroke, HR 0.70 (95% CI 0.45–1.09). In subgroup analyses, results did not change according to age group at baseline (70–76 or >76 years) or functional status. There was a suggestion that those >76 at baseline did not benefit from statins for mortality, HR 1.14 (95% CI 0.89–1.47), compared to those 70–76 at baseline, HR 0.83 (95% CI 0.61–1.11); however the CIs overlap between the two groups, suggesting no difference. Statin users with elevated total cholesterol had fewer major CVD events than non-users, HR 0.68 (95% CI 0.50–0.94) and HR 1.43 (95% CI 0.99–2.07)), respectively.

CONCLUSIONS: Statin use was associated with a significant lower risk of mortality in older male physicians ≥70 and a nonsignificant lower risk of CVD events. Results did not change in those who were >76 years at baseline or according to functional status. There was a suggestion that those with elevated total cholesterol may benefit. Further work is needed to determine which older individuals will benefit from statins as primary prevention. **J Am Geriatr Soc 65:2362–2368, 2017.**

Key words: prevention; cardiovascular disease; statins; aging

Guidelines suggest there is limited evidence to recommend statins for primary prevention of cardiovascular disease (CVD) in adults >75 years.[1,2] This may be a direct result of excluding older individuals, particularly those with multimorbidity, from randomized trials.[3] However, prescriptions for statins for individuals >70 has increased significantly in the last two decades.[4] In 2008, 40% of the Medicare population was prescribed a statin.[5] In 2011, 12.5 million Medicare beneficiaries were >80,[6] amounting to a significant investment of resources for a drug for which there is as yet no clear evidence of benefit in the oldest and fastest growing segment of the population.[7]

Multiple primary and secondary prevention trials[8–13] demonstrated that statins reduce mortality and cardiovascular (CV) events in those <75 years. A meta-analysis of primary prevention statin trials in older adults (mean age 73) revealed a reduction in CV events, but not mortality.[14] Limited, conflicting evidence has generated significant debate,[15–17] and calls for additional trials.[18]

One challenge involves identifying older adults at increased CVD risk who might benefit from statins for primary prevention. Using the Pooled Cohort Risk Assessment Equation,[1] as recommended by cholesterol guidelines, white men >70 with optimal risk factors have a predicted 10-year risk of CVD of 15.7%. The guidelines suggest that those with an estimated risk >7.5% should be offered a statin. No specific recommendations are made for patients >75. Existing risk assessments, such as the Framingham risk score and the European SCORE were

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not developed in older cohorts and do not account for multimorbidity, function, frailty, or life limiting illnesses.[19]

Additionally, the older adult population has long had inconsistent prescription patterns for many medications, including under-prescription of statins.[20] This may reflect clinicians' hesitancy to use a drug with side effects and drug-drug interactions that has not been studied in the very old.[21] Thus, we sought to examine the relationship between statin use for primary prevention of major CV events and mortality in men >70, with particular attention to those >75 years in subgroup analysis.

METHODS

Study Population

This study used data from Physicians' Health Study (PHS) participants. PHS methods have been described in detail.[22] Briefly, PHS I began in 1982 as a randomized, double-blind, placebo-controlled trial of aspirin and beta-carotene in 22,071 US male physicians aged 40 to 84 years, with no history of myocardial infarction (MI), stroke, transient ischemic attack, or cancer at randomization. PHS II[23] began in 1997 and was a randomized trial of efficacy of beta-carotene, vitamin C, vitamin E, and a multivitamin on CVD and cancer risk in 7,641 PHS I physicians who agreed to participate in the second trial and 7,000 newly recruited male physicians. All PHS subjects have been followed prospectively, using annual mailed health questionnaires to collect self-reported data, including new CVD diagnoses. Each participant signed an informed consent and the institutional review board at Brigham & Women's Hospital approved the study.

This analysis focused on all physicians ≥70 in the PHS cohort who completed annual questionnaires from 1999, the year a specific question regarding statin use was added. Of the 9,988 PHS participants (≥70 years in 1999), 2,670 participants were excluded because of prevalent CVD (MI, stroke, or peripheral vascular disease) and an additional 105 were excluded due to missing information on statin use at baseline.

Outcome

The primary outcome is a composite of self-reported and subsequently validated major CV events, MI, stroke, and coronary revascularization (PTCA or CABG). Outcomes were assessed annually by questionnaires; ascertainment of events has been described previously.[24] All-cause mortality was the co-primary outcome, confirmed by an endpoints committee after review of medical records, death certificates, and family report. Details on mortality validation in PHS have been published.[25] Secondary outcomes were coronary heart disease (CHD) alone, and stroke alone. All outcomes were updated through 2012.

Other Variables

Data on demographics, including age and race (white or other); anthropometrics, including age and body mass index (BMI); comorbidities, such as congestive heart failure (CHF), hyperlipidemia (HL), hypertension (HTN), diabetes, kidney disease, and dementia; and lifestyle factors, including smoking, alcohol consumption, and activities of daily living; and concurrent medications, such as aspirin and anti-hypertensive use were assessed by annual questionnaires. Alcohol consumption was classified as none, 1–3 drinks per month, 1–6 drinks per week, and ≥7 drinks per week. Smoking was classified as never, past, or current. Diagnosis of diabetes was self-reported and validated in a subsample.[26] HL was defined by self-report, elevated measured or self-reported cholesterol value, or history of anti-lipemic medication use. HTN was defined by self-report, report of blood pressure >140/90 mm Hg, or use of antihypertensive medications. Functional status was assessed with questions regarding difficulty with activities of daily living, such as bathing, grocery shopping, walking several blocks, or climbing stairs.

Statin use

Beginning in 1999, statin use was assessed by an annual questionnaire with the following question: "Over the past twelve months, on approximately how many DAYS did you take the following [medication]? Statins: (e.g., atorvastatin, cerivastatin, lovastatin, pravastatin, simvastatin, Zocor, etc.)." Respondents could choose varying amounts of use over a 12-month period: 0 (none), 1–13 days, 14–30 days, 31–60 days, 61–90 days, 91–120 days, 121–180 days, 181+ days. Because <4% of participants reported using statins for >0 and <180 days, statin exposure was dichotomized as users for those participants reporting ≥181 days and non-users for <180 days.

Statistical Analyses

Participant characteristics were summarized using descriptive statistics–the t-test for continuous variables and chi-square for binary and categorical variables. Cox proportional hazard models were run to estimate the hazard ratio (HR) and 95% confidence interval (CI) of having a major CV event. Proportional hazards assumptions were tested using product terms of variables and log-transformed person-time, and assumptions were met (all $P > .05$).

Due to significant differences between statin users and non-users, presumably due to the fact that statins are prescription drugs most often used for hypercholesterolemia and for those at increased risk of CV events due to comorbidities, such as diabetes, we used propensity score (PS) analysis to attempt to reduce confounding by indication.[27,28] We developed a multivariable logistic regression model to create a PS to assess the probability of being a statin user verses a statin non-user. The majority of variables were missing <5% of responses and <10% of participants were missing >10% of the variables for the PS. We therefore used indicator variables to account for the small amount of missing covariates.

Elevated cholesterol is the most important driver of statin prescription; therefore we excluded those without information on cholesterol. Additionally, questions on functional status were only sent to physicians from the original PHS cohort; therefore only physicians from the original cohort were included in the PS analysis. The final PS model included 27 predictors of statin use, including

comorbidities, markers of functional status, quadratic equation for age, and an interaction term for cholesterol and age. The propensity score is typically used in one of four ways: stratifying, matching, inverse probability of treatment weighting, or as a covariate.[28,29] Due to a considerable lack of overlap of the propensity scores amongst statin users and non-users (see Supplementary Appendix S1) we used the matching method.[29] Statin users and non-users were matched 1:1 using the ("greedy") nearest neighbor with caliper matching algorithm.[30] The paired-matches were maintained in all analyses. Person-time of follow up was calculated from 1999–2012 until the primary event occurred (MI, stroke, revascularization, or death).

Using Cox proportional hazards, we estimated the time to event HR and 95% CI of the risk of major CV events in the matched cohort. In a sensitivity analysis, we used age-at-event as the time scale. Subgroup analyses examined age, functional status, and total cholesterol. To ensure matched pairs were not broken, the PS was rerun within each subgroup. To examine function we created a dichotomous variable reflecting functional status as a proxy for frailty. Participants who reported any difficulty with either moderate activity, walking one block, climbing one flight of stairs, grocery shopping, bathing, or bending were considered to be functionally impaired.

Analysis was done using SAS® 9.3 and 9.4 (SAS Institute Inc.).

RESULTS

Seven thousand two hundred and thirteen participants were eligible for analysis. At baseline statin questionnaire, 1,531 (21.2%) reported using statins >180 days in the prior year. Median age was 76.9 ± 5.2 years (min 70, max 102). Statin users were more likely to be younger, have hyperlipidemia, hypertension, and diabetes. Users were also more likely to be taking aspirin. There was no significant difference in smoking, alcohol use, or weekly exercise. Non-users were more likely to have dementia and have limitations in physical activity, such as walking, bathing, or dressing. Median time of follow up was 7.1 years (inter-quartile range 4.8–8.4), during which a total of 1,137 CV events occurred.

A total of 5,758 individuals were available for propensity score analysis, of which 1,322 reported taking a statin at baseline. The C-statistic for the PS model was 0.86. Using the ("greedy") matching method there were 1,130 matched pairs, with excellent overlap in propensity score distribution between users and non-users, and with a mean score in both groups of 0.44 (SD 0.13, $P = .97$). A total of 362 major CV events occurred in the PS matched cohort. Baseline characteristics are shown in Table 1. In the PS matched group, statin use was associated with an 18% lower risk of mortality, HR 0.82 (95% CI 0.69–0.98), $P = .03$, and a non-significant lower risk of major CV events, HR 0.86 (95% CI 0.70–1.06), $P = 0.17$. (Table 2 and Supplementary Appendix S2).

In secondary analyses, we separated CHD events from stroke and found no significant relationship between statin use and stroke, HR 0.70 (95% CI 0.45–1.09), $P = .12$; or CHD events, HR 0.95 (95% CI 0.74–1.21), $P = .66$. We also considered the competing risk of mortality[31] and found no evidence in our study. As age is the most important predictor of CVD, to account for a possible cohort effect we repeated our main analysis using "age with left censoring" rather than "days from baseline" as the time scale. The results were similar for major CV events, HR 0.87 (95% CI 0.71–1.07), all-cause mortality HR 0.84 (95% CI 0.85–1.01), CHD events, HR 0.92 (95% CI 0.72–1.17), and stroke, HR 0.69 (95% CI 0.44–1.08).

In subgroup analyses, we examined the cohort effect of "age at baseline," dichotomizing at median age (76), functional status, and cholesterol. Results did not change according to age category at baseline or functional status, although there was a suggestion that those who were

Table 1. Baseline Characteristics of 2,260 US Male Physicians According to Statin Use and Propensity Score Matching

	Propensity Score Matched (%)		
Variable*	Statin (n = 1,130)	No Statin (n = 1,130)	P-value
Age, mean (SD)	76.0 ± 4.5	76.0 ± 4.6	.88
BMI, mean (SD)[a]	25.6 ± 3.1	25.6 ± 3.2	.68
White race[a]	94.3	94.0	.79
Smoking Status[a]			
Current	2.9	3.3	
Past	48.9	50.5	.61
Never	48.2	46.2	
Hyperlipidemia	98.1	97.9	.65
Hypertension[a]	73.8	75.3	.42
Diabetes[a]	13.0	13.1	.94
Heart failure[a]	2.9	3.0	.80
Renal disease[a]	10.8	10.6	.88
Liver disease[a]	15.2	16.1	.58
Cancer	20.0	20.9	.60
Depression[a]	12.7	13.1	.79
Dementia	2.7	2.7	.90
Aspirin use	72.5	71.3	.53
Hypertension medication[a]	52.2	48.4	.07
Diabetes medication[a]	9.1	8.9	.89
Alcohol Use[a]			
Daily	45.3	45.1	
Weekly	36.0	37.2	.90
Monthly	3.8	3.6	
Rarely/never	14.9	14.1	
Weekly exercise[a]	60.2	59.3	.67
Health Significantly limits:			
Moderate activity[a]	12.2	12.2	.99
Walking >1mile[a]	17.6	17.6	.97
Walking 1 block[a]	2.9	2.2	.26
Climbing one flight of stairs[a]	5.0	4.5	.60
Bending, kneeling[a]	24.8	24.4	.82
Lifting/carrying groceries[a]	6.2	6.5	.80
Bathing or dressing[a]	2.4	2.1	.65
Self-rated general health as excellent or very good[a]	82.4	83.1	.68

[a]Number missing variables: BMI = 11, race = 13, smoking = 6, hypertension = 94, diabetes = 142, heart failure = 157, renal disease = 127, liver disease = 220, depression = 73, aspirin use = 4, hypertension medication = 6, diabetes medication = 40, alcohol use = 27, weekly exercise = 16, moderate activity = 148, walking 1 mile = 144, walking 1 block = 149, one flight of stairs = 148, bending or kneeling = 152, groceries = 147, bathing or dressing = 142, general health = 135.

Table 2. Hazard Ratios and 95% Confidence Intervals for Major Cardiovascular Events and Mortality According to Statin Use in 2,260 Propensity Score Matched US Male Physicians

Outcome	Statin *N* = 1,130 N with event	No Statin *N* = 1,130 N with event	HR (95% CI)	P-value
Major CV Events[a]	169	193	0.86 (0.70-1.06)	.17
All-cause mortality	227	276	0.82 (0.69-0.98)	.03
CHD only[b]	125	137	0.95 (0.74-1.21)	.66
Stroke only[c]	33	47	0.70 (0.45-1.09)	.12

[a]MI, mortality from MI, stroke, mortality from stroke, CABG/PCI.
[b]MI, mortality from MI, CABG/PCI.
[c]Stroke or mortality from stroke.

>76 years at baseline did not benefit from statins, HR 1.14 (95% CI 0.89–1.47), compared to those who were 70–76 at baseline, HR 0.83 (95% CI 0.61–1.11), however as the confidence intervals overlap between the two groups of age, this suggests no difference between the groups. Amongst those who had elevated measured total cholesterol (>200 mg/dL) at baseline there was a statistically significant association between statin use and reduced risk of CVD events, HR 0.68 (95% CI 0.50–0.94) while those with a low total cholesterol who took statins had an increased risk of major CV events, HR 1.43 (95% CI 0.99–2.07), with overall *P*-interaction .003. This was not seen when we restricted the outcome to all-cause mortality (Table 3).

DISCUSSION

Our study found a significant inverse association between all-cause mortality amongst relatively healthy older male physicians who used statins compared to non-users, and a modest, though non-statistically significant, lower risk of major CV events in men ≥70 years that took statins for primary prevention for an average of 7 years. This is in contrast to findings from a subgroup analysis of 5,695 participants >70 years in the JUPITER (justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin) trial, which found a benefit in stroke and MI reduction, but not all-cause mortality in statin users;[32] and a meta-analysis of eight primary prevention trials of 24,674 adults >65 years (mean 73) which also reported no mortality benefit over 3.5 years of follow-up (relative risk (RR) 0.94 (95% CI 0.86–1.04, $P = 0.21$)), although there was a significant reduction in MI risk (RR 0.61 (95% CI 0.43–0.85, $P = .003$)) and risk of stroke (RR 0.76 (95% CI 0.63–0.93, $P = .006$)).[14]

Our observational findings for major CV events are similar to the effect size reported in the pravastatin in elderly individuals at risk of vascular disease (PROSPER) randomized controlled trial (n = 5,804, age range 70–82), which reported a significant 19% reduction in major CV events, HR 0.81 (95% CI 0.69–0.94, $P = .006$). However, in our study we specifically restricted to primary prevention and included individuals >82 years at baseline. In PROSPER, 44% of participants had a history of CVD, and in subgroup analysis examining primary prevention there was no significant reduction of CV events in those randomized to pravastatin verses placebo, HR 0.94 (95% CI 0.77–1.15), although $P = .19$ for interaction was not significant.[33] Additionally, PROSPER did not find a significant reduction in all-cause mortality, (HR 0.97 (95% CI 0.83–1.14, $P = .74$)), although results were not reported amongst those who did not have a history of CVD. Participants included in trials for primary prevention required at least one cardiovascular risk factor, as in the PROSPER trial, or an elevated C-reactive protein in JUPITER.[12] We did not have such restrictions in our cohort as current risk calculators assign a high risk of CV events to all men >70, even without risk factors.

An ongoing prospective cohort study in France has followed 7,484 men and women, mean age 74 years, for an average of 9 years.[34] Individuals taking lipid-lowering medications (including statins and fibrates) had a significant lower risk of stroke, HR 0.66 (95% CI 0.49–0.90), but no significant association with CHD. In our study we did not achieve a similar statistically significant association in reduction of strokes. This may be due to the small number of events in this relatively healthy cohort of older male physicians.

In an exploratory subgroup analysis we examined the impact of age cohort at baseline. This is important to consider in studies such as ours where a cohort effect of age can lead to a survival bias, as those who were >76 at baseline are more likely to experience mortality than those who are younger at baseline. We did not find a significant difference between those who were <76 at baseline or older on the outcome of major CVD events. For the outcome of all-cause mortality, although there was a difference between the two age categories (with possible benefit in those between the age of 70–76 at baseline and possible harm in those over 76 years), the confidence intervals for each group overlapped, suggesting no statistically significant difference between the two groups.

We also found a statistically significant lower risk of major CV events in those with elevated total cholesterol at baseline, while low cholesterol was associated with an increased risk of CV events. Although exploratory, this may reflect underlying illnesses such as malignancy or advanced frailty, which are associated with low cholesterol and mortality. Furthermore, those with higher cholesterol at baseline may have been prescribed a more potent statin, contributing to a lower risk. This result may also be reflective of residual confounding by indication. There was suggestion of benefit in those with no functional limitation, although this did not reach statistical significance, in part due to a relatively small sample size. Perhaps incorporating functional status into the CV risk assessment will better identify individuals who may benefit from preventive therapy, such as statins. For example, in a French cohort of 3,208 men and women ≥65 years, followed for 5 years, slow walking speed was associated with an increased risk of death from cardiovascular disease (HR 2.92 (95% CI 1.46, 5.84)).[35]

It is worth noting that one concern for providers and patients is that side effects of statins, such as myalgias, may lead to decreased functional status. A longitudinal study of 2,005 individuals aged 70–79, taking statins, were

Table 3. Hazard Ratios (95% Confidence Intervals) for Major Cardiovascular Events and Mortality Stratified by Age, Functional Status, and Total Cholesterol

		Statin		No Statin				
Outcome	Sub-group	Total number	Number with event (%)	Total number	Number with event (%)	HR (95% CI)	*P*-value	*P*-interaction
Major CVD Events	Age Category							
	<76	587	79 (13.5)	587	93 (15.8)	0.83 (0.61–1.11)	.21	.27
	≥76	398	77 (19.3)	398	76 (19.0)	1.05 (0.77–1.45)	.75	
	Functional status[a]							
	No limitation	725	103 (14.2)	725	129 (17.8)	0.78 (0.61–1.02)	.06	.62
	Any limitation	263	48 (18.2)	263	54 (20.5)	0.88 (0.60–1.30)	.52	
	Total Cholesterol							
	<200 mg/dL	308	67 (21.8)	308	48 (15.6)	1.43 (0.99–2.07)	.060	.003
	>200 mg/dL	472	65 (13.8)	472	92 (19.5)	0.68 (0.50–0.94)	.019	
Mortality	Age Category							
	<76	587	64 (10.9)	587	86 (14.7)	0.76 (0.55–1.05)	.093	.047
	≥76	398	130 (32.7)	398	117 (29.4)	1.14 (0.89–1.47)	.30	
	Functional status[a]							
	No limitation	725	134 (18.5)	725	146 (20.1)	0.93 (0.73–1.17)	.52	.92
	Any limitation	263	59 (22.4)	263	66 (25.1)	0.91 (0.64–1.29)	.60	
	Total Cholesterol							
	<200 mg/dL	308	65 (21.1)	308	79 (25.7)	0.83 (0.60–1.15)	.27	.79
	>200 mg/dL	472	82 (17.4)	472	92 (19.5)	0.88 (0.65–1.18)	.39	

[a]Any difficulty with moderate activities, walking 1 block, climbing 1 flight of stairs, grocery shopping, bathing, or bending.

followed for 5 years for evidence of functional decline over time.[36] The authors reported no evidence of worsening functional status measured by gait speed in statin users, OR = 0.90 (95% CI 0.77–1.06). The results of this study may be biased, as the authors did not employ statistical methods to address confounding by indication, such as the propensity score. A cost-effectiveness analysis of statins in the prevention of CVD, using data from the PROSPER trial, showed that while there may be a small (albeit statistically significant) lower risk of CV events for those over 75, this may be outweighed by the small (but significant) increased relative risk of mild cognitive impairment (1.10–1.24) and functional decline (1.12–1.29).[37]

The fact that the reduction in CV events in our study did not reach statistical significance may be due to low rates of outcomes in this relatively healthy cohort. When we performed sensitivity analysis, using age as the time scale, rather than the classic time-to-event analysis, in order to address the possibility of cohort effect and to acknowledge the increasing risk of CVD due to advanced age (e.g., an 85 year old at baseline has a higher risk of CVD than a 70 year old due to age alone), we found very similar results (absolute percent change when comparing hazard ratios obtained from time-to-event analysis with those derived from age at event ranging from 1.2% to 3.7%). These results did not reach statistical significance due to lack of power; however, the analysis should be repeated in a larger cohort.

The aging population is heterogeneous, and to date, evidence is lacking as to which older adults will benefit the most from statin therapy. There is increasing evidence that statins can, and perhaps should, be stopped in nursing home patients, particularly those with dementia[38] or those with a life-limiting illness.[39] Including dementia in the models or stratifying by frailty did not change our results, although this may be limited by sample size. It remains unknown whether older individuals with multi-morbidity, who have a life expectancy of at least 2 years, may benefit from CVD prevention with statins. A patient centered approach in the decision to start or continue a statin in an elderly patient is of the utmost importance,[40] with attention to function, multi-morbidity, cognition, and polypharmacy.[41]

STAREE (statins therapy for reducing events in the elderly) is an ongoing randomized clinical trial that has randomized individuals >70 without prior CVD, dementia, diabetes, or a life-limiting illness to atorvastatin or placebo.[42] The main outcome is mortality and functional status assessed by the need for institutionalization; results are expected in 2019. However, as with many trials before, this study excludes many patients routinely seen in primary care (e.g., the older adult with frailty and multi-morbidity, with or without cognitive impairment).[43]

Limitations of our study include the observational nature; only men participated, statin type and dose were not available, and covariates were not updated annually. As with any non-randomized trial of drug effects, there may be remaining confounding by indication, even with the propensity score matching approach. Our results may underestimate the effect of statins due to sample size or misclassification of statin use, which could not be updated over time in the propensity score model. This very healthy group of physicians may not represent the average community-dwelling older individual, but suggests that there may be a group of older individuals who might derive benefit from statin therapy.

Our data suggest that statins taken for primary prevention in relatively healthy men >70 years are associated

with a significant 18% lower risk of mortality but with a non-significant lower risk of major CV events. In exploratory analysis we found no statistically significant difference by age category at baseline, or functional status, while those with elevated total cholesterol may benefit from statins to reduce major CVD events. The finding of benefit in those with elevated cholesterol in subgroup analysis is intriguing and should prompt further study to better understand which individuals in the heterogeneous aging population may benefit from statin therapy for the primary prevention of cardiovascular disease. Given that the prevalence of CVD rises with age, evidence based preventive strategies are needed for the aging population.

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REFERENCES

1. 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. J Am Coll Cardiol 2014;63(25 Pt B):2889–2934.
2. Bibbins-Domingo K, Grossman DC, Curry SJ et al. Statin use for the primary prevention of cardiovascular disease in adults: US preventive services task force recommendation statement. JAMA 2016;316:1997–2007.
3. 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;26:783–790.
4. Lo-Ciganic WH, Boudreau RM, Gray SL et al. Changes in cholesterol-lowering medications use over a decade in community-dwelling older adults. Ann Pharmacother 2013;47:984–992.
5. Fang MC, Coca Perraillon M, Ghosh K et al. Trends in stroke rates, risk, and outcomes in the United States, 1988 to 2008. Am J Med 2014;127:608–615.
6. 2012 AARP Public Policy Institute Fact Sheet. Available at: http://www.aarp.org/content/dam/aarp/research/public_policy_institute/health/who-relies-on-medicare-factsheet-AARP-ppi-health.pdf (Accessed October 20, 2016).
7. 2010 US Census Briefs. Available at https://www.census.gov/prod/cen2010/briefs/c2010br-09.pdf (Accessed May 20, 2015.).
8. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–1389.
9. 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. New Engl J Med 1996;335:1001–1009.
10. Downs JR, 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;279:1615–1622.
11. 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.
12. Ridker PM, Danielson E, Fonseca FA et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. New Engl J Med 2008;359:2195–2207.
13. Baigent C, Blackwell L, Emberson J et al. 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;376:1670–1681.
14. 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;62:2090–2099.
15. Stone NJ, Intwala S, Katz D. Statins in very elderly adults (debate). J Am Geriatr Soc 2014;62:943–945.
16. Rich MW. Aggressive lipid management in very elderly adults: Less is more. J Am Geriatr Soc 2014;62:945–947.
17. Greenland P, Bonow RO. Interpretation and use of another statin guideline. JAMA 2016;316:1977–1979.
18. Gurwitz JH, Go AS, Fortmann SP. Use of statins in adults older than 75 years-reply. JAMA 2017;317:1081.
19. Cooney MT, Dudina A, D'Agostino R et al. Cardiovascular risk-estimation systems in primary prevention: Do they differ? Do they make a difference? Can we see the future? Circulation 2010;122:300–310.
20. Munson JC, Morden NE, Goodman DC et al. Dartmouth Atlas Project of Medicare Prescription Drug Use. 2013. Available at http://www.rwjf.org/en/research-publications/find-rwjf-research/2013/10/the-dartmouth-atlas-of-medicare-prescription-drug-use.html (Accessed on August 7, 2014).
21. Strandberg TE, Kolehmainen L, Vuorio A. Evaluation and treatment of older patients with hypercholesterolemia: A clinical review. JAMA 2014;312:1136–1144.
22. Steering Committee of the Physicians' Health Study Research Group. Findings from the aspirin component of the ongoing Physicians' Health Study. New Engl J Med 1988;318:262–264.
23. Sesso HD, Christen WG, Bubes V et al. Multivitamins in the prevention of cardiovascular disease in men: The Physicians' Health Study II randomized controlled trial. JAMA 2012;308:1751–1760.
24. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. New Engl J Med 1989;321:129–135..
25. Djousse L, Gaziano JM. Egg consumption in relation to cardiovascular disease and mortality: The physicians' health study. Am J Clin Nutr 2008;87:964–969.
26. Djousse L, Driver JA, Gaziano JM et al. Association between modifiable lifestyle factors and residual lifetime risk of diabetes. Nutr Metab Cardiovasc Dis 2013;23:17–22.
27. Seeger JD, Kurth T, Walker AM. Use of propensity score technique to account for exposure-related covariates: An example and lesson. Med Care 2007;45(10 Supl 2):S143–S148.
28. Kim DH, Pieper CF, Ahmed A et al. Use and interpretation of propensity scores in aging research: A guide for clinical researchers. J Am Geriatr Soc 2016;64:2065–2073.
29. Elze MC, Gregson J, Baber U et al. Comparison of propensity score methods and covariate adjustment: evaluation in 4 cardiovascular studies. J Am Coll Cardiol 2017;69:345–357.
30. Austin PC. A comparison of 12 algorithms for matching on the propensity score. Stat Med 2014;33:1057–1069.
31. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. Circulation 2016;133:601–609.
32. Glynn RJ, Koenig W, Nordestgaard BG 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;152:488–496.

33. Shepherd J, Blauw GJ, Murphy MB et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): A randomised controlled trial. Lancet 2002;360:1623–1630.
34. Alperovitch A, Kurth T, Bertrand M et al. Primary prevention with lipid lowering drugs and long term risk of vascular events in older people: Population based cohort study. BMJ 2015;350:h2335.
35. Dumurgier J, Elbaz A, Ducimetiere P et al. Slow walking speed and cardiovascular death in well functioning older adults: Prospective cohort study. BMJ 2009;339:b4460.
36. Lo-Ciganic WH, Perera S, Gray SL et al. Statin use and decline in gait speed in community-dwelling older adults. J Am Geriatr Soc 2015;63:124–129.
37. Odden MC, Pletcher MJ, Coxson PG et al. Cost-effectiveness and population impact of statins for primary prevention in adults aged 75 years or older in the United States. Ann Intern Med 2015;162:533–541.
38. Tjia J, Cutrona SL, Peterson D et al. Statin discontinuation in nursing home residents with advanced dementia. J Am Geriatr Soc 2014;62:2095–2101.
39. Kutner JS, Blatchford PJ, Taylor DH et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: A randomized clinical trial. JAMA Intern Med 2015;175:691–700.
40. Epstein RM, Peters E. Beyond information: Exploring patients' preferences. JAMA 2009;302:195–197.
41. American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity. Guiding principles for the care of older adults with multimorbidity: An approach for clinicians: American Geriatrics Society expert panel on the care of older adults with multimorbidity. J Am Geriatr Soc 2012;60:E1–E25.
42. ClinicalTrials.gov. A Clinical Trial of STAtin Therapy for Reducing Events in the Elderly (STAREE)–Full Text View. Available at https://clinicaltrials.gov/ct2/show/NCT02099123. (Accessed July 26, 2017).
43. Schubert CC, Boustani M, Callahan CM et al. Comorbidity profile of dementia patients in primary care: Are they sicker? J Am Geriatr Soc 2006;54:104–109.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Propensity Score Distributions before and after trimming

Appendix S2. Kaplan Meier Curves

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