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

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Abstract

Background/Objectives—We sought to determine whether statin use for primary prevention is associated with a reduction in 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

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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 were 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.

Introduction

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

Additionally, the elderly 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 ages 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 (Boston, MA) approved the study.

This analysis focused on all physicians 70 in the PHS cohort who completed annual questionnaires from 1999, when 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, dementia and lifestyle factors, including smoking, alcohol consumption, 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 annual questionnaire with the following question: "Over the past twelve months, on approximately how many DAYS did you take the following [medication]? Statins: (eg, 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 to user for participants reporting 181 days, and non-user for <180 days.

Statistical analyses

Participant characteristics were summarized using descriptive statistics, using 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 variable and log-transformed person-time and were met (all p>0.05).

Due to significant differences between statin users and non-users, presumably due to the fact that statins are prescription drugs for hypercholesterolemia, are most often used for this indication, and for those at increased risk of CV events due to co-morbidities 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 vs 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 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 or revascularization), or death.

Using Cox proportional hazards we estimate HR and 95% CI of the risk of major CV events in the matched cohort. 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., Cary, NC, USA.)

Results

7,213 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, with mean score in both groups 0.44 (S.D. 0.13, p=0.97). 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=0.03, 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=0.12, or CHD events, HR 0.95 [95% CI 0.74–1.21], p=0.66. We also considered the competing risk of mortality[31] and found no evidence in our study.

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 >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 (>200mg/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 0.003. 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 who took statins for primary prevention for an average of 7 years. This is in contrast to findings from 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=0.003]) and risk of stroke (RR 0.76 [95% CI 0.63–0.93 p=0.006,]).[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=0.006]. 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 vs. placebo, HR 0.94 [95% CI 0.77–1.15], although p=0.19 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=0.74]), 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 age 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 3208 men and women 65 years follow 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 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 might 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]

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. 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, might 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 it, this study excludes many patients routinely seen in

primary care: 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; 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 might 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

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

Variable	Propensity Score Matched (%)		
	Statin (n=1,130)	No Statin (n=1,130)	P-value[¥]
Age, mean (SD)	76.0±4.5	76.0±4.6	0.88
BMI, mean (SD) [*]	25.6±3.1	25.6±3.2	0.68
White race [*]	94.3	94.0	0.79
Smoking Status [*]			
Current	2.9	3.3	
Past	48.9	50.5	0.61
Never	48.2	46.2	
Hyperlipidemia	98.1	97.9	0.65
Hypertension [*]	73.8	75.3	0.42
Diabetes [*]	13.0	13.1	0.94
Heart failure [*]	2.9	3.0	0.80
Renal disease [*]	10.8	10.6	0.88
Liver disease [*]	15.2	16.1	0.58
Cancer	20.0	20.9	0.60
Depression [*]	12.7	13.1	0.79
Dementia	2.7	2.7	0.90
Aspirin use	72.5	71.3	0.53
Hypertension medication [*]	52.2	48.4	0.07
Diabetes medication [*]	9.1	8.9	0.89
Alcohol Use [*]			
Daily	45.3	45.1	
Weekly	36.0	37.2	0.90
Monthly	3.8	3.6	
Rarely/never	14.9	14.1	
Weekly exercise [*]	60.2	59.3	0.67
Health Significantly limits:			
Moderate activity [*]	12.2	12.2	0.99
Walking >1 mile [*]	17.6	17.6	0.97
Walking 1 block [*]	2.9	2.2	0.26
Climbing one flight of stairs [*]	5.0	4.5	0.60
Bending, kneeling [*]	24.8	24.4	0.82
Lifting/carrying groceries [*]	6.2	6.5	0.80

	Propensity Score Matched (%)		
Variable	Statin (n=1,130)	No Statin (n=1,130)	P-value[¥]
Bathing or dressing [*]	2.4	2.1	0.65
Self-rated general health as excellent or very good [*]	82.4	83.1	0.68

[*] 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	No Statin N=1,130		
	N with event	N with event	HR (95% CI)	p-value
Major CV Events [*]	169	193	0.86 (0.70–1.06)	0.17
All-cause mortality	227	276	0.82 (0.69–0.98)	0.03
CHD only [**]	125	137	0.95 (0.74–1.21)	0.66
Stroke only [***]	33	47	0.70 (0.45–1.09)	0.12

[*] MI, mortality from MI, stroke, mortality from stroke, CABG/PCI

[**] MI, mortality from MI, CABG/PCI

[***] Stroke or mortality from stroke

Table 3

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

Outcome	Sub-group		Statin		No Statin		HR (95% CI)	p-value	p-interaction
		Total number	Number with event (%)	Total number	Number with event (%)				
Major CVD Events	Age Category								
	<76	587	79 (13.5)	587	93 (15.8)	0.83 (0.61–1.11)	0.21	0.27
	76	398	77 (19.3)	398	76 (19.0)	1.05 (0.77–1.45)	0.75	
	Functional status *								
	No limitation	725	103 (14.2)	725	129 (17.8)	0.78 (0.61–1.02)	0.06	0.62
	Any limitation	263	48 (18.2)	263	54 (20.5)	0.88 (0.60–1.30)	0.52	
	Total Cholesterol								
	<200 mg/dL	308	67 (21.8)	308	48 (15.6)	1.43 (0.99–2.07)	0.060	0.003
	>200 mg/dL	472	65 (13.8)	472	92 (19.5)	0.68 (0.50–0.94)	0.019	
Mortality	Age Category								
	<76	587	64 (10.9)	587	8614.7)	0.76 (0.55–1.05)	0.093	0.047
	76	398	130 (32.7)	398	117 (29.4)	1.14 (0.89–1.47)	0.30	
	Functional status *								
	No limitation	725	134 (18.5)	725	146 (20.1)	0.93 (0.73–1.17)	0.52	0.92
	Any limitation	263	59 (22.4)	263	66 (25.1)	0.91 (0.64–1.29)	0.60	
	Total Cholesterol								
	<200 mg/dL	308	65 (21.1)	308	79 (25.7)	0.83 (0.60–1.15)	0.27	0.79
	>200 mg/dL	472	82 (17.4)	472	92 (19.5)	0.88 (0.65–1.18)	0.39	

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