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Statin use and decreased risk of benign prostatic enlargement and lower urinary tract symptoms

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Abstract

OBJECTIVE—

- To determine whether statin use is associated with a decreased risk of developing benign prostatic enlargement (BPE) and lower urinary tract symptoms (LUTS).

SUBJECTS AND METHODS—

- We conducted a retrospective, population-based cohort study of 2447 men, 40–79 years of age, residing in Olmsted County, MN, USA, in 1990, and followed these men biennially through 2007.
- Cox proportional hazard models were used to assess associations between statin use and new onset of moderate/severe LUTS (American Urologic Association Symptom Index score > 7), a decreased maximum urinary flow rate (< 12 mL/s) or BPE (prostate volume > 30 mL).

RESULTS—

- Statin use was inversely associated with new onset of LUTS (Hazard ratio (HR) 0.39; 95% confidence interval (CI) 0.31–0.49), a decreased maximum flow rate (HR 0.53; 95% CI 0.34–0.82) and BPE (HR 0.40; 95% CI 0.23–0.69) after adjustment for base-line age and body mass index, diabetes, hypertension, coronary heart disease, smoking, alcohol use, activity level and non-steroidal anti-inflammatory use.
- The longest duration of statin use was associated with the lowest risk of developing each outcome (all tests for trend: $P < 0.001$).

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CONFLICT OF INTEREST

Steven Jacobsen is an employee of Kaiser Permanente South. Ajay Nehra is a consultant for Pfizer, Glaxo-Smith Klein, and Sanofi. Cynthia Girman is an employee of and stockholder in Merck.

CONCLUSION—

- In this study, statin use was associated with a 6.5- to 7-year delay in the new onset of moderate/severe LUTS or BPE.
- While men typically take statin medications to prevent coronary heart disease events and related outcomes, these data suggest that men who use statins may also receive urologic benefits.

Keywords

Statins; BPH; prostate

INTRODUCTION

Statin medications are currently prescribed for both primary and secondary prevention of coronary heart disease, stroke, and peripheral artery disease. These medications act by inhibiting the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase enzyme, resulting in a decrease of intracellular low-density lipoprotein cholesterol levels. However, statins also have multiple effects, including apoptotic and anti-inflammatory properties [1].

Benign prostatic enlargement (BPE) and LUTS are among the most common health conditions that affect aging men [2–4]. Estimates of the prevalence of moderate to severe LUTS range from 18% to nearly 40% [5], and the presence of moderate to severe LUTS is strongly associated with a decreased quality of life [2,6,7]. In addition, health-care costs associated with treatment of both BPE and LUTS are substantial [5,8]. These conditions therefore have a considerable impact on public health, and strategies for improved treatment and prevention could significantly improve the quality of life and reduce health-care costs in aging men. However, few data are available regarding factors which may be protective against development of these conditions.

Accumulating evidence suggests that inflammatory processes may play a role in the development of both BPE and LUTS [9–11]. Factors that decrease systemic inflammation, such as statin use, may also decrease the development of BPE and LUTS. Statins also inhibit the formation of cholesterol, high levels of which are found in the prostate, and lowering cholesterol levels in the prostate may affect prostate cell growth and survival [12]. Therefore, we hypothesized that statin use might be associated with a decreased risk of developing BPE and LUTS. To investigate this hypothesis, we examined associations between statin use and the development of these outcomes among participants in a population-based, longitudinal cohort study.

METHODS

Our study population consisted of Caucasian men enrolled in the Olmsted County Study of Urinary Symptoms and Health Status among Men. Details of the study have been previously published [13]. Briefly, a stratified random sample of all male Olmsted County (MN, USA) residents between 40 and 79 years of age on January 1, 1990 was identified using the resources of the Rochester Epidemiology Project [14]. Men with a previous history of prostatectomy, prostate cancer or other urological conditions (bladder cancer or surgery, other bladder disorders or urethral surgery or strictures) were excluded, leaving 3874 eligible individuals. Of these men, 2115 (55%) agreed to participate in an in-home interview which included verbal questions about family history of urologic disease and medication use, completion of a self-administered questionnaire regarding severity of LUTS and measurement of maximum urinary flow rates with a portable urometer. Community medical

records were reviewed to assess development of urological conditions that came to medical attention. In addition, 475 (88%) of 537 men randomly selected from this group participated in a detailed clinical examination including transrectal sonographic examination of the prostate. Examinations and questionnaires were repeated biennially through 2007. To replace men who either died or dropped out of the study during the follow-up period, more men were randomly sampled from the community and 332 new participants were added during the first 4 years of follow-up (Fig. 1). Information obtained by questionnaire, in-home visits and medical record review was available for 2447 men, and clinical exam information (including prostate volume and maximum urinary flow rate) was available for 634 men.

At baseline, study participants were asked (by structured interview) to report all prescribed and over-the-counter medications that were taken on a daily basis. The dosage, unit of administration, starting date and directions for use of each medication were recorded when such information was available. When possible, medication information was recorded directly from the label of the bottle. Medication use was again ascertained by questionnaire in round 4 (1996), round 6 (2000), and during each biennial follow-up round thereafter.

Participants were asked to list all medications that they were currently taking every day, and the date of first use. LUTS were measured by a previously validated questionnaire that contains questions similar to the AUA symptom index, and from which an AUA composite score was calculated [13,15]. Moderate/severe LUTS were classified as ever having an AUA symptom score > 7 during follow-up. Maximum urinary flow rates were measured using a Dantec 1000 urometer (Dantec Medical, Santa Clara, CA, USA). A decreased maximum flow rate was defined as < 12 mL/s. Total prostate volume was measured via transrectal ultrasound using a 7.5 MHz biplanar endorectal transducer. In addition to assessing the echogenic pattern of the prostate gland, three measurements were made to calculate the total prostatic volume. Anterior–posterior and transverse diameters were measured at the maximal dimensions, and the superior–inferior diameter was measured at the maximal length from the base to the apex of the midline sagittal plane[16,17]. BPE was defined as a prostate volume > 30 mL.

Variables that might confound or modify associations between statin use and urologic outcomes were considered. Presence of diabetes was determined by the participant indicating that he had been told by a doctor that he had diabetes, or by report of anti-hyperglycemic medication use. Presence of hypertension was determined by the participant indicating that he had been told by a doctor that he had high blood pressure, or by report of anti-hypertensive medication use (angiotensin-converting enzyme inhibitors, angiotensin II receptor inhibitors, beta-blockers, calcium channel blockers, or diuretics; with the exception of loop diuretics, as these were expected to be prescribed to treat hypertension or edema following heart or renal failure rather than primary hypertension). Presence of coronary heart disease (CHD) was ascertained through ongoing surveillance of heart disease in the Olmsted County community (RO1 HL 59205; Principal Investigator: V Roger) [18,19]. All men in our cohort who would have developed CHD would be identified by this surveillance. CHD was defined as sudden cardiac death, myocardial infarction, and angiographically diagnosed coronary disease [19–21]. Smoking was assessed through the question ‘Have you smoked at least 100 cigarettes in your entire life?’ and subjects were classified as ‘ever smoker’ or ‘never smoker’ accordingly. Finally, anthropometric measures were obtained at baseline by trained study nurses using a standardized protocol. Body mass index (BMI) was calculated as weight (kg) divided by height (m²), and individuals with a BMI ≥30 kg/m² were classified as obese.

Separate analyses were conducted for each outcome, and men with moderate/severe LUTS, a decreased maximum flow rate or BPE at baseline were excluded from the analyses considering those outcomes. A total of 2447 men were initially eligible for analysis, and 729 (29.8%) of these men had participated in an in-clinic examination to obtain maximum flow rate and prostate volume information. Of the eligible men, 786 had moderate/severe LUTS at baseline, leaving 1661 eligible for the analysis of time-to-moderate/severe LUTS. Of the 729 men with maximum flow rate and prostate volume data, 194 had a maximum flow rate < 12 mL/s and 313 had a prostate volume > 30 mL at baseline. This left 535 men eligible for time-to-maximum flow rate < 12 mL/s analysis, and 416 men eligible for the time to time-to-volume > 30 mL analysis. Follow-up was from the start of the study until the first occurrence of the outcome being analysed or the last study visit. Participants who reported statin use prior to the development of the urological outcome in the analysis were considered exposed. Duration of medication use was defined as the time from the reported start of the medication to the event date or date of last follow-up (no event).

Observations after diagnosis of prostate or bladder cancer and surgical or medical treatment for BPE or LUTS were censored. Medical treatments for BPE or LUTS included 5 α -reductase inhibitors, α -adrenergic receptor inhibitors, and herbal medications. Cox proportional hazard models were used to estimate the associations between statin use or duration of statin use and each of the outcomes and are presented as hazard ratios (HR) and their associated 95% confidence intervals (CI). Proportional hazards assumptions were assessed using Schoenfeld residuals. Multivariable models were used to adjust for potential confounders including age, comorbidities (diabetes, hypertension, CHD), and use of NSAIDs. To assess potential interactions between statin use and other variables, age-adjusted Cox models were stratified by comorbidities, smoking status, and obesity. Multivariable models which included an interaction term for pair-wise interactions between statin use and each variable of interest were used to test for interactions.

RESULTS

The 2447 study participants were followed for a median of 13.8 years (25th, 75th percentiles: 9.2 years, 15.7 years, respectively) and 729 (29.8%) of the men in the study reported statin use at some point in the study. Median length of follow-up was longer for men who reported statin use compared with those who did not report statin use (15.5 years vs 11.9 years; $P < 0.001$). Statin users differed in age from non-statin users, and were more likely to have diabetes, hypertension, CHD and have used NSAIDs (Table 1). However, statin users were less likely to have moderate/severe LUTS compared with non-statin users (Table 1).

Statin users had a lower cumulative incidence of moderate/severe LUTS, decreased maximum flow rate, and BPE compared to those who did not use statins across all ages (Fig. 2). After adjusting for age, diabetes, hypertension, CHD, baseline BMI, smoking, alcohol use, activity levels and NSAID use, statin use remained inversely associated with new onset of all outcomes (Table 2). Longer duration of statin use was associated with a decreased risk of developing moderate/severe LUTS (Table 3; test for trend $P < 0.001$), decreased maximum flow rate ($P < 0.001$) and BPE ($P < 0.001$). The presence of diabetes, hypertension, CHD, smoking, and obesity did not significantly modify associations between statin use and moderate/severe LUTS, decreased maximum flow rate or BPE (Table 4). Finally, interactions between statin use and NSAID use were not statistically significant, but men who used both medications had the lowest risk of moderate/severe LUTS and BPE (Table 5).

DISCUSSION

Our results suggest that statin use was associated with decreased risks of developing moderate/severe LUTS, decreased maximum flow rate and BPE. The protective hazard ratios associated with these outcomes could be interpreted as delays to new-onset urological events. For example, statin use was associated with a 6.5- to 7-year delay in the new onset of moderate/severe LUTS or BPE. The delay in new onset of a decreased maximum flow rate was not as pronounced, approximately 2 years. However, longer use of statins was associated with greater risk reductions in each of the outcomes examined. While men typically take statin medications to prevent CHD events and outcomes, these data suggest that men who use statins may also receive urologic benefits.

Associations between statin use and benign urological diseases have not been extensively examined. However, in a randomized, double-blinded, placebo-controlled clinical trial, Mills *et al.* [22] found that atorvastatin was not effective in alleviating LUTS or benign prostatic hyperplasia in 319 affected men over a 6-month period. Stamatiou *et al.* [23] did not see any changes in LUTS, prostate volume or PSA concentrations after treating men with benign prostatic hyperplasia with lovastatin and finasteride. Our results are not necessarily inconsistent with these findings, as statins may help prevent onset of BPE or moderate/severe LUTS, but may not relieve these conditions once they have become established. Our results also suggested that longer duration of statin use (over a period of many years) was associated with decreased risks for developing moderate/severe LUTS, a decreased maximum flow rate, and BPE. It is therefore possible that 4–6 months of use may not have been enough time to effect an improvement in symptoms among men with established LUTS or benign prostatic hyperplasia.

A few studies have also examined the association between statin use and PSA levels, and have found decreased PSA levels among statin users [24,25]. In separate analyses, we found that statin use was associated with a decreased risk of exceeding age-specific PSA reference ranges, and a decreased risk of being diagnosed with prostate cancer, with a point estimate similar to that for BPE [26]. As PSA levels are associated with prostate volume, our results suggest that statin use may also have a direct effect on prostate volume.

Several studies have suggested that men with elevated low density lipoprotein cholesterol levels or other metabolic risk factors (such as obesity, hypertension, and diabetes) had an increased odds of also having BPE or LUTS [27–30]. Results from these studies are not consistent with others, including some conducted in this cohort, which have found mixed or no associations between presence of metabolic risk factors and an increased risk of developing BPE or LUTS [31–35]. However, as the men in our study who had several of these factors were also more likely to be taking a statin medication (Table 1), it was possible that these conditions could have confounded or modified associations between statin use and the outcomes examined. We adjusted for diabetes, hypertension and CHD, including use of medications used to treat diabetes and hypertension (including angiotensin-converting enzyme inhibitors, angiotensin II receptor inhibitors, beta-blockers, calcium channel blockers and diuretics). After adjusting, the associations between statin use and moderate/severe LUTS, decreased maximum flow rate, and BPE strengthened slightly, and interactions between these comorbidities and statin use were not statistically significant. Overall, a protective association between statin use and each of the outcomes was typically observed regardless of whether a metabolic condition was present or not (Table 4). In a previous study of this cohort, we found that use of NSAIDs was associated with a decreased risk of developing BPE and LUTS [11], suggesting that inhibition of inflammatory pathways might be useful in preventing these conditions. In the present study, men who used statins were more likely to also use NSAIDs. If inflammation is of primary importance for

developing BPE and LUTS, we might expect to see a synergistic association between NSAID and statin use and decreased risk of BPE and LUTS. While the interactions between NSAID use and statin use were not statistically significant for any outcomes examined, men who used both NSAIDs and statins had the lowest risk of new-onset moderate/severe LUTS and BPE (Table 5).

Strengths of our study include the population-based setting in which this study was conducted, which ensured that the men in our study spanned the range of LUTS and BPE, from mild to severe, as would be expected in the general community. In contrast, clinic-based studies of BPE and LUTS tend to focus on men with more severe LUTS or greatly enlarged prostates who seek care from urology specialists. Therefore, an association between statin use and LUTS or BPE could be missed in studies examining populations skewed toward severely affected men, because non-diseased men would have limited representation. In addition, this well-established cohort of men allowed us to examine these men for longitudinal development of these outcomes over a 17-year period. This length of follow-up allowed us to assess incident outcomes, which was especially important as prevalent cases can frequently differ from incident cases of disease. The long follow-up period also allowed us to determine that longer statin use was associated with a decreased risk of each of the outcomes examined. Studies with shorter periods of follow-up may therefore miss some of these effects.

Several potential limitations to our study must also be considered when interpreting these results. First, as we had a 55% initial participation rate in the cohort, it is possible that our study results were affected by participation bias. At baseline, the participants in the study were slightly more likely to have a diagnosis of urological disease than non-participants; however, participants and non-participants had virtually identical rates of non-urological diagnoses and number of general medical examination visits [36]. In addition, drop-out of study participants during the 17 years of follow-up may also have biased study results. We have previously shown that older baseline age (70+ years) and having a stroke were associated with dropping out of the study cohort, while being satisfied with overall health was associated with remaining in the study [37]. If those who dropped out were disproportionately likely to have both used statins and have urological conditions, our study results may overestimate true associations between statin use and the urological outcomes of interest. We actually had longer follow-up in our statin users than in our non-statin users, suggesting that those who used statins were not more likely to drop out of the study.

We examined a number of potential confounders that could have accounted for the protective associations observed in this study; however, it is possible that our results are due to an unknown confounder, such as a possible 'healthy user' effect. Men who use statins regularly may be more likely to engage in particular behaviors or have certain characteristics that could substantially reduce their risk of BPE or moderate/severe LUTS. We adjusted for several life-style characteristics (including smoking history, body mass index, frequency of regular physical activity and alcohol use), which did not significantly affect the point estimates (Tables 2 and 3). We also stratified our results by a number of co-morbid conditions, including diabetes, hypertension and CHD (Table 4). If a healthy user effect was affecting our results, we might have expected to see stronger associations between statin use and the urological outcomes among those who were unaffected by these chronic diseases compared with those who were likely taking statins for secondary prevention. Such differences were not observed, as the associations between statin use and the urological outcomes were of approximately the same magnitude whether or not the chronic disease was present. However, we cannot rule out the possibility that men prescribed a statin had other unmeasured characteristics that confounded the association between statin use and reduced risk of moderate/severe LUTS, decreased maximum flow rate and BPE.

Data on diabetes, hypertension and all medications were self-reported. We had little information on statin dose, limiting our ability to examine a dose–response relationship with risk of developing moderate/severe LUTS, decreased maximum flow rate and BPE. Moreover, statin use and date of first statin use were self-reported, and may not have been completely accurate. We also assumed that once a man reported use of a statin, he continued to take the statin for the duration of follow-up. A recent review article suggests that up to 60% of patients who are prescribed statins stop use within the first 6 months of prescription [38]. In this cohort, long-term medication adherence appeared to be more common. Of the 350 men who reported statin use at baseline (1990) and who had data available in 2000, 290 (83%) also reported statin use in 2000. In addition, of the 251 men who reported new use of statins in 2000, and who also had information in 2006, 208 (83%) again reported statin use. It was not possible, however, for us to assess interim changes in statin use, or whether men who reported statin use actually took the medications. Men who took a statin had a longer period of follow-up than men who did not take a statin (15.5 vs 11.9 years), creating the possibility of an underestimate of the true association if the men who were not taking a statin left the study and went on to develop any of the outcomes of interest. Finally, our study included only white men and the results may not be generalizable to men of other races or ethnicities if the effects of statins or the disease processes that lead to the development of LUTS and BPE differ among these groups.

Despite these potential limitations, our results suggest that statin use may be associated with a lower risk of developing moderate/severe LUTS, decreased maximum flow rate and BPE. If the associations we observed are real, statin use could have an important public health impact owing to the prevalence of these urological conditions, their impact on quality of life and the frequent use of statins in the community. However, the mechanisms by which statins might cause this reduced risk are not immediately apparent, and further studies are needed to provide insight into the potential utility of statin use in preventing these conditions in aging men.

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Abbreviations

CI	confidence interval
BMI	body-mass index
BPE	benign prostatic enlargement
HR	hazard ratio

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Fig. 1.
Flow chart of individuals participating during each round of follow-up

Fig. 2c

Fig. 2. (a) Cumulative incidence of moderate/severe LUTS (1661 participants eligible for this analysis). (b) Cumulative incidence of decreased maximum flow rate (535 participants eligible for this analysis). (c) Cumulative incidence of benign prostatic enlargement (BPE) (416 participants were eligible for this analysis).

TABLE 1

Characteristics of statin users and non-statin users

Characteristic	Statin use, <i>n</i> (%)	No statin use, <i>n</i> (%)	χ^2P -value	Age-adjusted χ^2P -value
Age (at 1/1/1990)				
40–49	277 (38.00)	866 (50.41)	< 0.0001	
50–59	251 (34.43)	349 (20.31)		
60–69	161 (22.09)	287 (16.71)		
70+	40 (5.49)	216 (12.57)		
Diabetes	159 (21.81)	126 (7.33)	< 0.0001	< 0.0001
Hypertension	553 (75.86)	670 (39.00)	< 0.0001	< 0.0001
Coronary heart disease	285 (39.09)	257 (14.96)	< 0.0001	< 0.0001
Ever smoker	472 (65.01)	1073 (62.53)	0.24	0.32
Obese	219 (32.54)	424 (29.92)	0.23	0.20
Use NSAIDs	640 (87.79)	935 (54.42)	< 0.0001	< 0.0001
Baseline alcohol use $\geq$ once per week	322 (48.94)	655 (46.36)	0.27	0.30
Moderate activity of at least 30 min atleast once per week	502 (69.15)	949 (62.07)	0.001	0.001
AUA symptom score $> 7^*$	103 (40.08)	701 (49.93)	0.004	0.004
Maximum flow rate < 12 mL/s [†]	32 (32.99)	144 (32.88)	0.98	0.91
Prostate volume > 30 mL [‡]	21 (31.82)	133 (38.00)	0.34	0.43

* Data reflect the 1661 men at risk for developing an AUA symptom score > 7 (did not have moderate/severe symptoms at baseline)

[†] Data reflect the 535 men who participated in the in-clinic examination and did not have a maximum flow rate < 12 mL/s at baseline

[‡] Data reflect the 416 men who participated in the in-clinic examination and did not have a prostate volume > 30 mL at baseline

TABLE 2

Associations between statin use and risk of urological outcomes

Outcome	Statin use		No statin use		Unadjusted hazard ratio (95% CI)	Multivariable-adjusted* hazard ratio (95% CI)
	Number of events	Person-years	Number of events	Person-years		
AUA symptom score > 7	103	3224	701	11388	0.49 (0.39–0.60)	0.39(0.31–0.49)
Maximum flow rate < 12 mL/s [†]	32	1095	144	3387	0.63 (0.43–0.92)	0.53(0.34–0.82)
Prostate volume > 30 mL [†]	21	783	133	2612	0.47 (0.30–0.75)	0.40(0.23–0.69)

* Adjusted for age, diabetes, hypertension, coronary heart disease, NSAID use, baseline body-mass index, smoking history, baseline alcohol usage and baseline activity

[†] Data reflect only the 634 men who participated in the in-clinic examination

Associations between duration of statin use and development of moderate/severe LUTS, decreased maximum flow rate and benign prostatic enlargement (BPE)

TABLE 3

Outcome	No statin use	Duration [*] > 0–33rd percentile, hazard ratio [‡] (95% CI)	Duration [*] > 33rd–66th percentile, hazard ratio [‡] (95% CI)	Duration [*] > 66 percentile, hazard ratio [‡] (95% CI)	P-value for trend
AUA symptom score > 7	Referent	0.55 (0.39–0.78)	0.32 (0.21–0.49)	0.32 (0.22–0.48)	< 0.001
Maximum flow rate < 12 mL/s [‡]	Referent	0.87 (0.48–1.57)	0.69 (0.38–1.25)	0.19 (0.08–0.46)	< 0.001
Prostate volume > 30 mL [‡]	Referent	0.76 (0.35–1.64)	0.64 (0.32–1.31)	0.08 (0.02–0.33)	< 0.001

^{*} Duration of statin use varies slightly depending on the outcome. Use before development of moderate/severe LUTS (years): tertile 1 > 0 to ≤4.0; tertile 2 > 4.0 to ≤7.8; tertile 3 > 7.8. Use before development of a decreased maximum flow rate (years): tertile 1: > 0 to ≤ 3.1; tertile 2: > 3.1 to ≤ 6.3; tertile 3: > 6.3. Use prior to development of BPE (years): tertile 1: > 0 to ≤ 3.1; tertile 2: > 3.1 to ≤ 6.0; tertile 3: > 6.0.

[‡] Data reflect only the 634 men who participated in the in-clinic examination.

[‡] Adjusted for age, diabetes, hypertension, coronary heart disease, NSAID use, baseline body-mass index, smoking history, baseline alcohol usage and baseline regular activity

TABLE 4

Age-adjusted associations between statin use and moderate/severe LUTS, decreased maximum flow rate, and benign prostatic enlargement (BPE) stratified by specific characteristics

Characteristic	AUA symptom score > 7, hazard ratio (95% CI)	P [†]	Maximum flow rate < 12 mL/s [*] , hazard ratio (95% CI)	P [†]	Prostate volume > 30 mL [*] , hazard ratio (95% CI)	P [†]
Age (1990)						
40–49	0.43 (0.30–0.60)	0.91	0.37 (0.19–0.75)	0.08	0.54 (0.31–0.94)	0.76
50–59	0.59 (0.42–0.83)		0.71 (0.35–1.41)		0.38 (0.13–1.10)	
60–69	0.29 (0.17–0.48)		1.22 (0.56–2.63)		0.55 (0.13–2.35)	
70+	0.60 (0.24–1.51)		0.80 (0.23–2.84)		–	
Diabetes	0.37 (0.23–0.59)	0.78	0.49 (0.20–1.20)	0.81	0.44 (0.11–1.69)	0.52
No diabetes	0.44 (0.34–0.55)		0.63 (0.41–0.99)		0.54 (0.32–0.90)	
Hypertension	0.40 (0.31–0.51)	0.71	0.58 (0.38–0.91)	0.41	0.43 (0.24–0.75)	0.60
No Hypertension	0.43 (0.28–0.66)		0.32 (0.10–1.01)		0.61 (0.24–1.52)	
Coronary heart disease (CHD)	0.40 (0.28–0.57)	0.16	0.55 (0.27–1.12)	0.71	0.46 (0.19–1.13)	0.83
No CHD	0.37 (0.28–0.49)		0.51 (0.29–0.90)		0.48 (0.27–0.86)	
Ever smoker	0.48 (0.38–0.62)	0.40	0.59 (0.36–0.97)	0.72	0.49 (0.28–0.88)	0.86
Never smoker	0.38 (0.26–0.56)		0.67 (0.35–1.27)		0.53 (0.24–1.16)	
Obese	0.41 (0.28–0.60)	0.86	0.32 (0.13–0.77)	0.08	0.22 (0.08–0.55)	0.09
Not obese	0.44 (0.33–0.57)		0.76 (0.49 to 1.17)		0.67 (0.39–1.15)	

* Data reflect only the 634 men who participated in the in-clinic examination

[†] P-value for interaction term between statin use and participant characteristic

TABLE 5

Associations between statin use, NSAID use, and both and development of moderate/severe LUTS, decreased maximum flow rate and benign prostatic enlargement (BPE)

Outcome	No medications	Statin use alone, hazard ratio* (95% CI)	NSAID use alone, hazard ratio* (95% CI)	Both Statin and NSAID use, hazard ratio* (95% CI)	P-value for interaction [†]
AUA symptom score > 7	Referent	0.44 (0.27–0.71)	0.49 (0.41–0.59)	0.24 (0.18–0.32)	0.64
Maximum flow rate < 12 mL/s [‡]	Referent	0.29 (0.07–1.19)	0.53 (0.36–0.78)	0.41 (0.25–0.66)	0.20
Prostate volume > 30 mL [‡]	Referent	0.76 (0.30–1.93)	0.48 (0.31–0.74)	0.23 (0.12–0.44)	0.42

* Hazard ratios adjusted for baseline age, diabetes, hypertension, coronary heart disease, baseline body-mass index, smoking history, baseline alcohol usage and baseline regular activity

[†] P-value for interaction between statin use and NSAID use

[‡] Data reflect only the 634 men who participated in the in-clinic examination