Original Contribution

A Prospective Study of Statin Drug Use and Lower Urinary Tract Symptoms in Older Men

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Dyslipidemia and chronic inflammation may play a role in the cause of lower urinary tract symptoms (LUTS) in older men. Use of statin drugs, which are prescribed to lower cholesterol and appear to reduce inflammation, may decrease the incidence or progression of LUTS. The associations of statin drug use with LUTS incidence and progression were prospectively evaluated in the Health Professionals Follow-up Study from 1992 to 2008. Hazard ratios and 95% confidence intervals of incident LUTS (from no or a low International Prostate Symptom Score (IPSS) of 0–7 to a moderate or worse IPSS of ≥ 15 ; $n = 5,790$ cases in 24,715 men) and of LUTS progression (from modest IPSS of 8–14 to severe IPSS of ≥ 20 ; $n = 2,238$ cases in 8,709 men) were calculated comparing current statin use with nonuse. The hazard ratios of LUTS incidence and progression comparing current use to nonuse were greater than 1. However, when comparisons were restricted to participants who used drugs to treat hypertension (a surrogate for uptake of medical care), statin use was not associated with LUTS incidence (hazard ratio = 1.02, 95% confidence interval: 0.94, 1.12) or progression (hazard ratio = 0.98, 95% confidence interval: 0.85, 1.13). Thus, statin use is unlikely to beneficially influence the development or course of LUTS. The present study highlights a methodological issue (confounding) that must be addressed in observational studies on the use of common drugs for indications other than the primary use.

cohort; lower urinary tract symptoms; risk; statin drug

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; IPSS, international prostate symptom score; LUTS, lower urinary tract symptoms.

Lower urinary tract symptoms (LUTS) are common in older men (1); they are frequently secondary to benign prostatic hyperplasia. Aging and sex steroid hormones play a role in the origin of these symptoms (2–4). Modifiable risk factors for cardiovascular disease (CVD), including dyslipidemia (3, 4), have been associated with increased LUTS risk. Another hypothesized cause of LUTS in older men is chronic prostatic inflammation (2). Because of their effectiveness in lowering cholesterol and because they may be anti-inflammatory (5), statin drugs have been hypothesized to prevent the incidence or progression of LUTS in older men (3).

Only 4 studies have addressed this hypothesis. A cross-sectional study reported that statin use was associated with a lower prevalence of LUTS in older men (6). The only prospective cohort study conducted to date, which was relatively small ($n = 2,447$), found that statin use was associated with a

lower risk of LUTS (7). Two small clinical studies that examined the efficacy of a statin in treating LUTS in older men found no effect (8, 9). Given the limited prospective evidence, we undertook an analysis of statin drug use and LUTS incidence and progression in the Health Professionals Follow-up Study (HPFS).

MATERIALS AND METHODS

Study population

The HPFS is a large prospective cohort study of 51,529 US male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians from all 50 states that began in 1986. At that time, the men completed a mailed questionnaire on exposures and medical history. Follow-up questionnaires

have been mailed every 2 years to update information, including data on LUTS; the response rate through 2008 was 94%. Deaths are ascertained by reports from family members or the postal service and by linkage to the National Death Index; the sensitivity of death ascertainment is greater than 98% (10). In the present analysis, we began follow-up in 1992, the year that the first questionnaire that assessed LUTS was administered.

Assessment of use of medications

On each questionnaire, participants were asked to report medications that they took regularly (≥ 2 per week) during the previous 2-year period; we provided a list of classes of medications, including cholesterol-lowering drugs and hypertension medications. Although the type of cholesterol-lowering drug used was not collected until 2000, it is likely that the majority were statins, given the national prescription patterns (11). In addition, in 2000–2006, approximately 96%–97% of the cholesterol-lowering drugs used by men in this cohort were statins. Thus, any reported cholesterol-lowering drug use was categorized as statin use, as was done in a previous study of this cohort (12). Information on dosage was not collected. Statin use was modeled as a time-dependent variable in 3 ways: 1) current use (yes vs. no), 2) ever use (yes vs. no), and 3) duration of use (< 5 years, 5 to < 10 years, or ≥ 10 years). Participants' medication use was assumed to be unchanged until the date of the next assessment of medication use. If information on statin use was missing, information from the previous questionnaire was carried forward into the next time period. Men were classified as using a hypertension medication if they reported taking diuretics, β -blockers, or calcium-channel blockers or if they checked the box for "other anti-hypertensive medication." Hypertension medication use was modeled as a time-dependent variable (ever use, yes vs. no) in the same way as described for statin use above.

Assessment of LUTS

LUTS were assessed in 1992, 1994, 1998, 2000, and 2008 using the American Urological Association Symptom Index (13), now called the International Prostate Symptom Score (IPSS). The possible score ranged from 0 to 35. Outcome assessment, including for irritative and obstructive LUTS, has been described previously (14). Data on history of surgery to treat benign prostatic hyperplasia, including transurethral resection of the prostate, were collected on every questionnaire. Data on use of medications to treat benign prostatic hyperplasia were collected on every questionnaire beginning in 1996.

LUTS incidence

Men were excluded from the analysis if they did not return a valid food frequency questionnaire in 1986; had cancer, died, or had a transurethral resection of the prostate before 1992; had prevalent LUTS (IPSS ≥ 8) in 1992; did not return the 1992 questionnaire or did not complete the section on medication use; or failed to return the IPSS twice consecutively. Men who were diagnosed with prostate cancer were censored at the date of diagnosis. After these exclusions, 24,715 men followed for 302,696 person-years comprised the incidence

analytic cohort. We used 2 definitions of incident LUTS: 1) "modest or worse LUTS," which was defined as an IPSS ≥ 8 , surgery, or medication use ($n = 10,884$) and 2) "moderate or worse LUTS," which was defined as an IPSS ≥ 15 , surgery, or medication use ($n = 5,790$).

LUTS progression

For progression analyses, men entered the analytic cohort when they first experienced an IPSS of 8–14. Men were ineligible to enter the cohort if they did not return a valid food frequency questionnaire in 1986; had cancer, died, or had a transurethral resection of the prostate before 1992; did not return the 1992 questionnaire or did not complete the section on medication use; or failed to answer the IPSS twice consecutively. Men who were diagnosed with prostate cancer were censored at the date of diagnosis. After these exclusions, 8,709 men followed for 50,191 person-years comprised the progression analytic cohort. We used 2 definitions of LUTS progression: 1) "moderate or worse LUTS," which was defined as an IPSS ≥ 15 , surgery, or medication use ($n = 3,022$), and 2) "severe LUTS," which was defined as an IPSS ≥ 20 , surgery, or medication use ($n = 2,238$).

Statistical analysis

We used Cox proportional hazards regression models to estimate the hazard ratios and 95% confidence intervals of LUTS incidence and progression. All models were adjusted for age (years). Multivariable models were further adjusted for waist circumference (quintiles); vigorous physical activity (quintiles of metabolic equivalent hours/week); dietary intake of total energy, polyunsaturated fatty acids, fruit, vegetables, red meat, alcohol, lycopene, β -carotene, lutein, and vitamin C (all in quintiles); use of supplemental vitamin E (0, < 100 , 100–250, > 250 –500, > 500 IU/day) and selenium (0, < 80 , 80–130, > 130 –250, > 250 IU/day); use of aspirin, non-aspirin nonsteroidal anti-inflammatory drugs, diuretics, and nondiuretic hypertension medications (time-dependent; yes vs. no); and history of diabetes, CVD, and high blood pressure (time-dependent; ever vs. never).

When conducting observational studies on use of medications for indications other than those for which they are usually prescribed, the possibility of confounding by factors correlated with the drug indication must be carefully addressed. The chief indication for use of a statin is hypercholesterolemia, which is a risk factor for CVD. Lifestyle risk factors for CVD have been associated with an increased risk of LUTS, and the prevalence of several CVD risk factors is higher in men prescribed a statin than in those who are not, which could lead to a spurious upward bias in the estimate of the association between statin drug use and LUTS. We used 3 approaches to address this probable source of confounding. First, we created a time-dependent variable to categorize men by mutually exclusive categories of the combination of their statin and hypertension medications use (statins alone, hypertension medications alone, both medications, or neither medication), with hypertension medication use alone as the reference. Men who were using hypertension medications must also have gone to a doctor to receive such a prescription and likely also had CVD risk

Table 1. Age-Adjusted^a Characteristics of the Incidence Cohort in the Year 2000^b by Statin Drug Use, Health Professionals Follow-up Study

Characteristic	Statin Drug Use in 2000			
	No (n = 13,644)		Yes (n = 4,238)	
	Mean (SD)	%	Mean (SD)	%
Age in 2000, years	63.7		63.7	
Waist circumference, inches	36.2 (3.3)		36.6 (3.3)	
Cigarette smoking in the 10 years before 2000		16		19
Vigorous physical activity in 2000, MET-hours/week	13.5 (24.5)		13.1 (25.3)	
Intake in 1998				
Energy, kcal/day	2,006 (526)		1,926 (506)	
Dietary lycopene, µg/day	8,238 (4,153)		8,877 (4,525)	
Dietary β-carotene, µg/day	4,563 (2,404)		4,627 (2,205)	
Dietary lutein, µg/day	3,332 (1,908)		3,362 (1,826)	
Dietary vitamin C, mg/day	162 (62)		165 (61)	
Polyunsaturated fatty acids, g/day	12.8 (2.5)		12.8 (2.4)	
Supplemental vitamin E, IU/day	58.2 (76.7)		68.8 (78.8)	
Supplemental selenium, µg/day	11.2 (28.5)		10.5 (27.1)	
Fruit, servings/day	2.4 (1.4)		2.3 (1.3)	
Vegetables, servings/day	3.3 (1.6)		3.4 (1.6)	
Cruciferous vegetables, servings/day	0.4 (0.3)		0.4 (0.3)	
Alcohol, g/day	11.1 (13.2)		11.3 (12.9)	
Red meat, servings/day	0.6 (0.4)		0.5 (0.3)	
Medications used regularly to treat cardiovascular disease or its risk factors in 2000				
Aspirin		46		69
Non-aspirin NSAIDs		26		28
Furosemide diuretics		2		4
Thiazide diuretics		4		7
β-blockers		9		23
Calcium channel blockers		5		11
Other antihypertensive drugs (including angiotensin-converting enzyme inhibitors)		9		16
History of myocardial infarction by 2000		2		11
History of angina pectoris by 2000		1		11
History of high blood pressure by 2000		34		49
History of type 2 diabetes mellitus by 2000		5		10

Abbreviations: MET, metabolic equivalent; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation.

^a Values are standardized to the age distribution of the analytic population.

^b All characteristics were assessed on the 2000 questionnaire except dietary factors, which were assessed on the 1998 questionnaire. Characteristics are shown for the year 2000 (i.e., the midpoint of follow-up) rather than baseline to better reflect changing patterns in statin use during the follow-up period. The sample size for this analysis (n = 20,119) was smaller than the total incidence analytic cohort (n = 24,715) because men who had moderate or worse lower urinary tract symptoms, who died, or who did not respond to 2 consecutive questionnaires before 2000 were censored.

factors; thus, using these participants as the reference group in theory should reduce the likelihood of confounding by indication. Second, we conducted sensitivity analyses in which we excluded men with a history of CVD (i.e., myocardial infarction, angina, stroke, coronary artery bypass grafting, angioplasty, carotid artery surgery, or surgery for arterial disease of the leg). Third, we conducted sensitivity analyses restricted to

men who reported ever having been diagnosed with hypercholesterolemia.

RESULTS

Characteristics of the LUTS incidence analytic population in 2000 (i.e., the midpoint of our follow-up period) by statin

use are shown in Table 1. Men who used statins were more likely to take aspirin, diuretics, and hypertension medications and to report a myocardial infarction, angina, hypertension, or diabetes (Table 1). The prevalence of statin use increased during the follow-up period, ranging from 5.7% in 1992 to 15.4% in 1998 and 43.6% in 2006.

Incident LUTS

After adjustment for age, the hazard ratio for current statin use and incidence of LUTS was greater than 1 (Table 2), including for obstructive and irritative LUTS (data not shown). The hazard ratio for current use was higher for moderate or worse LUTS than for modest or worse LUTS; both estimates were attenuated after multivariable adjustment (Table 2). Further adjustment for dietary factors did not change the findings (data not shown). Likewise, the hazard ratio for ever use of a statin was greater than 1 (for modest or worse LUTS, multivariable adjusted hazard ratio (HR) = 1.03, 95% confidence interval (CI): 0.98, 1.08; for moderate or worse LUTS, multivariable adjusted HR = 1.10, 95% CI: 1.03, 1.18). The hazard ratios did not decrease with duration of use (vs. never use; for modest or worse LUTS for <5 years, HR = 1.05, 95% CI: 0.98, 1.12; for modest or worse LUTS for ≥10 years, HR = 1.05, 95% CI: 0.96, 1.15; for moderate or worse LUTS for <5 years, HR = 1.12, 95% CI: 1.03, 1.22; for moderate or worse LUTS for ≥10 years, HR = 1.13, 95% CI: 1.02, 1.26). The findings for current statin use were very similar when restricted to men with a history of hypercholesterolemia (for modest or worse LUTS, multivariable adjusted HR = 1.00, 95% CI: 0.94, 1.06; for moderate or worse LUTS, multivariable adjusted HR = 1.05, 95% CI: 0.97, 1.14). The hazard ratios remained greater than 1 when analyses were restricted to men without a history of CVD (data not shown).

However, compared with men who used hypertension medications, men who used a statin, either alone or in combination with a hypertension medication, did not have a higher risk of modest or worse incident LUTS, moderate or

worse incident LUTS (Table 3), or obstructive and irritative LUTS (data not shown). Men who did not use either medication had a statistically significant lower risk of LUTS than did men who used hypertension medications; the association was stronger for moderate or worse LUTS than for modest or worse LUTS (Table 3). All findings were unchanged when diuretic users or diabetics were excluded (data not shown).

LUTS progression

After adjustment for age, the hazard ratios for current statin drug use and progression to moderate or worse LUTS or severe LUTS were slightly greater than 1 (Table 4), and they were attenuated after multivariable adjustment. Further adjustment for dietary factors did not alter the estimates (data not shown). Likewise, the hazard ratios for ever use of a statin drug were slightly greater than 1 (for moderate or worse LUTS, multivariable adjusted HR = 1.04, 95% CI: 0.95, 1.15; for severe LUTS, multivariable adjusted HR = 1.06, 95% CI: 0.95, 1.17). The hazard ratios did not decrease with duration of use (vs. never use; for moderate or worse LUTS for <5 years, HR = 0.98, 95% CI: 0.87, 1.11; for moderate or worse LUTS for ≥5 years, HR = 1.10, 95% CI: 0.98, 1.23; for severe LUTS for <5 years, HR = 1.00, 95% CI: 0.88, 1.15; for severe LUTS for ≥5 years, HR = 1.11, 95% CI: 0.98, 1.25). The findings for current statin use were very similar when analyses were restricted to men with a history of hypercholesterolemia (for moderate or worse LUTS, multivariable adjusted HR = 0.94, 95% CI: 0.83, 1.06; for severe LUTS, multivariable adjusted HR = 0.95, 95% CI: 0.85, 1.07). The hazard ratios remained slightly greater than 1 when analyses were restricted to men without a history of CVD (data not shown).

However, compared with men who used hypertension medications, men who used a statin drug in combination with a hypertension medication did not have a higher risk of progression to either moderate or worse LUTS or severe LUTS, although we could not rule out an inverse association between use of a statin only and LUTS progression (Table 5). Men

Table 2. Association Between Statin Drug Use and Incident Lower Urinary Tract Symptoms, Health Professionals Follow-up Study, 1992–2008

Statin Use	No. of Cases	Person-years	HR ^a	95% CI	HR ^b	95% CI
Modest or worse LUTS (IPSS ≥8)						
Not currently using a statin	8,359	222,124	1.0	Referent	1.0	Referent
Currently using a statin	2,525	50,804	1.14	1.08, 1.20	1.04	0.99, 1.10
Moderate or worse LUTS (IPSS ≥15)						
Not currently using a statin	4,008	243,544	1.0	Referent	1.0	Referent
Currently using a statin	1,782	59,152	1.24	1.16, 1.31	1.11	1.04, 1.19

Abbreviations: CI, confidence interval; HR, hazard ratio; IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms.

^a Adjusted for age.

^b Adjusted for age, waist circumference, cigarette smoking in the past 10 years, vigorous physical activity, use of aspirin, non-aspirin nonsteroidal anti-inflammatory drugs, diuretics, or nondiuretic hypertension medications, and history of diabetes, cardiovascular disease, or high blood pressure.

Table 3. Association Between Joint Categories of Statin and Hypertension Medication Use and Incident Lower Urinary Tract Symptoms, Health Professionals Follow-up Study, 1992–2008

Medication Use	No. of Cases	Person-years	HR ^a	95% CI	HR ^b	95% CI
Modest or worse LUTS (IPSS ≥8)						
No medication use	6,110	177,733	0.79	0.76, 0.83	0.91	0.86, 0.96
Statin only	1,126	25,967	0.90	0.84, 0.97	0.98	0.91, 1.06
Hypertension medications only ^c	2,249	44,391	1.0	Referent	1.0	Referent
Both	1,399	24,836	1.04	0.97, 1.11	1.00	0.93, 1.08
Moderate or worse LUTS (IPSS ≥15)						
No medication use	2,619	194,028	0.62	0.58, 0.67	0.74	0.69, 0.80
Statin only	741	30,058	0.79	0.72, 0.87	0.91	0.83, 1.01
Hypertension medications only ^c	1,389	49,516	1.0	Referent	1.0	Referent
Both	1,041	29,095	1.01	0.93, 1.10	1.02	0.93, 1.11

Abbreviations: CI, confidence interval; HR, hazard ratio; IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms.

^a Adjusted for age.

^b Adjusted for age, waist circumference, cigarette smoking in the past 10 years, vigorous physical activity, use of aspirin or non-aspirin non-steroidal anti-inflammatory drugs, and history of diabetes, cardiovascular disease, or high blood pressure.

^c The “hypertension medications only” group was selected as the reference group to investigate confounding by medical care access.

who did not use either medication had a statistically significant lower risk of LUTS progression than did men who used hypertension medications (Table 5). When we excluded from the analysis men taking a diuretic or those who were diabetic, all findings were unchanged (data not shown).

DISCUSSION

In the present large prospective cohort study of older US men in which we addressed confounding by indication, statin drug use did not protect against LUTS incidence or progression. Initially, we observed a positive association between statin drug use and the incidence and progression of LUTS. However, our findings were likely due to residual confounding rather than to this class of drugs causing LUTS or their

progression. After multivariable adjustment, the apparent positive association was attenuated, but the hazard ratios remained greater than 1. This residual association was likely due to insufficient adjustment for the very strong correlation between statin use and the factors included in the multivariable models, as well as unmeasured factors that are also associated with LUTS. Our analysis, in which men using a statin with or without hypertension medications were compared with men using only hypertension medications, supports that hypothesis that the apparent positive association between statin use and LUTS can be explained by confounding by indication. If statin drugs had a causal positive association with LUTS incidence and progression, we would have expected that men using a statin drug and hypertension medications would have had a higher risk of LUTS when compared with men using only hypertension

Table 4. Association Between Statin Drug Use and the Progression of Lower Urinary Tract Symptoms, Health Professionals Follow-up Study, 1992–2008

Statin Use	No. of Cases	Person-years	HR ^a	95% CI	HR ^b	95% CI
Moderate or worse LUTS (IPSS ≥15)						
Not currently using a statin	2,191	35,599	1.0	Referent	1.0	Referent
Currently using a statin	831	12,544	1.07	0.98, 1.17	1.03	0.94, 1.13
Severe LUTS (IPSS ≥20)						
Not currently using a statin	1,558	37,002	1.0	Referent	1.0	Referent
Currently using a statin	680	13,189	1.08	0.98, 1.19	1.02	0.92, 1.13

Abbreviations: CI, confidence interval; HR, hazard ratio; IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms.

^a Adjusted for age.

^b Adjusted for age, waist circumference, cigarette smoking in the past 10 years, vigorous physical activity, use of aspirin, non-aspirin nonsteroidal anti-inflammatory drugs, diuretics, or nondiuretic hypertension medications, and history of diabetes, cardiovascular disease, or high blood pressure.

Table 5. Association Between Joint Categories of Statin and Hypertension Medication Use and the Progression of Lower Urinary Tract Symptoms, Health Professionals Follow-up Study, 1992–2008

Medication Use	No. of Cases	Person-years	HR ^a	95% CI	HR ^b	95% CI
Moderate or worse LUTS (IPSS ≥ 15)						
No medication use	1,482	26,430	0.81	0.73, 0.88	0.87	0.78, 0.97
Statin only	357	6,070	0.85	0.75, 0.98	0.93	0.80, 1.07
Hypertension medications only ^c	709	9,169	1.0	Referent	1.0	Referent
Both	474	6,474	0.99	0.87, 1.11	1.00	0.88, 1.14
Severe LUTS (IPSS ≥ 20)						
No medication use	1,001	27,467	0.72	0.65, 0.80	0.79	0.70, 0.90
Statin only	278	6,351	0.77	0.66, 0.89	0.85	0.72, 1.00
Hypertension medications only ^c	557	9,535	1.0	Referent	1.0	Referent
Both	402	6,839	0.95	0.83, 1.08	0.97	0.97, 1.12

Abbreviations: CI, confidence interval; HR, hazard ratio; IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms.

^a Adjusted for age.

^b Adjusted for age, waist circumference, cigarette smoking in the past 10 years, vigorous physical activity, use of aspirin or non-aspirin nonsteroidal anti-inflammatory drugs, and history of diabetes, cardiovascular disease, or high blood pressure.

^c The “hypertension medications only” group was selected as the reference group to investigate confounding by medical care access.

medications. Instead, we observed that men using a statin drug and hypertension medications had essentially the same risk of LUTS as men only using hypertension medications. Men who were not using either medication had a lower risk of LUTS than did men taking hypertension medications, perhaps because they did not have shared risk factors for LUTS and hypertension.

Our findings differ from those of the one previous prospective study on statin drugs and incident LUTS, which found that statin users had a decreased risk of LUTS (7). One possible explanation for these different findings is that the prior study population had greater socioeconomic diversity than did that of the HPFS, which includes participants who are relatively affluent. In the present analysis, men who were not taking a statin were likely to be healthy men with access to medical care. In a more socioeconomically diverse population of older men, those not taking a statin drug may also include less healthy men who have reduced access to medical care. These latter men would likely be at an increased risk of LUTS compared with men taking prescription drugs, which could explain an inverse finding in the previous study. Lower socioeconomic status has been associated with higher IPSS scores in another study (15).

Statin drug use did not protect against LUTS incidence or progression in this large prospective cohort of older US men. Our study highlights an important methodological issue that must be addressed when conducting observational studies on common drugs for other indications.

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