Statin Adherence and Risk of Accidents: A Cautionary Tale

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Circulation. 2009;119:2051-2057; originally published online April 6, 2009;
doi: 10.1161/CIRCULATIONAHA.108.824151
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Statin Adherence and Risk of Accidents
A Cautionary Tale

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Background—Bias in studies of preventive medications can occur when healthier patients are more likely to initiate and adhere to therapy than less healthy patients. We sought evidence of this bias by examining associations between statin exposure and various outcomes that should not be causally affected by statin exposure, such as workplace and motor vehicle accidents.

Methods and Results—We conducted a prospective cohort study of statin patients using data from British Columbia, Canada, a multiethnic society with a population of 4.3 million people. Study subjects were 141 086 patients who initiated statins for primary prevention. We examined the association between adherence and multiple outcomes such as accidents and screening procedures using multivariable-adjusted Cox proportional hazards models. The study population was 49% female and had an average age of 61 years. The results from our multivariable-adjusted models showed that more adherent patients were less likely to have accidents than less adherent patients. This effect was greatest for motor vehicle accidents (hazard ratio, 0.75; 95% confidence interval, 0.72 to 0.79) and workplace accidents (hazard ratio, 0.77; 95% confidence interval, 0.74 to 0.81). More adherent patients had a greater likelihood of using screening services (hazard ratio, 1.17; 95% confidence interval, 1.15 to 1.20) and a lower likelihood of developing other diseases likely to be unrelated to a biological affect of a statin (hazard ratio, 0.87; 95% confidence interval, 0.86 to 0.89).

Conclusions—Our study contributes compelling evidence that patients who adhere to statins are systematically more health seeking than comparable patients who do not remain adherent. Caution is warranted when interpreting analyses that attribute surprising protective effects to preventive medications. **(*Circulation*. 2009;119:2051-2057.)**

Key Words: bias ■ confounding variables ■ pharmacoepidemiology ■ statins

Observational postmarketing studies of medications are conducted to evaluate the safety and effectiveness of drugs used in actual clinical settings. These studies are essential because randomized clinical trials often exclude populations most likely to use a drug, such as the elderly, and do not account for the complexity of using medications without the support and supervision of a clinical trial. One of the principal limitations of observational studies is confounding bias, ie, systematic differences in prognosis between a group of patients using a medication and the comparator group of patients.[1]

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The healthy-user effect is a hypothetical source of confounding bias that is thought to affect observational studies of drugs, diets, screening procedures, and other health-related behaviors.[2–4] This bias presumes that patients who initiate and adhere to preventive therapies are more likely to engage in behaviors consistent with a healthy lifestyle than are patients who do not initiate or adhere to such treatments. Aspects of a healthy lifestyle could include diet, exercise, moderation of alcohol, and avoidance of risky behaviors. These characteristics, which are unmeasured in typical pharmacoepidemiological databases, may be associated with morbidity and mortality outcomes in observational studies. Thus, failure to adjust for them can lead to bias in studies of preventive therapies.

The healthy-user bias has been suggested as an explanation for the discrepancy between several experimental and observational studies, including studies of the effects of long-term use of estrogen therapy[5–8] and vitamin E.[9] It has also been discussed as a potential source of bias in observational studies of the effectiveness of influenza vaccines in the elderly[2] and the association between use of 3-hydroxy-3-methylglutaryl coenzyme A reduc-

Received September 24, 2008; accepted February 11, 2009.

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Guest Editor for this article was Veronique L. Roger, MD, MPH.

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.108.824151**

tase inhibitors (statins) and reduced risk of hip fracture,[10] Alzheimer disease,[11] sepsis,[12] cancer,[13] and mortality.[14] This bias has also been observed in randomized controlled trials in which adherence to placebo was found to be associated with decreased mortality.[15] Although long suspected as a source of bias, a paucity of empirical data exists on the healthy-user effect.

We sought evidence of the healthy-adherer bias in a diverse population of patients taking statins in the province of British Columbia, Canada, a multiethnic society with comprehensive databases for prescription drugs, medical services, and hospital admissions for most of its population of 4.3 million people. We hypothesized that patients who were adherent to statins would be at decreased risk of accidental events such as motor vehicle and workplace accidents, burns, falls, and other diseases because they were more actively concerned about their health and well-being than otherwise comparable nonadherent patients. Evidence of this bias across a broad number of outcomes was needed as compelling evidence because alternative hypotheses could be used to counter any single association.

Methods

Drug Coverage in British Columbia

All residents of British Columbia can enroll in the provincial drug plan. The drug plan includes an income-based deductible of up to 3% of income, a 25% or 30% coinsurance for prescription costs above the deductible, and an out-of-pocket ceiling of 4% of income, after which the province covers all eligible costs. Residents receiving social income assistance do not pay for prescription drugs, and any resident may hold supplemental drug insurance either privately or through his or her employer.

Data Sources and Study Population

Prescriptions for statins were obtained from the British Columbia PharmaNet database that included records of all prescriptions dispensed at community pharmacies regardless of drug plan enrollment status. Drugs dispensed in hospitals were not included in the database but should account for <1% of statin prescriptions. Underreporting and misclassification should be low because all community pharmacies used the PharmaNet system, which also performed data quality checks when the claims were transmitted. Prescriptions were linked by encrypted personal health numbers to Ministry of Health databases for physician services and hospitalizations. These databases included diagnostic codes (*International Classification of Diseases, Ninth Revision* [*ICD-9*] [physician services], *International Statistical Classification of Diseases, 10th Revision* [hospitalizations]), procedure codes, and dates of service activity. The universal aspect of the Canadian healthcare system means that all hospital admissions and most insured physician visits were captured.

The source population included all residents of British Columbia (3.9 million in 1997 and 4.3 million 2005) who were not residents of a nursing home. We identified patients from the PharmaNet database who used a statin between January 1, 1997, and March 31, 2004. The statins included in our analysis were atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. New statin patients were identified as those who did not receive a statin in at least the previous 365 days. We defined the first date of a statin prescription as the index date. Patients who started a statin during the study period, discontinued, and then started again more than a year later were only analyzed during their first episode of care.

Patients with a history of coronary events or diabetes mellitus, because of their traumatic experiences and greater risk of future coronary events, have more compelling reasons to adhere to treatment than patients whose only indication for treatment is an elevated blood lipid value. We sought to eliminate the role of these confounders in our study by restricting the cohort to primary prevention patients without a recorded history of diabetes mellitus. Therefore, we excluded patients who received a statin for secondary prevention or had diabetes mellitus (*ICD-9* 250). Secondary prevention patients were those who, during the 365 days before the index date, had a recorded diagnosis in a hospital admission or physician service record of myocardial infarction (*ICD-9* 410 or 412), angina pectoris (*ICD-9* 413), or ischemic heart disease (*ICD-9* 411 or 414); a recorded procedure of coronary artery bypass graft, angioplasty, stenting, intracoronary or systemic thrombolysis, or angiography; or a prescription for nitroglycerin. We also excluded nursing home residents, patients who were not eligible for medical services coverage according to the provincial patient eligibility registry, and patients who received cerivastatin.

Exposure Assessment

Adherence to therapy was ascertained in the 1-year baseline period after statin initiation. Patients dispensed a supply of >120 days of statin medication in that year were categorized as "more adherent." Patients dispensed a supply of ≤120 days of statin medication in the first year were categorized as "less adherent." The typical number of days of supply in a statin prescription was 60 days, and the provincial drug plan did not pay for >100 days of medication in a single prescription. Therefore, more adherent patients needed to receive at least 2 prescriptions to qualify for that category, but most patients in the more adherent category received ≥3 prescriptions.

Covariates

We obtained baseline demographics, health service use, and health status information from the British Columbia Ministry of Health eligibility file, Medical Services Plan database (physician visits), hospitalization database, and PharmaNet database during the year before the first statin prescription. Covariates were defined during the baseline period and included age, sex, number of days spent in the hospital, number of physician visits, and presence of various medical conditions as ascertained from inpatient and outpatient records.

Study Outcomes

We evaluated a spectrum of events after the 1-year baseline period to assess the healthy-adherer bias. The outcomes were grouped into 4 broad categories: accident events, screening events, other events not expected to be associated with statin exposure, and other events for which a possible association with statin exposure could be expected. We included inpatient and outpatient events as well as primary and secondary diagnoses. Myocardial infarction, the prevention of which is the main purpose of statin treatment, was included in the latter category to provide a relative reference for comparison. Events and corresponding diagnostic codes and procedure codes are listed in Table 1. We only studied the first occurrence of an event in outcomes that could recur.

Statistical Analysis

Patients became eligible for follow-up if they survived the 1-year baseline period, had at least 1 prescription and 1 physician visit in both the first 6 months and second 6 months of the baseline year, and did not enter a nursing facility during that period. Patients contributed person-time beginning at the end of the baseline period and were followed until the earliest of March 31, 2007, death, or, in each analysis, the occurrence of the event.

The relationship between statin adherence and each outcome was examined with the use of both unadjusted and multivariable-adjusted Cox proportional hazards models. The first Cox model made no statistical adjustments for any covariates. The second model was stratified on age (<40 years, ≥75 years, and 5-year age groups for ages ≥40 and <75 years) and sex and included the following covariates: number of drugs; physician visits; days in hospital during the baseline period; history during the baseline period of chronic obstructive pulmonary disease, peripheral vascular disease, liver disease, rheumatoid arthritis, osteoarthritis, atrial fibrillation, cancer; and Romano comorbidity score, which is meant to adjust for confounding by concomitant illnesses by assigning weights to a patient's *ICD-9* diagnoses and summing those weights into a single score.[16] All data analysis was performed in SAS version 9.1.3.

Table 1. Outcome Definitions

Outcome	Definition
Asthma/COPD hospitalization	DAD* *ICD-9* codes: 491, 492, 493, 496; entry code=emergency
Asthma/COPD outpatient visit	MSP† *ICD-9* codes: 491, 492, 493, 496
Bacterial infection	*ICD-9* codes: 041
Bone mineral density test‡	MSP fee item: 8688, 8689, 8696
Burns	*ICD-9* codes: 940–949
Deep vein thrombosis and pulmonary embolism	*ICD-9* codes: 453.40, 453.41, 451, 415.1
Dental problems	*ICD-9* codes: 521, 522, 523, 525
Diverticulitis	*ICD-9* codes: 562
Drug dependency	*ICD-9* codes: 304
Emergency department admission	DAD entry code=emergency
Eye examinations	MSP fee item: 2015
Falls	*ICD-9* codes: E88
Fecal occult blood test	MSP fee item: 9234, 15110, 36509
Food-borne bacterial infection	*ICD-9* codes: 003, 004, 005, 006, 007, 008, 009, 988
Fractures	*ICD-9* codes: 800-829
Gallstones	*ICD-9* codes: 574
Gastrointestinal bleed	*ICD-9* codes: 531, 532, 533, 534, 578
Gout	*ICD-9* codes: 274
Kidney stones	*ICD-9* codes: 592
Lung cancer	*ICD-9* codes:162
Malignant melanoma	*ICD-9* codes:172
Migraine	*ICD-9* codes: 346
Motor vehicle accidents	MSP claim type=Insurance Corporation of British Columbia
Myocardial infarction	DAD first 2 diagnosis codes: 410
Nonelective surgery	DAD admit category=urgent
Open wound	*ICD-9* codes: 870-897
Papanicolaou test‡	MSP fee item: 14560
Poisoning	*ICD-9* codes: 960–987, 989
Prostate-specific antigen test§	MSP fee item: 9234, 15110, 36509
Screening mammography‡	MSP fee item: 8611
Sigmoidoscopy	MSP fee item: 716
Skin infection	*ICD-9* codes: 681, 682
Sexually transmitted disease	*ICD-9* codes: 042, 054.1, 090–099
Workers Compensation Board claim	MSP claim type=W (WCB)

COPD indicates chronic obstructive pulmonary disease; WCB, Workers Compensation Board.

*Discharge Abstract Database (DAD) contains summary "abstract" information from every hospital discharge or day surgery case in British Columbia hospitals and hospitalizations of British Columbia residents in other Canadian provinces.

†The Medical Services Plan (MSP) insures medically required services provided by physicians and supplementary healthcare practitioners, laboratory services, and diagnostic procedures.

‡Restricted to female patients.

§Restricted to male patients.

Approvals

The study received ethics approval from the University of British Columbia (UBC CREB No. H02-70020). The British Columbia Ministry of Health approved data access.

Table 2. Characteristics Assessed During a 1-Year Baseline Period

Characteristics	More Adherent*	Less Adherent*	Difference
No.	114 612	26 474	
Age, y, mean (SD)	61.3 (11.6)	58.5 (12.7)	2.8
Female, % (n)	47.9 (54 901)	51 (13 502)	−3.1
Median No. of physician visits in prior year (IQR)	10 (6, 17)	11 (6, 20)	1.0
Median No. of different physicians in prior year (IQR)	4 (2, 6)	4 (2, 6)	0
Median No. of distinct medications in prior year (IQR)	4 (2, 6)	4 (2, 7)	0
Median No. of total hospitalizations within the previous 5 years (IQR)	0 (0, 2)	0 (0, 2)	0
Median Romano score (IQR)†	0 (0, 0)	0 (0, 0)	0
Acute care hospitalized, % (n)	8.7 (9925)	8.6 (2272)	0.1
History of COPD, % (n)	4.9 (5560)	6.5 (1727)	−1.6
History of atrial fibrillation, % (n)	1.2 (1333)	0.9 (229)	0.3
History of peripheral vascular disease, % (n)	2.8 (3156)	2.2 (581)	0.6
History of liver disease, % (n)	0.3 (303)	0.4 (107)	−0.1
History of cancer, % (n)	3.7 (4272)	3.4 (902)	0.3
History of rheumatoid arthritis, % (n)	1.4 (1625)	1.8 (474)	−0.4
History of osteoarthritis, % (n)	7.5 (8593)	8.5 (2242)	−1.0

IQR indicates interquartile range; COPD, chronic obstructive pulmonary disease.

*Patients dispensed >120 days of medication within 1 year of initiation on a statin were classified as more adherent. Patients dispensed ≤120 days of medication were classified as less adherent.

†The majority of Romano scores were zero because the cohort was composed of primary prevention patients.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

We identified 247 348 patients who initiated a statin other than cerivastatin during the study period. We omitted 30 742 patients who lost eligibility during the baseline period (365 days after starting a statin) through de-enrollment or lack of system use during the year, 1409 patients who were admitted to a nursing home before start of follow-up, 30 935 patients with evidence of existing coronary artery disease, 43 083 with diabetes mellitus, and 93 patients who were dispensed a supply of >300 days of statin medication in 1 prescription. We were left with a final cohort of 141 086 patients whose characteristics during the baseline period are given in Table 2. The cohort was 49% female and had an average age of 61 years. During the 12-month baseline period, cohort members used 5 medications on average, and 9% experienced an acute care hospitalization. In a small number of patients, we observed a history of cancer (4%), osteoarthritis (8%), liver disease (0.3%), and peripheral vascular disease (3%). Follow-up times after the 1-year baseline period varied for each patient and outcome studied. The average follow-up time for all outcomes was 4.9 years. The lowest average follow-up time was 3.3 years for prostate-specific

Table 3. Association Between Adherence to Statin Therapy and Risk of Health-Related Events

Outcome	More Adherent Event Rate, /100 Person-Years	Less Adherent Event Rate, /100 Person-Years	Unadjusted HR	95% Confidence Limits for HR	Adjusted HR	95% Confidence Limits for HR
Accident events						
Both sexes (n=141 086)						
Burn	0.28	0.36	0.78	(0.71–0.87)	0.88	(0.79–0.97)
Fall	0.53	0.54	0.98	(0.90–1.06)	0.90	(0.83–0.98)
Fracture	2.20	2.38	0.93	(0.89–0.96)	0.92	(0.88–0.96)
Motor vehicle accident	1.48	2.25	0.66	(0.63–0.69)	0.75	(0.72–0.79)
Open wound	2.44	2.74	0.89	(0.86–0.92)	0.91	(0.88–0.95)
Poisoning	0.32	0.41	0.78	(0.71–0.86)	0.86	(0.78–0.94)
Workplace accident	1.31	2.13	0.62	(0.59–0.65)	0.77	(0.74–0.81)
All (first occurrence)	7.38	9.39	0.79	(0.77–0.81)	0.85	(0.83–0.87)
Screening events						
Both sexes (n=141 086)						
Eye examination	3.58	2.93	1.21	(1.17–1.26)	1.08	(1.05–1.12)
Fecal occult blood test	8.06	6.14	1.31	(1.27–1.34)	1.21	(1.18–1.24)
Sigmoidoscopy	0.53	0.49	1.09	(1.00–1.18)	1.07	(0.98–1.16)
All (first occurrence)	12.01	9.28	1.28	(1.25–1.31)	1.17	(1.15–1.20)
Women (n=68 403)						
Bone mineral density test	6.74	5.96	1.13	(1.09–1.17)	1.10	(1.06–1.14)
Papanicolaou test	5.27	6.06	0.87	(0.84–0.91)	1.03	(0.99–1.07)
Screening mammography	3.35	3.32	1.01	(0.96–1.06)	1.05	(1.00–1.10)
All (first occurrence)	6.43	6.76	0.95	(0.93–0.98)	1.07	(1.04–1.10)
Men (n=72 683)						
Prostate-specific antigen test	15.63	12.91	1.20	(1.16–1.23)	1.07	(1.04–1.10)
Other events, possible association expected						
Both sexes (n=141 086)						
Emergency hospital admission	5.59	5.96	0.94	(0.91–0.96)	0.87	(0.85–0.89)
Lung cancer	0.39	0.38	1.04	(0.94–1.14)	0.92	(0.83–1.01)
Myocardial infarction	0.50	0.61	0.82	(0.75–0.88)	0.72	(0.67–0.78)
Nonelective surgery	6.45	6.70	0.96	(0.94–0.99)	0.90	(0.88–0.92)
All (first occurrence)	6.81	7.12	0.96	(0.94–0.99)	0.90	(0.87–0.92)
Other events, no association expected						
Both sexes (n=141 086)						
Asthma/COPD hospitalization	0.38	0.42	0.91	(0.83–0.99)	0.87	(0.79–0.95)
Asthma/COPD outpatient visit	3.29	4.02	0.82	(0.80–0.85)	0.87	(0.85–0.90)
Bacterial infection	0.43	0.46	0.93	(0.85–1.01)	0.91	(0.83–0.99)
Deep vein thrombosis or other clot	0.58	0.56	1.03	(0.95–1.11)	0.98	(0.91–1.07)
Dental problem	0.71	1.02	0.69	(0.65–0.74)	0.76	(0.72–0.81)
Diverticulitis	1.34	1.28	1.04	(0.99–1.10)	0.98	(0.93–1.03)
Drug dependency	0.17	0.29	0.59	(0.53–0.67)	0.73	(0.65–0.83)
Food-borne bacterial infection	1.77	2.18	0.81	(0.78–0.85)	0.85	(0.82–0.89)
Gallstone	0.63	0.78	0.81	(0.75–0.86)	0.81	(0.76–0.87)
Gastrointestinal bleed	1.71	1.86	0.92	(0.88–0.96)	0.90	(0.86–0.94)
Gout	1.35	1.44	0.94	(0.89–0.99)	0.89	(0.85–0.94)
Kidney stone	0.51	0.55	0.93	(0.85–1.00)	0.96	(0.89–1.04)
Malignant melanoma	0.19	0.14	1.35	(1.16–1.58)	1.23	(1.05–1.43)

(*Continued*)

Table 3. Continued

Outcome	More Adherent Event Rate, /100 Person-Years	Less Adherent Event Rate, /100 Person-Years	Unadjusted HR	95% Confidence Limits for HR	Adjusted HR	95% Confidence Limits for HR
Migraine	0.81	1.20	0.67	(0.63–0.71)	0.82	(0.78–0.87)
Sexually transmitted disease	0.13	0.16	0.82	(0.71–0.95)	0.93	(0.80–1.09)
Skin infection	3.08	3.41	0.90	(0.87–0.93)	0.93	(0.90–0.96)
All (first occurrence)	14.58	17.47	0.85	(0.83–0.86)	0.87	(0.86–0.89)

COPD indicates chronic obstructive pulmonary disease. The analysis is stratified on age and sex. Multivariable adjustments are made for all the other covariates given in Table 2. Subjects were censored by end of follow-up and death.

antigen tests in men, and the largest was 5.2 years for sexually transmitted diseases (both sexes).

The results of our Cox proportional hazards regressions are summarized in Table 3. In the full model, stratifying on age and gender and adjusting for comorbid conditions, we found that patients defined as more adherent to statins were less likely than less adherent statin patients to have accidents in all of the types that we measured: burns (hazard ratio [HR]=0.88; 95% confidence interval [CI], 0.79 to 0.97), falls (HR=0.90; 95% CI, 0.83 to 0.98), fractures (HR=0.92; 95% CI, 0.88 to 0.96), motor vehicle accidents (HR=0.75; 95% CI, 0.72 to 0.79), open wounds (HR=0.91, 95% CI, 0.88 to 0.95), poisoning (HR=0.86; 95% CI, 0.78 to 0.94), and workplace accidents (HR=0.77; 95% CI, 0.74 to 0.81).

In our adjusted Cox models, patients in the more adherent category were more like to receive eye examinations (HR=1.08; 95% CI, 1.05 to 1.12), fecal occult blood testing (HR=1.21; 95% CI, 1.18 to 1.24), bone mineral density testing (HR=1.10; 95% CI, 1.06 to 1.14), and prostate-specific antigen testing (HR=1.07; 95% CI, 1.04 to 1.10) during the subsequent follow-up period. No association or only borderline association was found between statin adherence and undergoing mammography (HR=1.05; 95% CI, 1.00 to 1.10), Papanicolaou test (HR=1.03; 95% CI, 0.99 to 1.07), or sigmoidoscopy (HR=1.07; 95% CI, 0.98 to 1.16).

Among the other events we analyzed, 15 of 20 showed a statistically significant (type I α=0.05) association with statin adherence in our multivariable Cox model. All 5 of the remaining events had nonsignificant point estimates $<$1.0. Of the 15 associations that were significant, 14 showed a reduced risk of the event in more adherent patients (Table 3). The exception was an increased association with malignant melanoma (HR=1.23; 95% CI, 1.05 to 1.43).

Discussion

In a cohort of new statin patients in British Columbia, we found that patients who were more adherent to therapy during a 1-year baseline period during which adherence was ascertained were significantly less likely to be involved in motor vehicle and workplace accidents requiring medical attention than less adherent patients. Adherent patients were also less likely to experience a variety of negative health outcomes unlikely to have been related to a therapeutic effect of statins. Our results are consistent with the hypothesis that patients who are more adherent to drug treatment take better care of themselves by engaging in various behaviors aimed at improving or maintaining health. Some examples of such health-related behaviors include better nutrition, regular exercise, seat belt use, improved dental hygiene, less smoking, and moderation of alcohol consumption.

We analyzed 14 types of accident and screening events and found significant differences in event rates between more adherent and less adherent patients for all events except sigmoidoscopy, Papanicolaou tests, and mammography. However, all the accident and screening events, statistically significant and otherwise, were in directions that would be predicted under a heathy-adherer bias (a decrease for accidents and an increase for screening). The screening results are consistent with associations between adherence and use of preventive services discovered in a frail elderly American population.[3] Increased relative use of fecal occult blood tests and bone mineral density tests was similar in British Columbia and in the elderly Medicaid patients in Pennsylvania. Greater use of mammography and prostate-specific antigen tests in Pennsylvania could be attributable to the older age of that cohort. In the present study, we observe the healthy adherence phenomenon in a much broader and more representative population, and, additionally, we found that patients more adherent to statins were less likely to experience all of the adverse clinical outcomes we evaluated, with the exception of malignant melanoma. The increase in malignant melanoma was possibly due to screening bias (ie, more health-seeking patients being more likely to visit a dermatologist and have a skin lesion biopsied).

An apparent reduction in myocardial infarction in more adherent patients may have been due to a drug effect[17–21] in addition to the adherer bias, but the magnitude of the relative effect (relative risk, 0.72) is not appreciably different than the reduction in motor vehicle accidents (relative risk, 0.75) and workplace accidents (HR, 0.77), for which a drug effect is unlikely. Relative reductions in emergency hospital admissions and nonelective surgeries could also have been partially due to a drug effect.

We speculate that the observed association between adherence and accident events, screening tests, and the negative health outcomes we studied is due to unmeasured confounding by health-seeking behaviors of healthier patients. However, other explanations are possible for these findings. Our definition of adherence could not be validated because of privacy constraints. Bias resulting from the definition and its ascertainment would come from patients who were classified as nonadherent but became adherent during follow-up or adherent patients who became nonadherent. In both cases, this misclassification would bias our estimate toward the null. Observational studies have attributed a protective effect of statins on cognitive functioning.[22–30] If true, statin adherence

could decrease the risk of accidents by improving cognition, but the magnitude of our effect estimates for accidents, especially in workplace accidents (younger patients), lacks plausibility as a drug effect. Other observed associations could be due to confounding by factors other than unmeasured health-related behaviors. For example, the association between statin adherence and reduced risk of fracture could be due to body mass index, a variable unavailable in our database. Heavier patients may have a greater clinical need for a statin yet are at decreased risk for osteoporosis and therefore less likely to experience a fracture. We also did not have reliable income data or information on whether a patient paid out-of-pocket or with private insurance. Income might be a relevant predictor of adherence and disease risk. However, most screening services are available free of charge to all residents in the province's universal system, and our results showing significant increased use of those services in adherent patients provide reassurance that our findings were not the result of an income effect. Although the association between adherence and any individual outcome could be plausibly attributed to a variety of different effects, the results as a whole are consistent with the healthy-adherer hypothesis, as well as a recent and large cohort study of 129 000 statin initiators and 600 000 controls that found little evidence to support wide-ranging effects of statins on nonvascular outcomes.[24] The principle of Occam's razor leads us to prefer the most parsimonious explanation, which is that the associations reported in this study are largely due to unmeasured healthy behaviors that are correlated with both adherence and the outcomes.

Our study contributes new evidence of a heathy-adherer association between statin treatment and numerous other health outcomes and accidental events that are not known to be a pharmacological effect of statin treatment. These data provide a compelling reason to expect that the heathy-adherer effect may be a confounder in studies of statins and health outcomes. Patients who are adherent to 1 medication are probably more likely to adhere to others, and our results could extend to other long-term preventive medications and health-related behaviors in general. Furthermore, the direction of heathy-user bias can be anticipated. When the effect is inversely associated with the outcome, the apparent HR will be less than the true estimate. When it is positively associated with an outcome, the apparent HR will be greater than the true estimate. Therefore, a heathy-adherer effect that is unaccounted for in the design or analysis of a study will make null effects appear protective, exaggerate protective effects, and attenuate harmful effects or even make them appear protective.

Our study proposes the idea that the heathy-adherer effect might be detectable by examining the association between adherence to treatment and the downstream occurrence of events that should not be affected by the treatment. The British Columbia databases included medical encounters related to motor vehicle and workplace accidents. Databases in other jurisdictions may not contain those data but should contain data for other accidents such as burns, falls, fractures, and open wounds. Data for screening procedures should also be ubiquitous in administrative databases. Further work in the area is clearly needed to gain a better understanding of the heathy-adherer effect and to develop methods to adjust for it in observational studies. Choices in study design and analytical methods could potentially be used to control for the bias. Some possibilities are a new user design that uses an active comparator, controlling for past adherence to treatments, and instrumental variable analysis. Until this phenomenon is better understood, however, the results from our research suggest that caution is warranted when interpreting any observational analyses that report moderate protective effects to preventive medications, preventive screening, or other "healthy" behaviors known to be associated with adherence.

Sources of Funding

The study was partly funded by a contribution from the British Columbia Ministry of Health Services. Dr Brookhart was partly supported by a career development award from the National Institutes of Health (AG-027400), and Dr Glynn was partly supported by a National Institutes of Health grant (AG-018833).

Disclosures

Dr Dormuth has been employed by and has received consultant's fees from the British Columbia Ministry of Health. Dr Brookhart has received research support from Amgen Inc for unrelated work. Dr Shrank has received funds from the National Heart, Lung, and Blood Institute and CVS Caremarch to study medication adherence. Dr Glynn has received past grant support from AstraZeneca and Bristol-Myers Squibb. The remaining authors report no conflicts.

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CLINICAL PERSPECTIVE

Clinicians need to read observational studies reporting surprising benefits of drug therapy with a healthy skepticism. Observational studies of preventive medications and health behaviors are susceptible to various sources of bias including the so-called healthy-user and healthy-adherer biases. In this article, evidence of the healthy-adherer effect is demonstrated by showing that adherence to statins is associated with a reduction in the risk of accidents (eg, workplace or motor vehicle), outcomes that would not be expected to be affected by a statin. The approximate magnitude of the adherer effect was a 15% relative risk reduction. The most likely explanation for this association is that good adherence to statin therapy is a marker for other healthy behaviors, most of which cannot be accounted for in this type of study. In keeping with this explanation, the study also shows that adherence predicts a 7% to 17% increased incidence of medical screening procedures (eg, fecal occult blood testing, mammography). Risk of myocardial infarction, which has been demonstrated to be reduced by statin therapy in randomized placebo-controlled trials, was found in this study to be reduced by 28%. This observed relative reduction must be interpreted as reflecting a combination of the healthy-adherer effect and the drug effect. Clinicians can also learn from this study that patients who follow their advice are also likely to have other healthy behaviors and a lower risk of adverse events.