ORIGINAL ARTICLE

Statin treatment is associated with a decreased risk of active tuberculosis: an analysis of a nationally representative cohort

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ABSTRACT

Background Epidemiological data suggest that statins improve the clinical outcome of respiratory infections. We sought to examine whether statin therapy decreases the risk of active TB.

Methods We conducted a nested case-control study on data obtained from a national health insurance claims database between 1999 and 2011. The use of statins was classified as current, recent, past or chronic use. Three conditional logistic regression models were used to estimate the incidence rate ratios (RRs). The first assessed the effect of statin use without further adjustment; the second adjusted (individually) for 75 potential confounders; and the third adjusted for the Disease Risk Score (DRS).

Results A total of 8098 new TB cases and 809 800 control patients were examined. All four types of statin users showed a decreased risk of active TB. Chronic use (>90 days in a calendar year) of statins was associated with the lowest unadjusted risk of TB (RR 0.74; 95% CI 0.63 to 0.87). The protective effect of active TB remained after adjusting for individual confounders (RR 0.66; 95% CI 0.56 to 0.78) and after DRS adjustment (RR 0.62; 95% CI 0.53 to 0.72). The effect estimates obtained for chronic and current use of statins were very similar. We also found that the active TB protection increased with increasing length of statin prescription.

Conclusions We found that statin therapy was associated with a decreased risk of active TB, and the length of statin therapy affected the TB protection. Given the observational nature of this study, the protective effect against active TB must be confirmed in future randomised trials.

Key messages

What is the key question?
- Whether statin therapy is associated with a decreased risk of active TB.

What is the bottom line?
- The use of statins was associated with a protective effect against active TB, and the decrease in TB risk was affected by the length of statin therapy.

Why read on?
- TB is a critical public health threat around the world, and statins may help to decrease the risk of active TB.

INTRODUCTION

Statins (3-hydroxy-3-methylglutaryl-coenzyme-A inhibitors) are a widely used class of medication for the primary and secondary prevention of cardiovascular diseases.[1] Statins reduce the serum levels of low-density lipoprotein cholesterol by inhibiting cholesterol synthesis in the liver.[2] In addition to modifying lipid metabolism, statins exhibit pleiotropic effects on the immune and coagulation systems.[3–7] Basic research has shown that statins could reduce the production of proinflammatory cytokines, lower platelet aggregability, prevent coagulation, and reduce injury caused by oxidative stress.[6 8 9] Because local and systemic inflammation play critical roles in human infectious disease, several meta-analyses have found that the use of statins could improve clinical outcome in patients with severe infections such as sepsis and pneumonia.[10–13]

Of all infectious diseases, TB remains one of the most important public health threats in the world. Each year, approximately nine million people develop new TB diseases. WHO aims to eradicate TB by 2050, but at the current rate of infection, this goal is unattainable. Thus, our goal is to evaluate whether statin therapy can prevent the active onset of TB.

Several in vitro studies have shown that host cholesterol is one of the most important factors during *Mycobacterium tuberculosis* infection.[14–19] It is therefore of interest to determine whether the use of statins—inhibitors of cholesterol biosynthesis—is associated with a decreased risk of contracting TB. We therefore carried out a population-based study to examine the relationship between the use of statins and the risk of active TB.

METHODS

Study population

Taiwan's National Health Insurance is a government-run single-payer compulsory system that enrols approximately 24 million residents with 99.6% coverage. All NHI participants receive the same access to healthcare services regardless of income. Using the claims database established by

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the National Health Insurance Research Database (NHIRD) of Taiwan, we conducted a population-based nested case–control study. The NHIRD consists of 1 million subjects who were randomly sampled from the 24 million individuals enrolled in Taiwan's National Health Insurance. Complete outpatient and inpatient electronic claim records, individual diagnoses, surgical procedures and prescribed medications are available in the NHIRD database. Several studies have shown that the NHIRD is appropriate for pharmacoepidemiologic investigations.[20–22] Our study was approved by the institutional review board of the National Taiwan University Hospital.

Study cohort

The study cohort consisted of all patients from the NHIRD who were followed longitudinally between January 1999 and December 2011. All patients aged 18 years or older on 1 January 1999 were eligible for inclusion in this study. We designated 1999 as a pre-enrolment period for the assessment of drug exposure status for cases and controls occurring in 2000. Thus, cohort members were followed from 1 January 2000 until the onset of these four occurrences, whichever of the following occurred first: active TB diagnosis, termination of health insurance coverage, death or the end of the study.

Selection of cases and controls

We identified newly diagnosed active TB cases using the following criteria: at least one outpatient visit or one hospital admission with ICD-9-CM codes for TB (010–018, including all subcategories), plus the prescription of more than two anti-TB medications for more than 28 days. Patients with a subsequent diagnosis of non-TB mycobacterial infection or lung cancer were excluded. This TB case definition has been used in previous studies and was validated in a linked survey database.[21 23] The index date referred to the first date of TB diagnosis. The 1-year period preceding the index date was used for the assessment of statin exposure status. For each case, 100 controls were randomly selected using the incidence density sampling method and were matched by index date, 5-year age group and sex.

Medication exposure

Users with exposure to medications of interest were defined as having a drug prescription record ≥7 days. Statins were defined as drugs containing any of the following compounds: simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, rosuvastatin and pitavastatin. Exposure was defined using four different time frames. Current user status referred to patients with a statin prescription that was filled within 30 days of the index date. Recent user status referred to patients with a statin prescription filled between 31 and 90 days prior to the index date. Past user status referred to patients with a statin prescription filled between 91 days and 1 year prior to the index date. Chronic use status referred to patients with a cumulative prescription length of more than 90 days in the year in which the TB diagnosis was made.

Statistical analysis

The baseline characteristics of the enrolees were described and compared among TB cases and controls (table 1). Categorical variables (type of statin user, sex, index year, area of stay, insurance premiums, baseline cardiovascular comorbidities, conditions included in the Charlson index, additional comorbidities, risk factors and medication use) were presented as a frequency and percentage and were compared between cases and controls using the χ^2 test. Continuous variables were presented as the mean±SD or as the median and IQR, depending on the normality of the variable distribution. Outpatient department (OPD) visits and hospitalisation were described using medians and IQRs due to non-normality and were compared between cases and controls using the Mann–Whitney U test. Age was described using means and SDs and was compared between cases and controls using the t test.

Under a time-matched case-control sampling scheme, the OR estimates the rate ratio. The incidence rate ratios (RRs) of active TB (plus 95% CIs) were estimated by three conditional logistic regressions using the Proc logistic plus Strata command. The first assessed the effect of statin use without further adjustment; the second adjusted (individually) for 75 potential confounders (see online supplementary appendix 1); and the third adjusted for the Disease Risk Score (DRS). For all the conditional logistic regressions, a stratum was created for each case and his/her specific controls, comprising a total of 8098 strata. Each stratum was defined by three variables: index date, 5-year age group and gender. Thus, three matching variables (year of TB diagnosis, age and gender) were not entered in any of the regression models.

A study-specific DRS was created using the all adults in the source population using the approach initially proposed by Miettinen.[24–27] The DRS was defined as the probability of developing active TB among all adult participants not exposed to statins, conditional on each individual's baseline covariates. Operationally, we calculated the DRS by a logistic regression model wherein active TB was used as the dependent variable and all empirical clinical predictors were treated as independent variables. In online supplementary appendix 1, we report the c-statistics of the DRS model, component variables, the respective weights of the component variables, and the same set of covariates used in the individual confounder and the DRS model. Briefly, the covariates are: cardiovascular comorbidities, risk factors for TB, the burden of comorbid conditions, indicators for frailty, and the use of specific medications. Risk factors for TB include COPD; silicosis; cancer; diabetes mellitus; chronic renal failure; solid organ transplantation; malnutrition-related disorders such as cachexia, anorexia, and abnormal loss of weight; alcoholism-related diseases; and post-gastric surgery. The groups of medications included were systemic corticosteroids, non-steroidal anti-inflammatory drugs, aspirin, and systemic immunosuppressive agents and biological drugs.

To further assess the robustness of our results, we performed subgroup analyses. Predefined subgroups included area of stay, insurance premium, the presence of cardiovascular diseases, the presence of diabetes and the presence of obesity. In addition, we performed duration response analyses by testing the linear association between drug use duration and the risk of active TB. All analyses were carried out using SAS V.9.3 for Windows (SAS Institute Inc, Cary, North Carolina, USA), and the data are reported in accordance with STROBE guidelines.

RESULTS

Participant enrolment and baseline characteristics

Table 1 summarises the baseline clinical characteristics of 8098 active TB cases and 809 800 controls. The mean duration of follow-up for the cases and controls was 9.8 years. The distributions of living region and insurance premiums were significantly different between the TB cases and the control group. In general, the patients with TB exhibited a higher burden of comorbidity, a higher prevalence for TB risk factors, more OPD visits, and a greater use of cardiovascular medicine than the control group.

Table 1 The baseline characteristics of 8098 active TB cases and 809 800 controls

	Case group N=8098	Control group N=809 800	p Value
Demographics			
Male; n (%)	5573 (68.8)	557 300 (68.8)	1.000
Age, years; mean±SD	60.3±19.3	60.2±19.2	0.741
Site; n (%)			<0.0001
Area: urban region	3529 (43.6)	375 847 (46.4)	
Area: metro area	2047 (25.3)	204 415 (25.2)	
Area: suburban area	1621 (20.0)	155 078 (19.2)	
Area: countryside area	901 (11.1)	67 010 (8.3)	
Insurance premiums; n (%)			<0.0001
Dependent	712 (8.8)	75 058 (9.3)	
$1–$19 999	2918 (36.0)	239 135 (29.5)	
$20 000–$39 999	3400 (42.0)	329 046 (40.6)	
≥$40 000	1068 (13.2)	159 110 (19.6)	
Conditions included in the Charlson index; n (%)			
Peripheral vascular disease	496 (6.1)	44 277 (5.5)	0.040
Congestive heart failure	957 (11.8)	68 749 (8.5)	<0.0001
Myocardial infarction/acute coronary syndromes	245 (3.0)	18 847 (2.3)	<0.0001
Cerebrovascular disease	1582 (19.5)	128 220 (15.8)	<0.0001
Dementia	441 (5.5)	27 636 (3.4)	<0.0001
Chronic pulmonary disease	3601 (44.5)	254 492 (31.4)	<0.0001
Rheumatologic disease	262 (3.2)	19 101 (2.3)	<0.0001
Peptic ulcer disease	2977 (36.8)	246 737 (30.4)	<0.0001
Mild liver disease	2358 (29.1)	190 530 (23.5)	<0.0001
Diabetes without chronic complications	1868 (23.1)	136 206 (16.8)	<0.0001
Diabetes with chronic complications	707 (8.7)	42 452 (5.2)	<0.0001
Hemiplegia or paraplegia	386 (4.8)	27 248 (3.4)	<0.0001
Renal disease	834 (10.3)	53 708 (6.6)	<0.0001
Any malignancy, including leukaemia and lymphoma	878 (10.8)	59 997 (7.4)	<0.0001
Moderate or severe liver disease	90 (1.1)	3554 (0.4)	<0.0001
Metastatic solid tumour	121 (1.5)	6392 (0.8)	<0.0001
AIDS/HIV	17 (0.2)	397 (0.04)	<0.0001
Additional comorbidities; n (%)			
Alcohol/drug use	399 (4.9)	16 622 (2.1)	<0.0001
Psychiatric disorder	2299 (28.4)	201 356 (24.9)	<0.0001
Neurologic disorder	592 (7.3)	36 877 (4.6)	<0.0001
Obesity	26 (0.3)	5276 (0.7)	<0.0001
Cancers except metastatic solid tumours	2205 (27.2)	189 124 (23.4)	<0.0001
COPD	2780 (34.3)	182 130 (22.5)	<0.0001
Silicosis	15 (0.2)	860 (0.1)	0.010
Gastrointestinal or oesophageal haemorrhage	653 (8.1)	37 338 (4.6)	<0.0001
Risk factors; n (%)			
Solid organ transplantation, such as kidney or heart	7 (0.09)	134 (0.01)	<0.0001
Malnutrition	98 (1.2)	3062 (0.4)	<0.0001
Post-gastric surgery	5 (0.06)	130 (0.01)	<0.0001
OPD and hospitalisation (within 1 year before the index date); median and inter-quartile range			
The number of OPD visits	20 (8–37)	15 (5–29)	<0.0001
The number of emergency department visits	0 (0–0)	0 (0–0)	<0.0001
The number of hospitalisations	0 (0–0)	0 (0–0)	<0.0001
Medication use; n (%)			
Non-steroidal anti-inflammatory drugs	3076 (37.9)	247 727 (30.6)	<0.0001
Aspirin	1271 (15.7)	112 824 (13.9)	<0.0001
Systemic immunosuppressive agents and biologics	49 (0.6)	1413 (0.2)	<0.0001
Systemic corticosteroids	1520 (18.8)	92 717 (11.4)	<0.0001
Disease-modifying anti-rheumatic drugs	162 (2.0)	7475 (0.9)	<0.0001
Angiotensin-converting enzyme inhibitor	858 (10.6)	77 402 (9.6)	0.020
β blockers	926 (11.4)	93 141 (11.5)	0.440
Angiotensin II antagonists	608 (7.5)	62 186 (7.7)	0.249
Nitrates	486 (6.0)	41 115 (5.1)	<0.0001

Continued

Table 1 Continued

	Case group N=8098	Control group N=809 800	p Value
Proton-pump inhibitors	399 (4.9)	25 526 (3.2)	<0.0001
Calcium channel blocker	1678 (20.7)	163 917 (20.2)	0.285
Acetaminophen	3361 (41.5)	263 214 (32.5)	<0.0001

OPD, outpatient department.

Association between use of statins and the risk of TB

Table 2 shows the association between statin use and active TB. The statin usage rate is highest for chronic users and lowest for recent users; it is comparable among recent and past users. All four types of statin users (current, recent, past or chronic use) showed a decreased risk of active TB. The chronic use of statins was associated with the lowest unadjusted risk of TB (RR 0.74; 95% CI 0.63 to 0.87), and the decrease in TB risk remained after adjusting for individual confounders (RR 0.66; 95% CI 0.56 to 0.78) and after DRS adjustment (RR 0.62; 95% CI 0.53 to 0.72). We observed that all the different effect estimates obtained for the chronic and current use of statins are very similar.

Effect of chronic statin use on active TB risk in different patient populations

To investigate whether there is a differential risk among different populations, we performed analyses of pre-defined subgroups (table 3). The DRS-adjusted effect estimates were obtained by comparing pre-defined statin chronic users with non-users. We found that all different subgroups exhibited a decreased risk of active TB, and the countryside subgroup had the highest risk of active TB (RR 0.85; 95% CI 0.57 to 1.29). However, the interaction term did not reach statistical significance (p value <0.05) for any of the subgroups.

Duration-response analysis

To gain insight into whether increasing the length of statin therapy might affect the risk of TB, we carried out a duration response analysis. We used 7–30 days of statin usage as a reference (table 4), and found that the crude TB incidence rate and the DRS-adjusted incidence rate ratio decrease with increasing duration of statin usage. The incremental change in the risk of incidence active TB was also calculated by treating cumulative days of statin use as a continuous variable. We found that for every additional day of statin use, there was a 0.002% decrease in the risk of active TB (p<0.010).

DISCUSSION

In this population-based study, we found that the use of statins was significantly associated with a decreased risk of active TB in a nationally representative cohort. There was a consistent and protective effect against TB of statins among current, recent, past and chronic users. The effect estimates obtained for the chronic and current use of statins were very similar. We also found that the risk of active TB decreases with increasing length of statin prescription. None of the subgroups investigated appeared to modify the effect of statins on active TB.

To the best of our knowledge, this is the second study to investigate an association between the use of statins and the risk of active TB. However, there are significant differences in the study design and results between our study and Kang *et al*'s study conducted in South Korea. In that study, it was found that the use of statins in patients with diabetes did not affect the risk of active TB (adjusted HR 0.98; 95% CI 0.89 to 1.07).[28] We believe that this finding cannot be applied to the general population because diabetes is associated with a threefold higher risk of TB, as determined by a meta-analysis.[29] In line with their findings, our subgroup analyses also show that patients with diabetes have a higher risk of TB compared with patients without diabetes. Second, we observed that the protective effects of statins are mainly observed in current or chronic users but not in past users. Unfortunately, the different types of statin users were combined in Kang *et al*'s work.[28] Thus, the protective effect of statins might have been overlooked.

Our duration response and trend analysis suggested that increasing the length of statin use could increase the TB protective effect. We therefore investigated whether the recency of statin use had an effect in chronic users. We found that the current user group contained 30% more chronic users than the combination of recent and past users (see online supplementary appendix 2). We speculate that this might explain why current users exhibit a better protective effect than recent or past users.

Our study design does not permit mechanistic insights of the protective effects on active TB infection. However, our results are in agreement with reports that statins improve the clinical outcome of sepsis or community-acquired pneumonia.[12 13 30] Thus, based on basic research and the known protective effect of statins in other infectious diseases, we can speculate as to the non-exclusive biological mechanisms by which statins might prevent the active onset of TB.

Table 2 Unadjusted and adjusted effect measures for the association between statin use and the risk of active TB

Status of statin use	Statin usage rates for all the TB cases	Statin usage rates for all the controls	Effect estimates matched by age group, gender and year, RR (95% CI)	Confounder-adjusted effect estimates**, RR (95% CI)	DRS, adjusted RR (95% CI)
Current use	134/8098=0.016	17 836/809 800=0.022	0.76 (0.64 to 0.90)**	0.67 (0.56 to 0.80)***	0.64 (0.54 to 0.76)***
Recent use	52/8098=0.006	5812/809 800=0.007	0.87 (0.69 to 1.09)	0.87 (0.66 to 1.15)	0.78 (0.59 to 1.03)
Past use	148/8098=0.018	16 996/809 800=0.021	0.86 (0.72 to 1.03)	0.76 (0.64 to 0.90)**	0.72 (0.61 to 0.85)***
Chronic user	160/8098=0.020	22 153/809 800=0.027	0.74 (0.63 to 0.87)***	0.66 (0.56 to 0.78)***	0.62 (0.53 to 0.72)***

The reference group in the calculation of RR is participants who did not use statins.
**p<0.01; ***p<0.001.
DRS, Disease Risk Score; RR, incidence rate ratio.

Table 3 Effects of statins on the risk of TB

TB	Patient subgroups	DRS, adjusted RR (95% confidence interval)	Interaction p value
Chronic statin user vs non-user	Urban area	0.64 (0.51 to 0.81)	0.230
	Countryside area	0.85 (0.57 to 1.29)	
	≥$40 000, New Taiwan dollars	0.55 (0.34 to 0.90)	0.721
	$1–$19 999, New Taiwan dollars	0.63 (0.49 to 0.82)	
	With heart failure	0.67 (0.50 to 0.89)	0.514
	Without heart failure	0.59 (0.49 to 0.71)	
	With cerebrovascular disease	0.61 (0.48 to 0.77)	0.852
	Without cerebrovascular disease	0.62 (0.50 to 0.77)	
	With myocardial infarction	0.69 (0.45 to 1.06)	0.576
	Without myocardial infarction	0.60 (0.51 to 0.72)	
	With diabetes (with chronic complication)	0.70 (0.54 to 0.91)	0.118
	Without diabetes (with chronic complication)	0.54 (0.44 to 0.66)	

DRS, Disease Risk Score; RR, incidence rate ratio.

The first hypothesis is that statin prevents reinfection in a subgroup of patients exposed to *M. tuberculosis*. In vitro studies have demonstrated that cholesterol plays a critical role in the pathogenesis of *M. tuberculosis* infections in several ways, including the entry of *M. tuberculosis* into host macrophages,[14 31 32] phagosome formation,[15 32 33] the arrest of phagosomal maturation in *M. tuberculosis*-containing phagosomes,[16 19] and the energy utilisation of intracellular *M. tuberculosis*.[17 18] Statins can prevent TB infection by reducing macrophage cholesterol[34 35] and phagocytosis.[36] Statin can also reduce cholesterol levels within phagosomal membranes and counteract the *M. tuberculosis*-induced inhibition of phagosomal maturation to promote host-induced autophagy in human macrophages and experimental mouse models.[19] Thus, statins might exert a protective effect against TB infection.

The second hypothesis is that the use of statins can modulate the hosts' inflammatory response, thereby resulting in reduced reactivation of latent TB. The use of statins has been found to modulate levels of T cells and cytokines during sepsis infection.[37 38] T cells and cytokines are also critical for controlling latent TB.[39] The optimal level of immune cell activation for preventing the reactivation of latent TB is unclear, but there is evidence[40–42] that patients with renal failure have a cytokine imbalance, and up to 10-fold increased risk of active TB. Thus, it is reasonable to hypothesise that the use of statins can result in a decrease in the risk of TB reactivation by altering patients' immune function.

This study has strengths and weaknesses. The large number of TB cases is a main strength of this study. TB remains endemic in Taiwan, where its incidence is approximately 65–70 cases per 100 000 people per year.[43] In contrast, the incidence of TB is approximately 5–10/100 000 in most western countries.[44] Thus, the large number of active TB cases lends better statistical power to our analysis of different exposure categories, subgroups and covariate adjustments.

Nevertheless, several inherent limitations must be considered. First, as with all claims databases, the data describing lifestyle factors such as body mass index and smoking are not available. Thus, residual confounding variables cannot be totally excluded. However, we attempted to adjust for these missing confounding factors by including obesity and smoking-related disorders such as a diagnosis of morbid obesity, hyperlipidaemia, hypertension, ischaemic heart disease and COPD. Second, we defined active TB by ICD-9 codes and a compatible anti-TB prescription history. Although this TB definition has been found to be highly accurate using linked survey data, we cannot exclude the possibility of outcome misclassification for active TB[21 23]; as with all claims databases, microbiological data are lacking. Third, a screening or surveillance bias is a possible concern in our study because users of statins were reported to have more frequent contact with physicians.[45] To reduce this bias, we adjusted for the intensity of healthcare facility utilisation, such as the annual number of outpatient or emergency department visits as well as the annual frequency of hospitalisation. Finally, our study population precludes testing any possible interaction between intravesical BCG therapy and statin use. A previous study[46] showed that statins might affect the treatment response of BCG therapy for patients with bladder cancer via immunomodulatory interactions between statins and BCG. It would have been interesting to compare the risk of active TB among BCG-vaccinated and non-BCG-vaccinated statin users, however there is a compulsory neonatal BCG vaccination in Taiwan, thus we could not test this.

In conclusion, if we assume that the protective effects observed in the present study were caused by chronic statin use, the number needed to treat to prevent one active TB case was 2563–3479 (see online supplementary appendix 3). We also found that the TB protective effect is consistent among different types of statin users and different patient subgroups. However, given the observational nature of this study, further randomised trials are necessary to confirm our findings.

Table 4 Duration response analysis

Use of statin	Trend in the p value (frequency classified as >90 days, 31–90 days, and 7–30 days and <7 days)		
	IR% (case/person-years)	DRS, adjusted RR (95% CI)	Trend p value
7–30 days (reference)	0.98% (78/7955)	Reference	<0.0001
31–90 days	0.87% (101/11 594)	0.90 (0.66 to 1.21)	
>90 days	0.72% (155/21 445)	0.73 (0.56 to 0.96)	

DRS, Disease Risk Score; IR, incidence rate; RR, incidence rate ratio.

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Contributors C-CL obtained funding, analysed the data, and wrote the first and final draft. MGL analysed the data, and wrote the final draft. S-HL, W-TH and S-SC conducted statistical analysis. S-CC analysed the data, and provided critical feedback. C-CL designed the study, obtained funding, analysed the data and authorised the final manuscript.

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Competing interests None declared.

Ethics approval This study was approved by the institutional review board of National Taiwan University Hospital.

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