The Impact of Statin Dose, Class, and Intensity on Sepsis Mortality in Type 2 Diabetes Patients

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Research Article

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Abstract

Aims: The study aims to investigate the impact of statin use on sepsis mortality in patients with type 2 diabetes (T2DM) in a dose-, class-, and use intensity-dependent manner.

Methods: A retrospective cohort of 850,326 T2DM patients was analyzed using an inverse probability treatment-weighted Cox hazard model, with statin use status as a time-dependent variable.

Results: Results showed that statin use was associated with a significant reduction in sepsis mortality risk (aHR=0.29) compared to non-users. Pitavastatin, rosuvastatin, pravastatin, atorvastatin, simvastatin, fluvastatin, and lovastatin were all associated with a lower sepsis mortality risk. Higher cumulative defined daily dose per year of statins was also associated with a lower sepsis mortality, with an optimal daily dose of 0.86 defined daily doses.

Conclusion: These findings suggest that statin use may reduce sepsis mortality in T2DM patients and that higher doses are associated with greater protection.

Research in context

There is evidence suggesting that statins may have protective effects against sepsis, but the relationship between statin use and sepsis mortality in patients with type 2 diabetes mellitus (T2DM) is not well understood. Previous studies have focused on the relationship between statin use and sepsis incidence or the effect of statin therapy on sepsis outcomes in specific populations or settings, but have not specifically examined the relationship between different doses, classes, and intensities of statin use and sepsis mortality in patients with T2DM.

Evidence before this study:

Several studies have demonstrated that statin therapy may have protective effects against sepsis. For example, a systematic review and meta-analysis of randomized controlled trials found that statin therapy was associated with a reduction in sepsis incidence and sepsis-related mortality. Another study found that statin use was associated with a lower risk of sepsis in patients with acute coronary syndrome. However, these studies did not specifically examine the relationship between different doses, classes, and intensities of statin use and sepsis mortality in patients with T2DM.

Added value of this study:

This study is the first to specifically examine the relationship between different doses, classes, and intensities of statin use and sepsis mortality in patients with T2DM. The study used a large, national population-based cohort and analyzed the data using an inverse probability of treatment-weighted Cox hazard model, providing a more comprehensive and accurate assessment of the relationship between statin use and sepsis mortality in this patient population.

Implications of all the available evidence:

The results of this study suggest that persistent statin use may reduce sepsis mortality in patients with T2DM, and that higher cumulative daily defined doses per year of statins are associated with a greater reduction in sepsis mortality. Additionally, the study found that certain statin classes, such as pitavastatin, had higher protective effects against sepsis mortality compared to others. These findings provide important insights for clinicians treating patients with T2DM and may inform clinical practice guidelines for the prevention of sepsis in this population. However, further research is needed to confirm these findings and to examine the mechanisms by which statins may reduce sepsis mortality in patients with T2DM.

Introduction

Sepsis is a life-threatening condition that occurs when the body's immune system overreacts to an infection, leading to organ dysfunction. It is a major cause of death globally, with a mortality rate of over 10%.[1] In 2017, there were approximately 50 million incident cases of sepsis and 11 million deaths due to sepsis reported worldwide, making up 20% of all deaths globally.[2] Septic shock, which occurs in 10% of intensive care unit patients and is a serious complication of sepsis, is associated with high mortality risk, with nearly 40% of cases resulting in death.[3]

People with diabetes are at a higher risk of developing wounds that do not heal and infections that may lead to sepsis.[4] Type 2 diabetes mellitus (T2DM), which affects over 90% of all diabetes patients and hundreds of millions of people worldwide, is characterized by high blood sugar, insulin resistance, impaired insulin secretion, and abnormal lipid levels.[5–8] T2DM is linked to an increased risk of recurrent, hospital-acquired, and secondary infections that can lead to sepsis.[4, 9] Patients with T2DM have a two to six times higher risk of sepsis and higher sepsis mortality compared to those without T2DM.[10–14] They also experience higher rates of postsepsis complications and contribute to the increasing sepsis mortality.[12] T2DM and its complications are a leading cause of hospitalization, disability, and death.[15]

Despite recent advances in diagnosis and treatment, T2DM and sepsis continue to be common, costly, and deadly worldwide. [3, 16] To date, there is no safe medication for the long-term prevention of sepsis mortality in T2DM populations at risk. Statins, which have cholesterol-lowering, anti-inflammatory, immunomodulatory, antioxidant, antithrombotic, and endothelium-stabilizing properties, may be able to prevent various types of diseases through various underlying mechanisms. [17–21] However, these effects have not been observed in hospitalized patients with severe conditions such as pneumonia, sepsis, and active infections.[22–29] This may be because the disease-preventive effects of statins work relatively slowly. As a result, statins may be more beneficial for patients in relatively good health, potentially helping to prevent the progression of diseases such as cardiovascular disease[30, 31] or stroke[32, 33] and reducing mortality.[34] However, the results of previous studies on this topic are controversial, as they used different designs, populations, and endpoints.[17, 18, 22–29] Therefore,

examining the use of statins as protective medications in specific patient populations is still valuable. For example, statins may be effective in T2DM patients who have a high prevalence of inflammatory and immune disorders, excessive oxidative stress, and thrombotic and endothelial issues related to atherosclerosis, all of which can increase the risk of sepsis mortality.[13, 35, 36] The current study aims to analyze the effects of different statin doses, classes, and intensity of use on sepsis mortality risk in T2DM patients.

Methods

Study population

We conducted a population-based cohort study using Taiwan National Health Insurance (NHI) Research Database (NHIRD) data between 2008–2020. The NHIRD includes all medical claims data, including disease diagnoses, procedures, drug prescriptions, demographics, and enrollment profiles, of all beneficiaries,[37] all of which is encrypted using unique patient identifiers. NHIRD data are also linked to the death registry data; this facilitates the determination of vital statuses and causes of death of each included patient.

In our cohort, we included ≥ 40-year-old patients diagnosed as having T2DM aged during the index date. Patients with missing age data were excluded. To specifically estimate the protective effects of different statin classes against sepsis mortality, we excluded patients with T2DM who had crossover use of different classes of statins during the follow-up period. Statin use was defined as use of a statin on most days for > 1 month within 1 year, with a mean statin dose of ≥ 28 cumulative defined daily doses (cDDDs) per year (cDDD-year). The index date was the date when statin use of ≥ 28 cDDD-year commenced. The observation period for each patient began on the index date and continued until mortality due to sepsis or the end of the study period (December 31, 2021), whichever occurred first. The primary outcome of interest was sepsis mortality. Patients with T2DM who were prescribed ≥ 28 cDDD-year of statins annually with a prescription duration of > 1 month over the follow-up period formed the case group (statin users), whereas those who were prescribed 0 cDDD of statins over the follow-up period formed the control group (statin nonusers).

The study protocols were reviewed and approved by the Institutional Review Board of Tzu-Chi Medical Foundation (IRB109-015-B).

Study covariates

We included other covariates in our analyses to adjust for potential confounding effects. The patients were divided into four age groups: 40–50, 51–60, 61–70, and ≥ 71 years at index date. We used the date of ≥ 28 cDDD-year statin use commencement as the index date for statin users. For matched statin nonusers, variables collected at the index date were used. Repeat comorbidities were excluded from the CCI calculations to prevent repetitive adjustment in multivariate analysis. Comorbidity onset during 1 year before the index date was identified using the *International Classification of Diseases, Ninth Revision,*

Clinical Modification (ICD-9-CM) and *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) codes indicated in the main inpatient diagnosis or in outpatient diagnoses given during at least two visits within 1 year.

Statin exposure

We coded all statin prescriptions according to the Anatomical Therapeutic Chemical (ATC) coding system of the NHIRD pharmaceutical subsidies, which were used as an interface for retrieving pharmaceutical claims data. We selected lipophilic (atorvastatin, fluvastatin, lovastatin, simvastatin, and pitavastatin) and hydrophilic (pravastatin and rosuvastatin) statins[38] as the major exposures of interest. We also examined statin use intensity by continually estimating the average statin dose as the DDD divided by the total number of prescription days. Statin use intensity was divided into average DDDs of > 1 or < 1. Moreover, we estimated the lowest hazard ratio (HR) for sepsis mortality and the DDD of statins to determine the statin use intensity affording the optimal sepsis mortality reduction. Furthermore, we divided the patients into four subgroups that were stratified by quartiles (Q) of cDDD-year.

Statistical analysis

In this study, all continuous variables are presented as means ± standard deviations (SDs) or medians (first quartile, third quartile), where appropriate. To reduce the effects of potential confounders when comparing sepsis mortality between statin users and nonusers, the data were adjusted for age groups, sex, income levels, urbanization levels, types of antidiabetic drugs used, antidiabetic drug use status, diabetic severity (based on adapted Diabetes Complications Severity Index [aDCSI] scores), comorbidities, and Charlson's comorbidity index (CCI) scores. This was followed by comparison of sepsis mortality between statin users and nonusers by using an inverse probability of treatment weighted (IPTW)[39] time-dependent Cox hazard model.

Data on statin prescriptions were collected every 3 months to define every user's status and were estimated as time-dependent variables. To prevent bias, "event-free" person-times of users before their first prescription and during the 3-month period without a statin prescription were classified as unexposed follow-up durations. We also estimated sepsis mortality risk based on individual statin classes. Analyses were also performed in subgroups, for which the baseline characteristics were adjusted using stratification, rather than weighting postdiagnosis statins, because both methods would have yielded similar results.

Cumulative sepsis mortality was estimated using the Kaplan–Meier method. We plotted and compared the resulting cumulative incidence curves to differences in cumulative sepsis mortality between statin users and nonusers and between statin users taking statins at different dosages or classes by using the stratified log-rank test (Figs. 1 and 2).

All statistical analyses were conducted using SAS version 9·4 (SAS Institute, Cary, NC, USA).

Results

Over 2008–2020, 850 326 patients were diagnosed as having T2DM; the mean age at T2DM diagnosis was 56·64 and 56·93 years in statin nonusers and users, respectively. Of them, 36·17% of patients received atorvastatin, making it the most prescribed statin, followed by rosuvastatin (19·88%) and simvastatin (19·70%). For postmatch balancing, we used the absolute standardized mean difference (ASMD) of < 0·1 after IPTW for all baseline covariates.[40] In Table 1, the ASMDs for all covariates were < 0·1, demonstrating that after IPTW, the covariates between the statin users and nonusers were balanced (Table 1).[40]

Effects of different statin classes and dose on sepsis mortality

In our T2DM cohort, 58 071 (13·47%) statin nonusers and 22 551 (5·38%) statin users died of sepsis (Table 1). In general, sepsis mortality was significantly lower in statin users than in nonusers (all P< 0·0001, log-rank test; Supplemental Fig. 1). The adjusted HR (aHR) for sepsis mortality in statin users compared to nonusers was 0·29 (95% confidence interval [CI] 0·28–0·29; Table 2). This difference was also noted for statin users of all the included classes and dosages (P< 0·0001, log-rank test; Figs. 1 and 2, respectively): The aHRs (95% CIs) for sepsis mortality in pitavastatin, rosuvastatin, pravastatin, atorvastatin, simvastatin, fluvastatin, and lovastatin users compared to nonusers were 0·04 (0·02–0·07), 0·26 (0·25–0·27), 0·26 (0·24–0·28), 0·28 (0·27–0·29), 0·28 (0·27–0·29), 0·32 (0·3–0·34), and 0·39 (0·37–0·42), respectively (Table 2). Finally, the users of statins at Q1, Q2, Q3, and Q4 cDDD-year demonstrated aHRs for sepsis mortality of 0·43 (0·41–0·44), 0·31 (0·30–0·32), 0·21 (0·20–0·22), and 0·12 (0·11–0·13), respectively (P for trend < 0·0001).

Statin use intensity

The optimal dose intensity of statin use was 0·86 DDD, which led to the lowest aHR (0·29; Fig. 3). In general, the protective effects of statin use (in DDD) on sepsis mortality demonstrated a U-shaped dose–response relationship.[41] In other words, a higher DDD may not always remain associated with lower sepsis mortality risk. Nevertheless, statin users demonstrated effects on sepsis mortality superior to those in statin nonusers (Fig. 3).

Sensitivity analyses

We next analyzed the effects of statin use at different dose intensities (≤ 1 or > 1 DDD) after adjusting the data for CCI scores (≤ 1), age groups, sex, income levels, urbanization levels, types of antidiabetic drugs used, antidiabetic drug use status, diabetic severity, and comorbidities. The aHRs for sepsis mortality in users taking > 1 and ≤ 1 DDD of statin compared to statin nonusers were 0·70 (0·52–0·95) and 0·28 (0·27–0·29), respectively. Reductions in sepsis mortality identified in the sensitivity analyses were comparable to those in the main analysis (Table 3 and Fig. 3): a higher (> 1) DDD of statins has a less protective effect against sepsis mortality.

Discussion

T2DM and diabetes-related complications are major contributors to hospitalization, disability, and sepsis mortality.[15] T2DM is an independent risk factor for sepsis mortality and patients with T2DM have high rates of sepsis.[13, 42, 43] Therefore, it is important to develop safe medications that can provide long-term protection against sepsis mortality in T2DM patients. Statins may have anti-inflammatory properties, such as the ability to suppress the upregulation of toll-like receptors (TLRs) 4 and 2 in response to endotoxins.[9, 44] However, the data on the relationship between statin use and sepsis risk is inconsistent due to the heterogeneity of the populations and endpoints in the relevant studies.[9, 17, 18, 22–29] These studies also used different statin classes and unclear daily defined doses (DDDs), making it difficult to accurately assess the dose-dependent protective effects of statins on various outcomes, such as sepsis, sepsis mortality, or all-cause mortality, in T2DM patients who have a high risk of sepsis mortality.[13, 42] In the current study, we used inverse probability of treatment weighting to estimate the relationship between sepsis mortality and specific classes, cumulative daily defined doses per year (cDDD-year), and DDDs of statins in T2DM patients.

This is the first study to delineate class-stratified protective effects of statins against sepsis mortality in patients with T2DM; we noted that pitavastatin exhibited the most protective effects, followed by rosuvastatin, pravastatin, atorvastatin, simvastatin, fluvastatin, and finally lovastatin (Table 2 and Fig. 1). These differences in the protective effects of these statins against sepsis mortality may be linked to their low-density lipoprotein cholesterol (LDL-C)-lowering, high-density lipoprotein cholesterol (HDL-C)-elevating, and triglyceride-lowering properties.[45–47] For instance, rosuvastatin is slightly more potent than atorvastatin,[45, 46] whereas it is significantly more potent than simvastatin, fluvastatin, and lovastatin.[46, 47] At maximal prescribed doses, LDL-C reduction is greater with rosuvastatin than with simvastatin, atorvastatin, fluvastatin, and lovastatin.[46, 47] The potencies of the aforementioned five statins for LDL-C lowering were compatible in terms of the protective effect against sepsis mortality for T2DM (Table 2 and Fig. 1). Statin therapy typically increases HDL-C levels, but these effects vary by statin class and dose.[48] For instance, simvastatin and rosuvastatin appear to increase HDL-C levels as their doses increase; by contrast, when atorvastatin is attenuated at higher doses, an increase is noted in HDL-C levels.[48] Moreover, in patients with hypercholesterolemia, rosuvastatin is more effective at lowering triglyceride levels than other statins.[46] However, the association of the LDL-C- and triglyceride-lowering and HDL-C-raising potency of statins with sepsis mortality remains unclear. In the current study, the potency of the LDL-C- and triglyceride-lowering and HDL-C-raising potency of various statin classes appeared to be proportional to the order of intensity of the statins' protective effects against sepsis mortality in patients with T2DM. In addition, pitavastatin, pravastatin, and rosuvastatin are less likely to have drug interactions or produce muscle toxicity than are some other statins.[49, 50] Fewer pharmacokinetic drug interactions are likely to occur with pravastatin, rosuvastatin, pitavastatin, and fluvastatin because they are not metabolized through CYP3A4.[49, 50] Our patients with T2DM had received various types of medications (Table 1); therefore, statins with low drug–drug interactions such as pitavastatin or pravastatin might be the choice that best balances the positive effects and toxicities.[49, 50] Although the criteria for selecting specific statin classes for sepsis mortality prevention remain unclear, statins with fewer pharmacokinetic drug–drug interactions (e.g., pitavastatin, pravastatin)[49, 50]

or those with stronger LDL-C- and triglyceride-lowering and HDL-C-raising effects (e.g., rosuvastatin)[45–47] might be preferable options (Table 2 and Fig. 1). However, further research to determine the criteria for selecting statins appropriate for sepsis mortality reduction is warranted.

A DDD of statins affects not only sepsis mortality but also the LDL-C, HDL-C, and triglyceride levels.[48, 51] Thus, the occurrence of a U-shaped dose–response curve for the relationship between statin DDD and its protective effects on sepsis mortality represents pharmacological, biological, as well as toxicological effects (Fig. 3),[41] and a higher statin DDD may not necessarily lead to a better protective effect.[52] The current study is the first to demonstrate that in patients with T2DM, the optimal DDD of statins is 0·86, which is associated with the lowest sepsis mortality risk (HR 0·29). Part of the variability in the response to and the side effects related to statins may be associated with the genetic differences in the drug metabolism rates.[53–55] For instance, CYP2D6, a member of the cytochrome P450 superfamily of drug-oxidizing enzymes, is functionally absent in 7% of Caucasian and African American individuals; however, CYP2D6 deficiency is rarely noted among Asian individuals. Individuals from Asia (mostly China, Japan, and Korea) may thus have a greater response to low doses of statins than European American individuals do.[54] Therefore, statin therapy should be initiated at a lower initial daily dose in Asian individuals compared with that in individuals from other ethnic groups.[54, 56] Therefore, based on the current study, the optimal DDD of statin can be as low as 0·86 for Asian patients with T2DM.

The LDL-C-, HDL-C-, and triglyceride-lowering effects of statins may differ according to the cDDD-year prescribed; thus, statins at different cDDD-year values might also have different levels of protective effects against sepsis mortality in patients with T2DM. Therefore, we estimated the effects of Q1, Q2, Q3, and Q4 cDDD-year of statins on sepsis mortality in patients with T2DM. Our findings suggested that the higher the cDDD-year of statins is, the greater is the reduction in sepsis mortality in patients with T2DM. Our results confirmed the dose-dependent protective effects of statins against sepsis mortality in patients with T2DM.

This is the first study to clarify the dose- and class-dependent protective effects of statin use on sepsis mortality in patients with T2DM. The strength of our study is its large sample size, including patients with T2DM using statins of different classes at various doses and use intensities (Figs. 1–3 and Supplemental Fig. 1). Compared with the debatable results in different populations in previous studies,[9, 17, 18, 22–29] the current study provides more reliable real-world evidence based on long-term follow-up demonstrating that persistent statin use can reduce sepsis mortality in patients with T2DM (Tables 2–3). In addition, the statin DDD for optimal reduction in sepsis mortality was noted to be 0·86 (Fig. 3). Moreover, the order of intensity of protective effects of different statin classes on sepsis mortality in statin users compared with nonusers is as follows: pitavastatin > rosuvastatin > pravastatin > atorvastatin > simvastatin > fluvastatin > lovastatin (Table 2 and Fig. 1).

This study, however, has some limitations. First, this study used a claims database, from which the patient blood biochemistry and lipid profile data were unavailable. Therefore, we could not evaluate whether changes in lipid profile after statin use initiation were associated with sepsis mortality. Second,

we could not completely avoid the possibility of statin users being a differently composed population than that of the statin nonusers; this may have been an unmeasured confounding factor in the current study. We used IPTW to balance the differences in covariates and conducted several subgroup analyses to examine potential bias due to unmeasured confounders. We also examined the effects of statin use in patients with differences in age, sex, income levels, urbanization levels, types of antidiabetic drugs used, antidiabetic drug use status, aDCSI scores, comorbidities, and CCI scores. The reduction in sepsis mortality with statin use for patients with T2DM was similar in the main and sensitivity analyses. Third, we could not collect data on lifestyle-related factors such as body mass index at the time of T2DM diagnosis. Therefore, we were unable to evaluate the effects of these factors on sepsis mortality. Fourth, event numbers were small in some statin class subgroups, which limited the statistical power of our results. Finally, 95% of our study population was Han Chinese,[57] which limits the generalizability of our results to other ethnic groups. The prevalence of statin use is approximately 76·5% in North America, 69·9% in Western Europe, and 60·5% in Asia.[58] Therefore, individuals of ethnicities other than Han Chinese may have only slightly different effects: studies in other ethnic populations have also demonstrated reductions in sepsis mortality risk associated with statin use.[28]

Conclusion

According to our real-world evidence, persistent statin use can reduce sepsis mortality in patients with type 2 diabetes mellitus (T2DM). The higher the cumulative daily defined doses per year of statin use, the greater the reduction in sepsis mortality. The optimal daily defined dose of statins that leads to the lowest mortality is 0.86. Among the different statin classes, pitavastatin provides the most optimal protection against sepsis mortality, followed by rosuvastatin, pravastatin, atorvastatin, simvastatin, fluvastatin, and lovastatin.

Declarations

Ethics approval and consent: The study protocols were reviewed and approved by the Institutional Review Board of Tzu-Chi Medical Foundation (IRB109-015-B).

Consent for publication: Not applicable

Availability of data and material: Data analyzed during the study were provided by a third party. Requests for data should be directed to the provider indicated in the Acknowledgments

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contact info for which data requests may be sent to are as follows: http://nhird.nhri.org.tw/en/Data_Subsets.html#S3 and http://nhis.nhri.org.tw/point.html.

Declaration of interests

The authors have no potential conflicts of interest to declare. The datasets supporting the study conclusions are included within the manuscript.

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Tables

***Table 1*: Baseline characteristics of the T2DM cohort stratified by statin use**

	Statin nonusers		Statin users		ASMD
	N = 431,132		N = 419,194		
Characteristics	**n**	**%**	**n**	**%**	
Age (mean ± SD), years	56·64 ± 20·91		56·93 ± 19·09		
Age, median (IQR), years	56·00 (46·00, 68·00)		56·00 (47·00, 67·00)		
Age group, years					0·0010
≤50	148 019	34·33%	143 175	34·15%	
51–60	113 442	26·31%	110 761	26·42%	
61–70	85 772	19·89%	85 342	20·36%	
≥71	83 899	19·46%	79 916	19·06%	
Sex					0·0044
Female	200 468	46·50%	196 741	46·93%	
Male	230 664	53·50%	222 453	53·07%	
Income level (NT$)					0·0030
Low income	7014	1·63%	6641	1·58%	
Financial dependent	134 302	31·15%	131 175	31·29%	
≤20 000	205 089	47·57%	199 360	47·56%	
20 001–30 000	39 534	9·17%	38 227	9·12%	
30 001–45 000	28 612	6·64%	27 743	6·62%	
>45 000	16 581	3·85%	16 048	3·83%	
Urbanization					0·0026
Rural	124 348	28·84%	119 808	28·58%	
Urban	306 784	71·16%	299 386	71·42%	
Types of antidiabetic drugs use					0·0119
0	153 624	35·63%	152 391	36·35%	
1	108 596	25·19%	104 937	25·03%	
2	107 535	24·94%	103 409	24·67%	
3	44 513	10·32%	42 388	10·11%	
≥4	16 864	3·91%	16 069	3·83%	

Antidiabetic drugs					
Insulin	72 910	16·91%	46 087	10·99%	0·0592
Metformin	181 083	42·00%	181 129	43·21%	0·0121
SU	204 217	47·37%	205 506	49·02%	0·0166
AGI	25 319	5·87%	26 393	6·30%	0·0042
TZD	16 289	3·78%	19 982	4·77%	0·0099
DPP4i	548	0·13%	227	0·05%	0·0007
SGLT2i	3180	0·74%	3309	0·79%	0·0005
Others	25 121	5·83%	24 408	5·82%	0·0000
Diabetes Severity					
aDCSI score, mean ± SD	0·99 ± 1·90		1·00 ± 1·89		0·0005
aDCSI score, median (IQR)	0·00 (0·00, 2·00)		0·00 (0·00, 2·00)		
aDCSI score					0·0060
0	222 357	51·58%	217 708	51·93%	
1	89 829	20·84%	87 362	20·84%	
2	65 370	15·16%	63 044	15·04%	
≥3	53 576	12·43%	51 080	12·19%	
aDCSI					
Retinopathy	19 511	4·53%	24 073	5·74%	0·0122
Nephropathy	53 171	12·33%	49 636	11·84%	0·0049
Neuropathy	39 963	9·27%	44 317	10·57%	0·0130
Cerebrovascular	47 894	11·11%	42 869	10·23%	0·0088
Cardiovascular	112 592	26·12%	109 020	26·01%	0·0011
Peripheral vascular disease	17 486	4·06%	16 072	3·83%	0·0022
Metabolic disorder	11 195	2·60%	8037	1·92%	0·0068
Coexisting Ccomorbidities					
Hypertension	222 525	51·61%	214 201	51·10%	0·0055
Rheumatoid arthritis	0	0·00%	0	0·00%	0·0000
Ankylosing spondylitis	6474	1·50%	6222	1·48%	0·0002

Psoriasis	3257	0·76%	3141	0·75%	0·0001
Psoriatic arthritis	295	0·07%	355	0·08%	0·0002
Crohn's Disease	6263	1·45%	6014	1·43%	0·0002
Ulcerative Colitis	956	0·22%	952	0·23%	0·0001
COPD	88 285	20·48%	84 499	20·16%	0·0032
Chronic liver disease	113 457	26·32%	111 018	26·48%	0·0017
Chronic kidney disease	11 329	2·63%	10 698	2·55%	0·0008
Heart failure	28 461	6·60%	26 852	6·41%	0·0020
Coronary artery disease	96 592	22·40%	93 093	22·21%	0·0020
Stroke	62 301	14·45%	59 090	14·10%	0·0036
Coagulopathy	1015	0·24%	943	0·22%	0·0001
Dementia	12 375	2·87%	10 567	2·52%	0·0035
Psychosis	949	0·22%	924	0·22%	0·0000
SLE	7545	1·75%	7335	1·75%	0·0000
AIDS	157	0·04%	168	0·04%	0·0000
CCI Scores					
Mean (SD)	0·96 ± 1·77		0·97 ± 1·86		0·0001
Median (Q1–Q3)	0·00 (0·00, 2·00)		0·00 (0·00, 2·00)		
CCI Scores					0·0018
0	231 864	53·78%	226 201	53·96%	
≥1	199 268	46·22%	192 993	46·04%	
Different classes of statins					
Lipophilic statins					
Atorvastatin	0	0·00%	151 626	36·17%	
Lovastatin	0	0·00%	27 890	6·65%	
Simvastatin	0	0·00%	82 579	19·70%	
Fluvastatin	0	0·00%	38 731	9·24%	
Pitavastatin	0	0·00%	3257	0·78%	
Hydrophilic statins					

Rosuvastatin	0	0·00%	83 343	19·88%	
Pravastatin	0	0·00%	31 768	7·58%	
Cumulative dose of statins (cDDD per year)					
Q1	0	0·00%	123 715	29·51%	
Q2	0	0·00%	113 737	27·13%	
Q3	0	0·00%	99 458	23·73%	
Q4	0	0·00%	82 284	19·63%	
DDD					
≤1	0	0·00%	369 394	88·12%	
>1	0	0·00%	49 800	11·88%	
					P
Follow-up time					
Mean ± SD, years	8·08 ± 4·15		8·56 ± 2·47		<0·0001
Median (IQR), years	8·13 (6·32, 9·35)		8·72 (7·64, 9·82)		
Mortality from sepsis					<0·0001
No	373 061	86·53%	396 643	94·62%	
Yes	58 071	13·47%	22 551	5·38%	

ASMD=absolute standardized mean difference. SD = standard deviation. IQR = interquartile range. T2DM = type 2 diabetes mellitus. Q = quartile. DDD=defined daily dose. cDDD-year = cumulative DDD per year. AIDS = acquired immunodeficiency syndrome. CCI = Charlson's comorbidity index. COPD = chronic obstructive pulmonary disease. SLE = systemic lupus erythematosus. NT$ = New Taiwan dollar. aDCSI = adapted diabetic complication severity index. SU = sulfonylurea. AGI = alpha-glucosidase inhibitor. TZD = thiazolidinedione. DPP4i = dipeptidyl peptidase 4 inhibitors. SGLT2i = sodium–glucose cotransporter-2 inhibitors.

***Table 2*: Sepsis mortality and aHRs for statin use in patients with T2DM**

	HR (95%CI)		*P*	aHR (95%CI)*		*P*
Stain use						
Nonusers	**Reference**					
Users	0·34	(0·33, 0·34)	<0·0001	0·29	(0·28, 0·29)	<0·0001
Different classes of statins						
Nonusers	**Reference**					
Hydrophilic statins						
Pravastatin	0·30	(0·28, 0·33)	<0·0001	0·26	(0·24, 0·28)	<0·0001
Rosuvastatin	0·29	(0·28, 0·31)	<0·0001	0·26	(0·25, 0·27)	<0·0001
Lipophilic statins						
Pitavastatin	0·03	(0·02, 0·06)	<0·0001	0·04	(0·02, 0·07)	<0·0001
Fluvastatin	0·42	(0·4, 0·45)	<0·0001	0·32	(0·3, 0·34)	<0·0001
Simvastatin	0·31	(0·3, 0·32)	<0·0001	0·28	(0·27, 0·29)	<0·0001
Lovastatin	0·49	(0·46, 0·52)	<0·0001	0·39	(0·37, 0·42)	<0·0001
Atorvastatin	0·34	(0·33, 0·35)	<0·0001	0·28	(0·27, 0·29)	<0·0001
Cumulative dose of statins DDD per year						
Nonusers	**Reference**					
Q1	0·55	(0·53, 0·56)	<0·0001	0·43	(0·41, 0·44)	<0·0001
Q2	0·36	(0·35, 0·38)	<0·0001	0·31	(0·30, 0·32)	<0·0001
Q3	0·23	(0·22, 0·24)	<0·0001	0·21	(0·20, 0·22)	<0·0001
Q4	0·13	(0·12, 0·14)	<0·0001	0·12	(0·11, 0·13)	<0·0001
***P* for trend**			<0·0001			<0·0001

aHR = adjusted hazard ratio. HR = hazard ratio. CI = confidence interval. DDD = defined daily dose. T2DM = type 2 diabetes mellitus. Q = quartile.

*aHR was derived from our inverse probability-weighted Cox model considering statin use as a time-dependent covariate and adjusted for age group, sex, income level, urbanization, types of antidiabetic drugs use, antidiabetic drug use status, diabetic severity (i.e., aDCSI Score), comorbidities, and CCI scores.

***Table 3*: Sensitivity analyses of sepsis mortality–statin use association in patients with T2DM**

Subpopulation or exposure	No. of patients	Sepsis mortality			
		No. of deaths	aHR*	95% CI	*P*
Age group, years					
≤50	291 194	7967	0·24	(0·22, 0·26)	<0·0001
51–60	224 203	11 180	0·28	(0·26, 0·30)	<0·0001
61–70	171 114	17 706	0·3	(0·29, 0·32)	<0·0001
≥71	163 815	43 769	0·28	(0·28, 0·29)	<0·0001
Sex					
Female	397 209	33 358	0·28	(0·27, 0·29)	<0·0001
Male	453 117	47 264	0·29	(0·28, 0·30)	<0·0001
Income level (NT$)					
1. Low income	13 655	2708	0·29	(0·26, 0·33)	<0·0001
1. Financial dependent	265 477	43 494	0·3	(0·29, 0·31)	<0·0001
1. ≤20 000	404 449	2251	0·27	(0·27, 0·28)	<0·0001
1. 20 001–30 000	77 761	1341	0·34	(0·30, 0·39)	<0·0001
1. 30 001–45 000	56 355	534	0·24	(0·20, 0·29)	<0·0001
1. >45 000	32 629	30 294	0·31	(0·23, 0·40)	<0·0001
Urbanization					
Rural	244 156	29 936	0·28	(0·27, 0·29)	<0·0001
Urban	606 170	50 686	0·29	(0·28, 0·30)	<0·0001
Types of antidiabetic drugs use					
0	306 015	23 478	0·28	(0·27, 0·29)	<0·0001
1	213 533	21 053	0·27	(0·26, 0·28)	<0·0001
2	210 944	18 664	0·31	(0·29, 0·32)	<0·0001
3	86 901	12 155	0·28	(0·26, 0·29)	<0·0001
≥4	32 933	5272	0·29	(0·26, 0·31)	<0·0001

aDCSI Score					
0	440 065	22 931	0·29	(0·28, 0·31)	<0·0001
1	177 191	12 111	0·32	(0·30, 0·34)	<0·0001
2	128 414	19 214	0·27	(0·25, 0·28)	<0·0001
≥3	104 656	26 366	0·28	(0·27, 0·29)	<0·0001
CCI Scores					
0	440 065	22 931	0·29	(0·28, 0·31)	<0·0001
≥1	392 261	52 955	0·26	(0·25, 0·27)	<0·0001
Coexisting comorbidities					
Hypertension	436 726	55 987	0·29	(0·28, 0·30)	<0·0001
Ankylosing spondylitis	12 696	1421	0·3	(0·25, 0·35)	<0·0001
Psoriasis	6398	829	0·27	(0·22, 0·34)	<0·0001
Psoriatic arthritis	650	92	0·04	(0·01, 0·11)	<0·0001
Crohn's disease	12 277	1487	0·3	(0·26, 0·36)	<0·0001
Ulcerative colitis	1908	234	0·23	(0·14, 0·37)	<0·0001
COPD	172 784	30 147	0·26	(0·26, 0·27)	<0·0001
Chronic liver disease	224 475	19 324	0·26	(0·25, 0·28)	<0·0001
Chronic kidney disease	22 027	6144	0·27	(0·25, 0·29)	<0·0001
Heart failure	55 313	14 196	0·28	(0·27, 0·30)	<0·0001
Coronary artery disease	189 685	29 624	0·29	(0·28, 0·30)	<0·0001
Stroke	12 1391	27 067	0·26	(0·25, 0·27)	<0·0001
Coagulopathy	1958	445	0·1	(0·06, 0·15)	<0·0001
Dementia	22 942	7866	0·21	(0·20, 0·23)	<0·0001
Psychosis	1873	294	0·25	(0·17, 0·37)	<0·0001
Ankylosing spondylitis	12 696	1421	0·3	(0·25, 0·35)	<0·0001
SLE	1873	410	0·34	(0·27, 0·36)	<0·0001
DDD					
≤1	798 907	77 479	0·28	(0·27, 0·29)	<0·0001
>1	51 419	3143	0·70	(0·52, 0·95)	0·0207

Metformin users	362 212	32 210	0·32	(0·31, 0·34)	<0·0001

DDD = defined daily dose. AIDS = acquired immunodeficiency syndrome. CCI = Charlson's comorbidity index. COPD =chronic obstructive pulmonary disease. SLE = systemic lupus erythematosus. NT$ = New Taiwan dollar. aDCSI = adapted diabetic complication severity index. aHR = adjusted hazard ratio. CI = confidence interval.

*aHR was derived from our inverse probability-weighted Cox model considering statin use as a time-dependent covariate and adjusted for age group, sex, income level, urbanization, types of antidiabetic drugs use, antidiabetic drug use status, diabetic severity (i.e., aDCSI Score), comorbidities, and CCI scores.

Figures

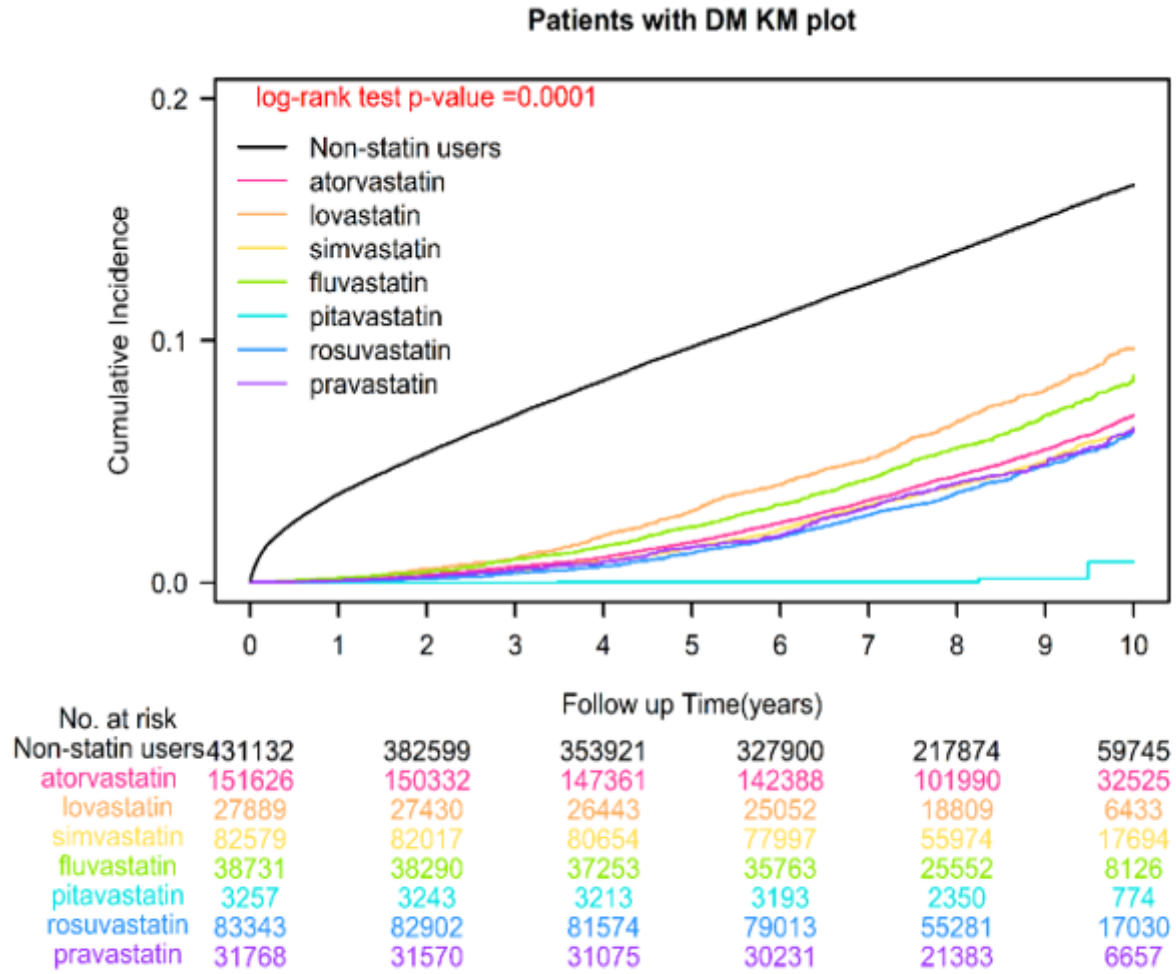

Figure 1

Kaplan–Meier cumulative survival curves for sepsis mortality in patients with T2DM who used different classes of statins

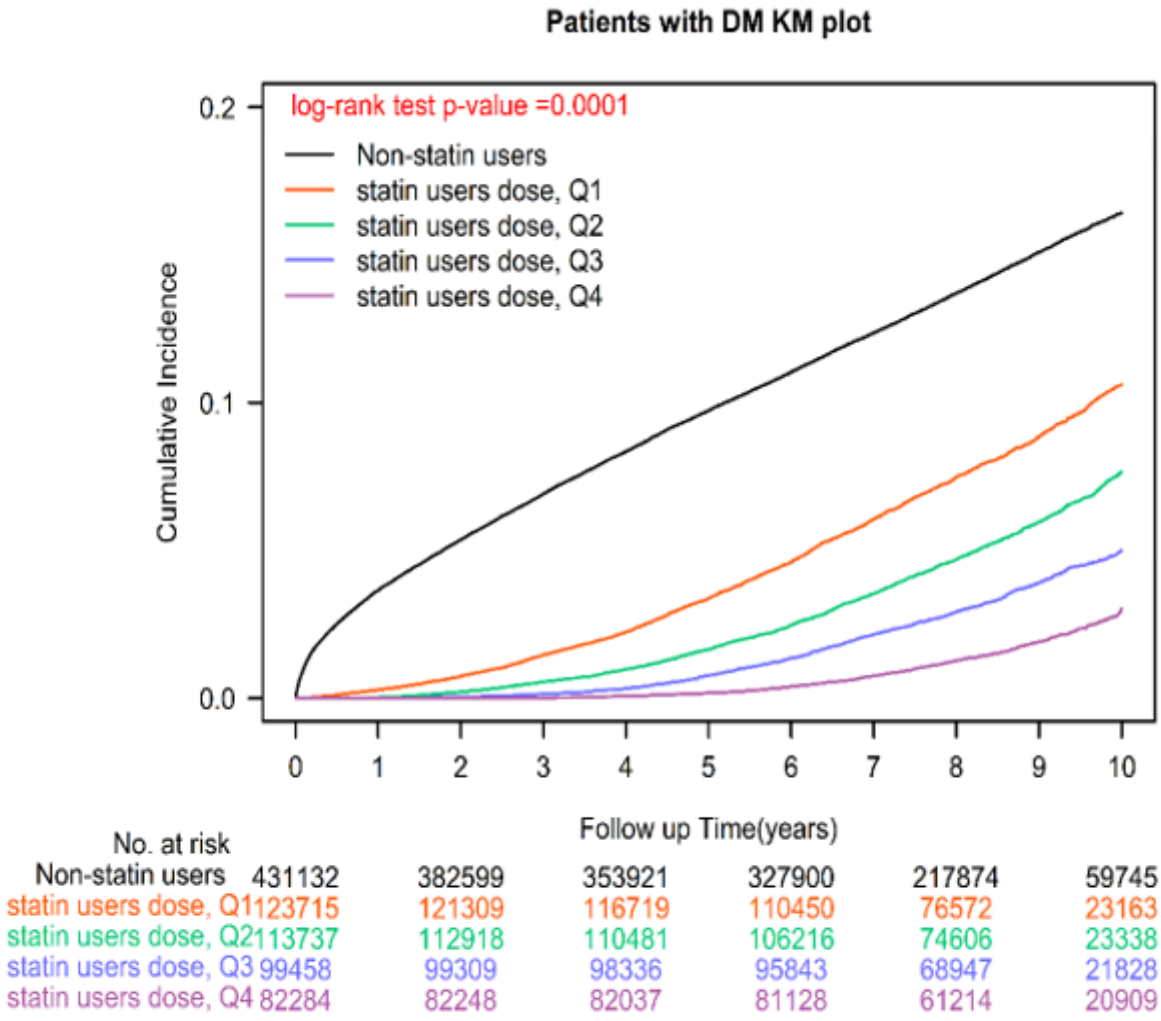

Figure 2

Kaplan–Meier cumulative survival curves for sepsis mortality in patients with T2DM who used statins at different cDDDs-year.

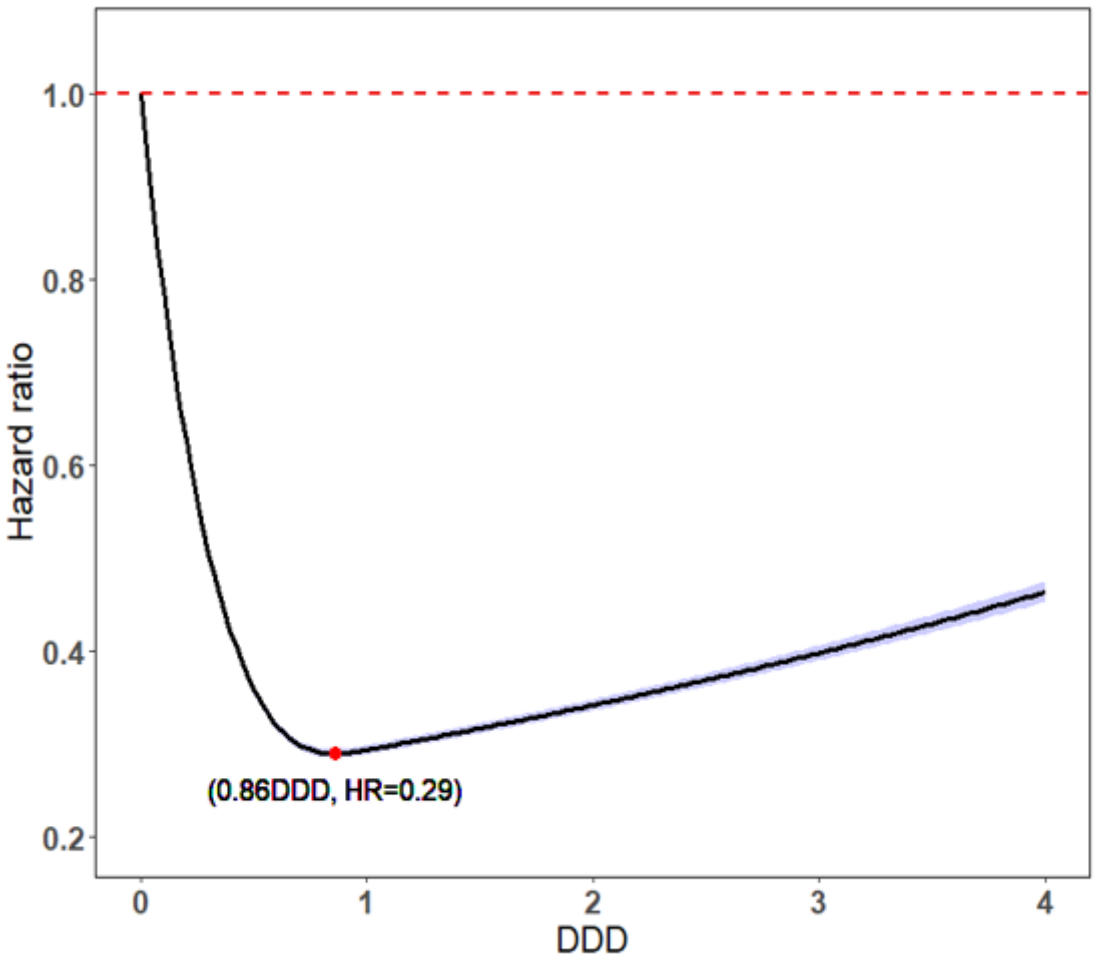

Figure 3

Statin use intensity (DDD) versus HR for sepsis mortality.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalFigure1.docx