Statins, Risk of Diabetes, and Implications on Outcomes in the General Population

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Objectives   This analysis aimed to evaluate the association of statin exposure and incident diabetes, and subsequent outcomes in the general population.

Background   Cardiovascular events as consequences of atherosclerosis and diabetes are reduced by statins. However, statins are associated with excessive risk of diabetes occurrence according to clinical trial analyses. From daily-practice perspectives, it remains unclear whether statin use increases risk; prognoses of diabetes after exposure require further clarification.

Methods   From Taiwan National Health Insurance beneficiaries age ≥45 years (men) and ≥55 years (women) before 2004, subjects continuously treated with statins ≥30 days during 2000 to 2003 and nonusers before 2004 were identified. Among nondiabetic individuals at the cohort entry, controls were matched to statin users on a 4:1 ratio by age, sex, atherosclerotic comorbidities, and year of their entry. Outcomes as diabetes, major adverse cardiovascular events (MACE, the composite of myocardial infarction and ischemic stroke), and in-hospital deaths were assessed.

Results   Over a median of 7.2 years, annual rates of diabetes were significantly higher in statin users (2.4% vs. 2.1%, $p < 0.001$), whereas MACE (hazard ratio [HR]: 0.82; 95% confidence interval [CI]: 0.68 to 0.98 for myocardial infarction; HR: 0.94; 95% CI: 0.86 to 1.03 for ischemic stroke; HR: 0.91; 95% CI: 0.84 to 0.99 for MACE]) and in-hospital mortality (HR: 0.61; 95% CI: 0.55 to 0.67]) were less. The risk–benefit analyses suggested that statin treatment was favorable in high-risk (HR: 0.89; 95% CI: 0.83 to 0.95) and secondary prevention (HR: 0.89; 95% CI: 0.83 to 0.96) populations. Among diabetic patients, prior statin use was associated with fewer MACE (HR: 0.75; 95% CI: 0.59 to 0.97). In-hospital deaths were similar in statin-related diabetes among high-risk (HR: 1.11; 95% CI: 0.83 to 1.49) and secondary prevention (HR: 1.08; 95% CI: 0.79 to 1.47) subjects compared with nondiabetic controls.

Conclusions   Risk of diabetes was increased after statins, but outcomes were favorable.   (J Am Coll Cardiol 2012;xx:xxx)
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Tackling low-density lipoprotein cholesterol by statin therapy successfully reduces atherosclerotic events in patients at risk, including individuals with diabetes (1). The latest analysis from the Cholesterol Treatment Trialists' Collaboration further confirms the efficacy of more intensive lipid-lowering regimens in the attenuation of cardiovascular (CV) risk (2). Studies targeting major concerns regarding long-term statin treatment have shown its safety on issues of elevated transaminases, myopathy, and cancer (3,4). As for glucose metabolism, pravastatin was first reported to reduce diabetes occurrence among initial nondiabetic individuals enrolled in the WOSCOP (West of Scotland Coronary

Abbreviations and Acronyms

CHD = coronary heart disease

CI = confidence interval

CV = cardiovascular

HR = hazard ratio

ICD-9 = International Classification of Diseases-Ninth Revision

MACE = major adverse cardiovascular events

MI = myocardial infarction

NHI = National Health Insurance

NHIRD = National Health Insurance Research Database

Prevention) study (5), but the regard of excessive risk of incident diabetes soon emerged in the era of high-potency statins (6,7). A meta-analysis of 13 clinical trials showed that statin therapy by a mean of 4 years was associated with a higher incidence of diabetes (odds ratio: 1.09; 95% CI: 1.02 to 1.17) (8). Furthermore, the more-intensive regimens correlated with an increase in risk of diabetes in analyses from selected trials (9,10). However, the potential mechanisms by which statins influenced glucose homeostasis are still in question.

All reported meta-analyses used tabulated information instead of individual source data. Most trials incorporated into the meta-analyses enrolled subjects at higher CV risk or with documented vascular complications. The diagnoses and adjudications of diabetes, mostly based on reports of physicians or few occasions of abnormal fasting glucose, were not standardized (8). Studies involving more intensive treatment included only certain statins (9,10). The relative harm and benefit were explored simply in trials enrolling extremely high-risk patients but not in the general population at predominately lower risk. In addition, whether prognoses differ in subjects complicated with incident diabetes after exposure and the benefits of treatment against the risk of diabetes in clinical practice need to be elucidated (11). To address those gaps among trials, meta-analyses, and routine practices, we conducted a retrospective cohort study by using the Taiwan National Health Insurance Research Database (NHIRD).

Methods

Data source. The longitudinal data from 1997 to 2009 were obtained from the NHIRD consisting of 1 million subjects (≈5% sample of National Health Insurance [NHI] beneficiaries). Taiwan NHI is a universal, state-operated health program with the coverage of >98% of the population. The NHIRD collects all original NHI claims, which are updated and maintained regularly by National Health Research Institutes, and is open to scientific research after encryption of all personal information.

Study groups. From the NHIRD, individuals without endocrine disorders and naive to systemic steroid were selected. Men age ≥45 years and women age ≥55 years during 2000 to 2003 who continuously received statins ≥30 days during 2000 to 2003 and those naive to statins before 2004 were identified to build the cohort. Those who had follow-up <30 days, who had the presence of International

Classification of Diseases-Ninth Revision (ICD-9) codes of diabetes or exposure to antidiabetic medications, who had myocardial infarction (MI), or who received revascularization before the entry were excluded. The scheme of enrolling subjects before 2004 and excluding subjects with established coronary events was to ensure similar distributions of background risk between statin users and nonusers because the National Cholesterol Education Program recommends more aggressive management in patients at higher risk (12). Comorbidities were confirmed by ICD-9 codes. MI and ischemic stroke were ascertained by ICD-9 codes in the first position of the hospital discharge diagnoses. Ischemic stroke was further validated by the use of brain images or thrombolysis at the index admission. Hemodialysis was identified by the procedure claims. The Charlson index was assessed as the overall severity of comorbidities (13). Healthcare utilization was measured by the annual ambulatory care visits. From those naive to statins before 2004, the controls were matched to statin counterparts on a 4:1 ratio on the basis of age, sex, comorbid risk for atherosclerotic events listed in Table 1, and year of their entry into the cohort.

Endpoints and follow-up. Possible diabetes was first identified as the presence of ICD-9 coding for diabetes in the NHIRD, which has been validated (14,15). The diagnosis was then further ascertained by the continuous dispensing of antidiabetic medications for ≥30 days. Major adverse cardiovascular events (MACE) were the composite of MI and ischemic stroke. The follow-up started from the cohort entry to the date of in-hospital death, the last medical claim, or the prescription of any statin in the controls, whichever came first.

Risk–benefit studies. The composite of diabetes and in-hospital mortality was used for the overall risk–benefit assessment across various risk subgroups. Another outcome follow-up after diabetes development was created to evaluate whether statins before the diagnoses subsequently offered favorable outcomes. The diabetes outcome follow-up started from the date of continuous dispensing of antidiabetic medications for ≥30 days to the same definition of overall follow-up.

Statistical analysis. Baseline characteristics were compared by Student t test and chi-square test. Kaplan-Meier plots were generated, and the log-rank test was used to assess the difference between curves. Cox proportional hazards models were applied to estimate the crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). The data were linked and processed by Microsoft SQL Server 2008 (Microsoft Corporation, Redmond, Washington), and the statistical analyses were performed with the Statistical Package for the Social Sciences version 16 (SPSS Inc., Chicago, Illinois). A 2-tailed $p < 0.05$ was considered statistically significant for all analyses.

Results

Baseline characteristics. There were 8,412 and 33,648 eligible subjects in the statin and control groups, respec-

Table 1	Baseline Characteristics of the Subjects		
Variable	Statin (n = 8,412)	Control (n = 33,648)	p Value
Age, yrs	63 ± 9	63 ± 9	0.711
Women	4,199 (50)	16,500 (49)	0.149
Comorbid risk for atherosclerotic events			
Hypertension	6,241 (74)	24,824 (74)	0.437
CHD	3,600 (43)	14,623 (44)	0.273
Stroke	555 (7)	2,082 (6)	0.165
CKD	1,083 (13)	4,354 (13)	0.873
Hemodialysis	365 (4)	1,530 (5)	0.411
Low risk*	3,964 (47)	15,961 (47)	0.608
Secondary prevention	3,918 (47)	15,719 (47)	0.818
Other comorbidity			
Heart failure	706 (8)	2,923 (9)	0.390
Connective tissue disease	364 (4)	1,347 (4)	0.179
Hemiplegia	240 (3)	960 (3)	1.000
Charlson index	2 ± 1	2 ± 2	0.328
Ambulatory care visit, no. per year	28 ± 19	27 ± 35	0.789
Statins and doses			
Atorvastatin	4,133 (49)	NA	NA
Daily dose, mg	10 ± 4	NA	NA
Fluvastatin	2,542 (30)	NA	NA
Daily dose, mg	47 ± 20	NA	NA
Lovastatin	3,721 (44)	NA	NA
Daily dose, mg	21 ± 6	NA	NA
Pravastatin	2,357 (28)	NA	NA
Daily dose, mg	12 ± 7	NA	NA
Rosuvastatin	1,149 (14)	NA	NA
Daily dose, mg	8 ± 2	NA	NA
Simvastatin	3,833 (46)	NA	NA
Daily dose, mg	18 ± 6	NA	NA
≥2 statin exposure	5,185 (62)	NA	NA
Persistence			
≥6 months	5,856 (70)	NA	NA
≥3 yrs	2,002 (24)	NA	NA

Values are mean ± SD or n (%). *No risk factor or hypertension only.
CHD = coronary heart disease; CKD = chronic kidney disease; NA = not applicable.

tively, for this analysis. The mean age was 63 years, and approximately 49% of them were women. Most subjects had hypertension, followed by coronary heart disease (CHD). There were 6,324 subjects with no risk factor, and 13,601 subjects had hypertension alone. For those who had CHD as a diagnosis, none of them had prior MI or revascularization. In addition, 6% of subjects had been hospitalized for an ischemic stroke before their entry; a minority had chronic kidney disease or received hemodialysis. A smaller proportion of the subjects (47%) were qualified for the secondary prevention, reflecting the nature of the lower-risk cohort of this study than in meta-analyses. The baseline characteristics were similar with respect to age, sex, and comorbid atherosclerotic risk as the result of matching (Table 1). The distributions of other comorbidities and the overall severity evaluated by the Charlson index were similar, which were concordant with the healthcare utilization indexed by the
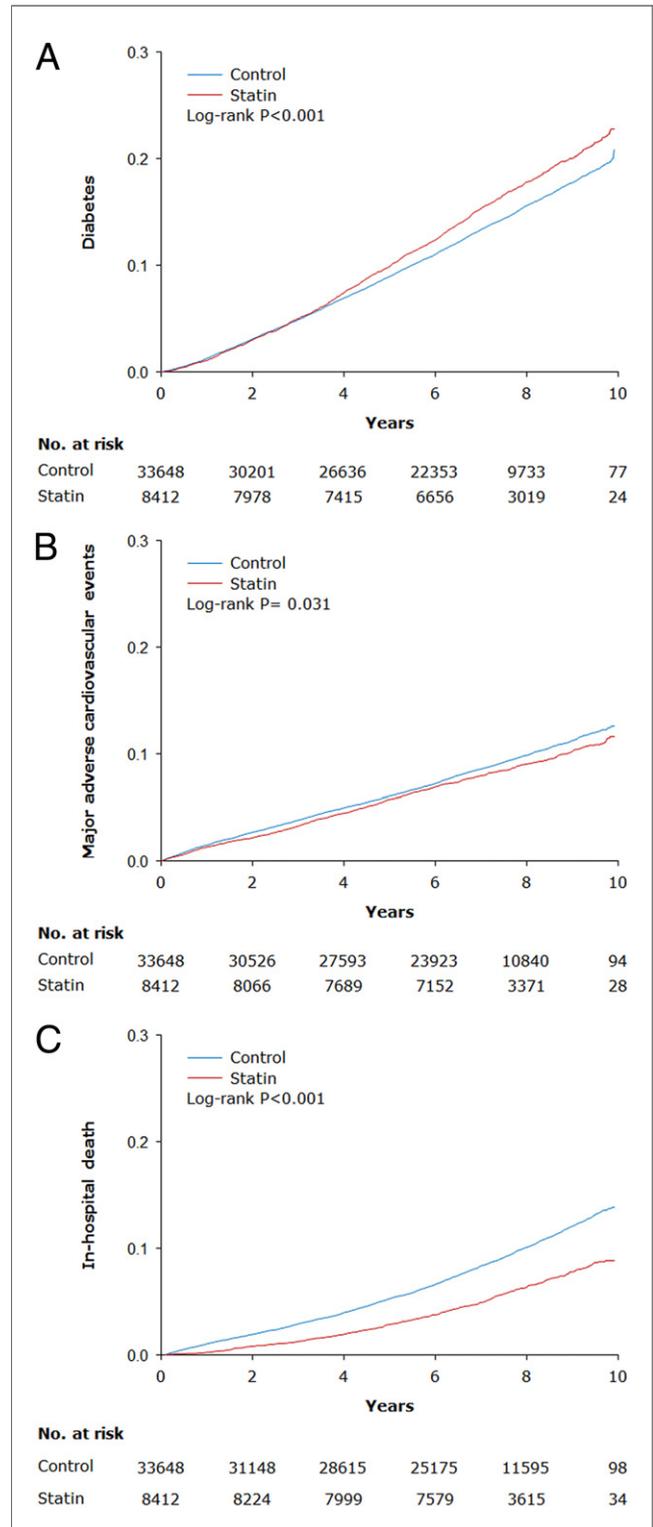
| Figure 1 | Kaplan-Meier Curves for Outcomes Among Statin and Control Groups |

(A) Cumulative incidences for newly developed diabetes in the statin and control groups were 22.7% and 20.8%, respectively. (B) Cumulative incidences for major adverse cardiovascular (CV) events (the composite of myocardial infarction [MI] and ischemic stroke) in the statin and control groups were 11.6% and 12.6%, respectively. (C) Cumulative incidences for in-hospital death from all causes in the statin and control groups were 8.8% and 13.8%, respectively.

annual ambulatory care visits. More than half of statin users had been exposed to ≥2 statins (32% had been exposed to ≥3 statins), and the mean daily doses were relatively small. The persistence of statins was considerably low.
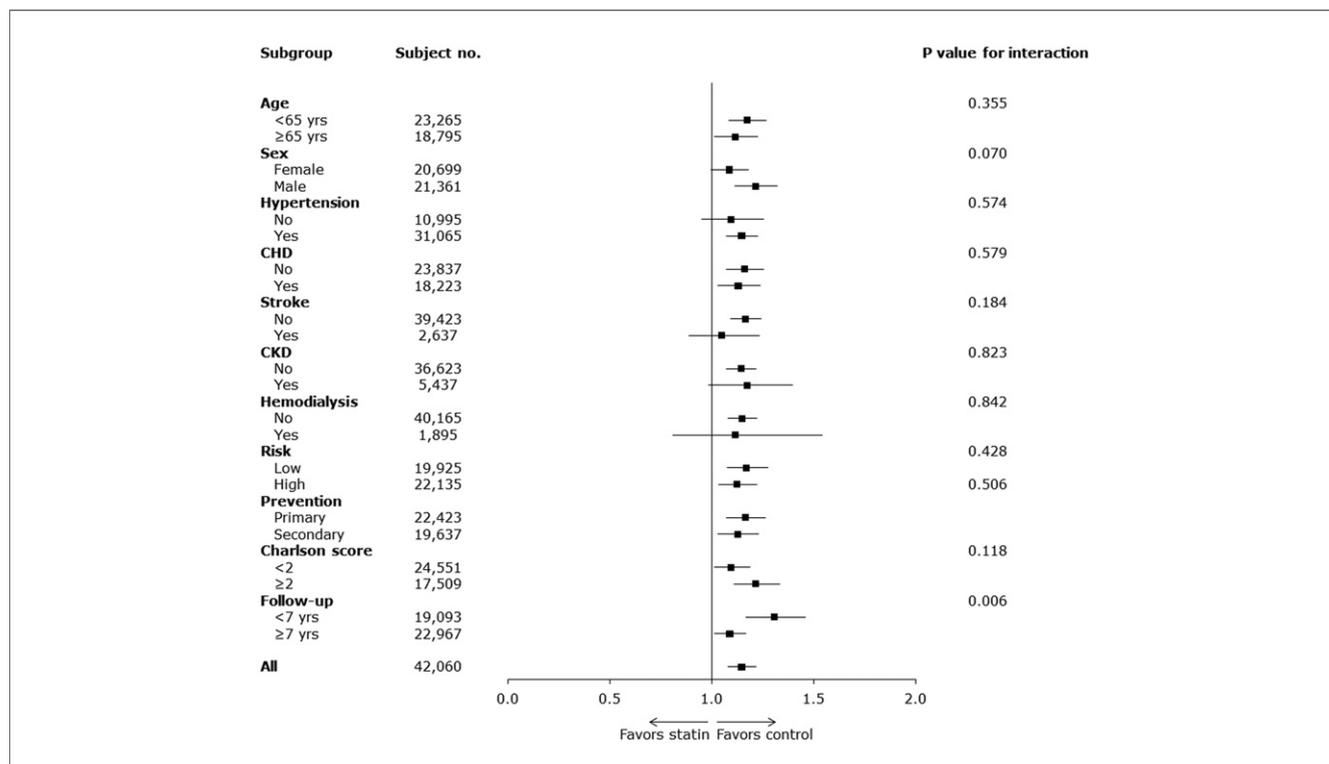
Endpoints. During the median follow-up of 7.2 years (interquartile range: 6.1 to 8.7 years), there were 5,754 cases of incident diabetes. Kaplan-Meier curves suggested statin use increased the hazards of diabetes occurrence (HR: 1.15; 95% CI: 1.08 to 1.22; p < 0.001). In addition, there were 769 MI cases, 2,961 new ischemic stroke cases, and 3,484 in-hospital deaths. Statin users had a reduction in risk for MI (HR: 0.82; 95% CI: 0.68 to 0.98; p = 0.028) and a trend for fewer ischemic strokes (HR: 0.94; 95% CI: 0.86 to 1.03; p = 0.176), leading to overall fewer MACE (HR: 0.91; 95% CI: 0.84 to 0.99; p = 0.031) and in-hospital deaths (HR: 0.61; 95% CI: 0.55 to 0.67; p < 0.001) (Fig. 1).

Subgroup analyses. The susceptibility to diabetes after statin therapy was similar across age, sex, comorbid risk for atherosclerotic events, and overall severity of comorbidities. Statins were significantly associated with an incremental risk for diabetes regardless of follow-up duration (Fig. 2).

The composite of diabetes and in-hospital mortality examined whether statin treatment offered preferable prognoses in subgroups according to overall CV risk. In both low-risk and primary prevention subgroups, the Kaplan-Meier plots suggested statin users sha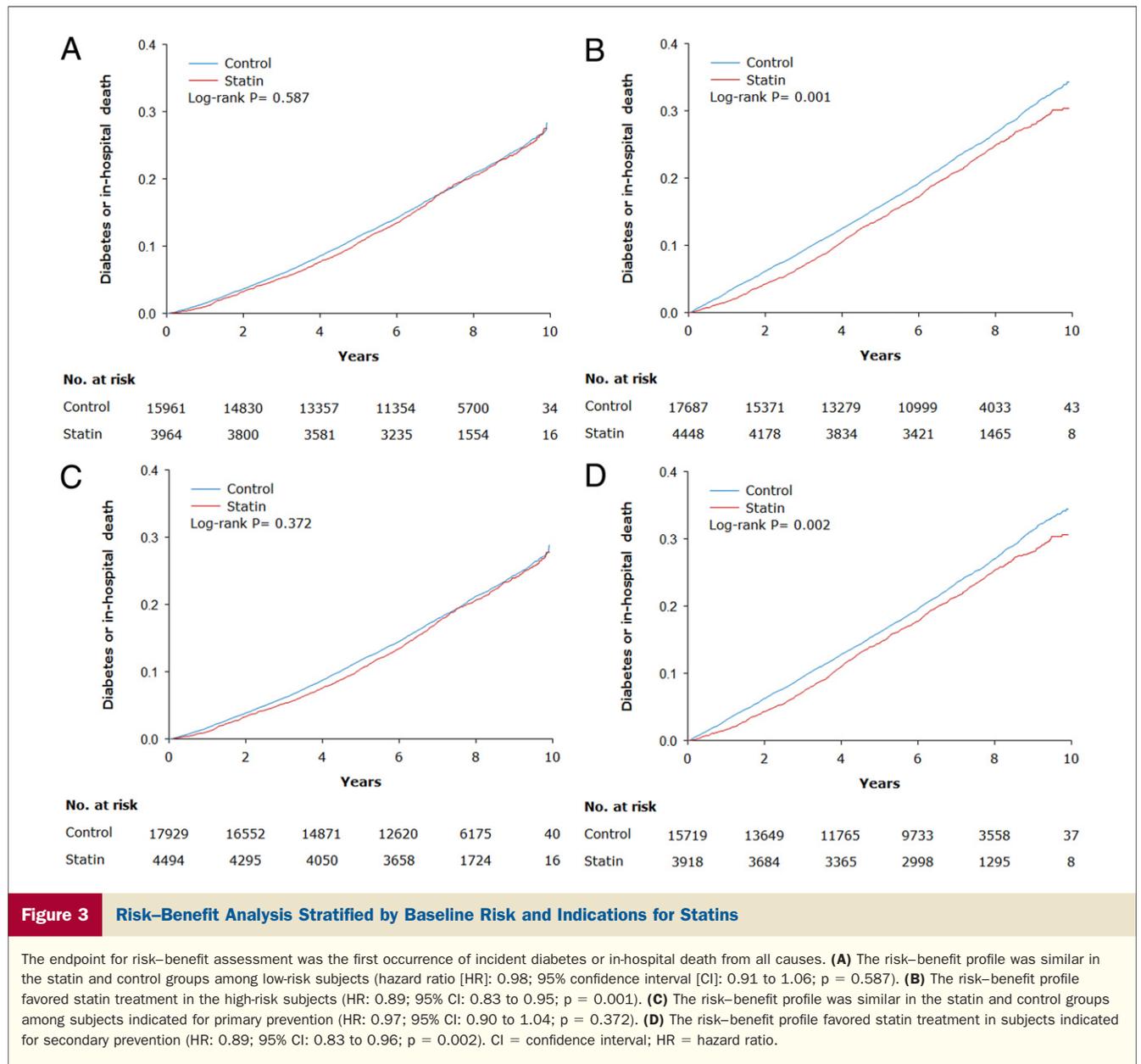red similar risk–benefit profiles with controls. Furthermore, compared with the control group, the benefit of statin use in preventing in-hospital fatalities outweighed the risk of developing diabetes in the high-risk subgroup (HR: 0.89; 95% CI: 0.83 to 0.95; p = 0.001) and in secondary prevention subjects (HR: 0.89; 95% CI: 0.83 to 0.96; p = 0.002) (Fig. 3).

Outcomes after developing diabetes. The cohort was recategorized according to the presence of diabetes and prior statin therapy. To evaluate the subsequent prognoses of diabetic subjects after exposure, 4 groups were created comprising nondiabetic controls (n = 29,332), diabetic controls (n = 4,316), diabetic patients with prior statin use (n = 1,387), and nondiabetic patients with prior statin use (n = 7,025). Among these 4 groups, the incidences of MACE were 12, 21, 16, and 12 per 1,000 person-years, respectively, and the annual in-hospital mortality rates were 1.4%, 2.0%, 1.6%, and 0.8%, respectively. Kaplan-Meier curves suggested that subjects who received statins without developing diabetes had significantly better outcomes, and those developing diabetes without prior statin use were at an increase in hazards of MACE and in-hospital death. Subjects treated with statins followed by diabetes occurrence had an increase in risk of MACE (HR: 1.30; 95% CI: 1.03 to 1.64; p = 0.025) and in-hospital death (HR: 1.38; 95% CI: 1.10 to 1.73; p = 0.005) compared with nondiabetic controls. Among diabetic patients, prior statin therapy

Subgroup	Subject no.		P value for interaction
Age			0.355
<65 yrs	23,265		
≥65 yrs	18,795		
Sex			0.070
Female	20,699		
Male	21,361		
Hypertension			0.574
No	10,995		
Yes	31,065		
CHD			0.579
No	23,837		
Yes	18,223		
Stroke			0.184
No	39,423		
Yes	2,637		
CKD			0.823
No	36,623		
Yes	5,437		
Hemodialysis			0.842
No	40,165		
Yes	1,895		
Risk			0.428
Low	19,925		
High	22,135		0.506
Prevention			
Primary	22,423		
Secondary	19,637		
Charlson score			0.118
<2	24,551		
≥2	17,509		
Follow-up			0.006
<7 yrs	19,093		
≥7 yrs	22,967		
All	42,060		

0.0 0.5 1.0 1.5 2.0
← Favors statin   Favors control →

Figure 2 **Subgroup Analysis for Incident Diabetes**

The risk of incident diabetes in the statin group compared with the control group (presented by hazard ratios and 95% confidence intervals) is shown, stratified by the baseline characteristics and the duration of follow-up. The low-risk group included subjects with no atherosclerotic risk factor or hypertension only. CHD = coronary heart disease; CKD = chronic kidney disease.
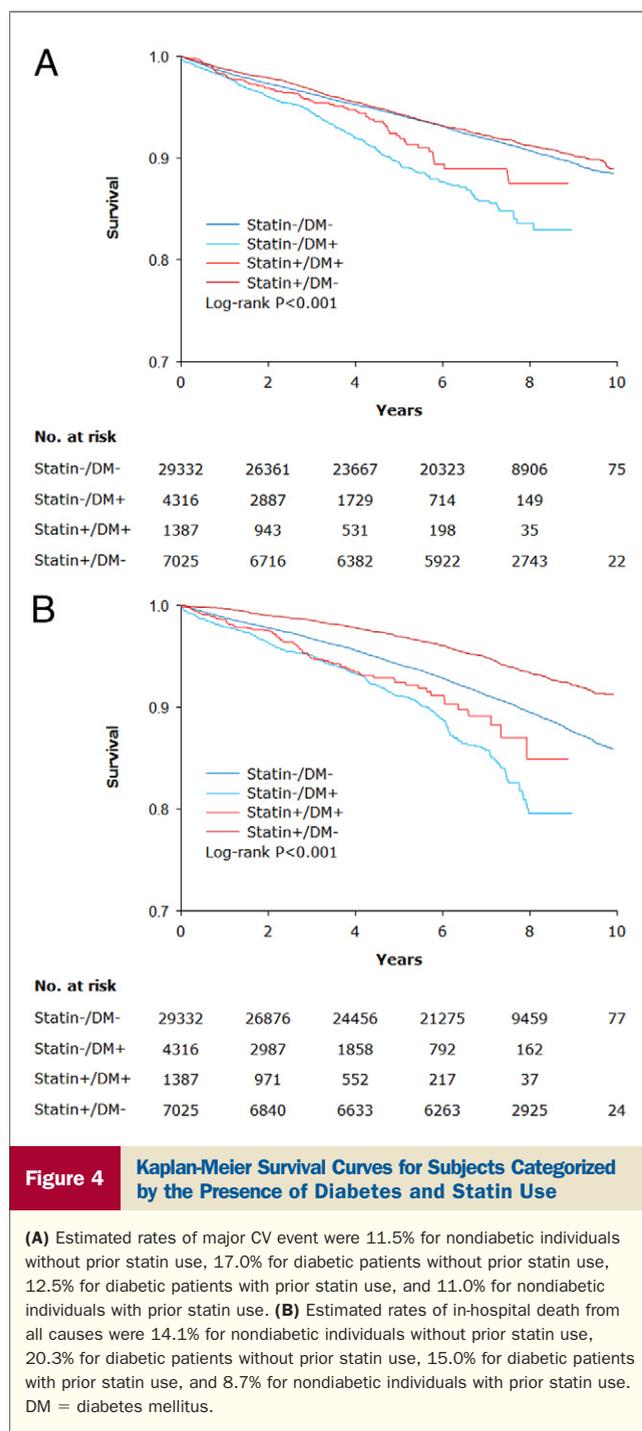
Figure 3   Risk–Benefit Analysis Stratified by Baseline Risk and Indications for Statins

The endpoint for risk–benefit assessment was the first occurrence of incident diabetes or in-hospital death from all causes. **(A)** The risk–benefit profile was similar in the statin and control groups among low-risk subjects (hazard ratio [HR]: 0.98; 95% confidence interval [CI]: 0.91 to 1.06; p = 0.587). **(B)** The risk–benefit profile favored statin treatment in the high-risk subjects (HR: 0.89; 95% CI: 0.83 to 0.95; p = 0.001). **(C)** The risk–benefit profile was similar in the statin and control groups among subjects indicated for primary prevention (HR: 0.97; 95% CI: 0.90 to 1.04; p = 0.372). **(D)** The risk–benefit profile favored statin treatment in subjects indicated for secondary prevention (HR: 0.89; 95% CI: 0.83 to 0.96; p = 0.002). CI = confidence interval; HR = hazard ratio.

provided an advantage in the reduction of MACE (HR: 0.75; 95% CI: 0.59 to 0.97; p = 0.027) and a trend for less in-hospital mortality (HR: 0.82; 95% CI: 0.64 to 1.04; p = 0.105) (Fig. 4). After accounting for background risk, incident diabetes after statin therapy was associated with an increased risk for in-hospital death overall but not in the high-risk and secondary prevention cohorts compared with the nondiabetic controls (Table 2).

Discussion

In this longitudinal cohort study, we found that statin exposure was associated with excessive risk of incident diabetes. The risk–benefit analyses favored statin use in the high-risk and secondary prevention subjects. Another principal result is that subjects developing diabetes after statin

therapy had higher rates of MACE and in-hospital death, but the hazard was insignificant in the high-risk and secondary prevention subjects.

Unlike in the WOSCOP study, suggesting a 30% risk reduction by pravastatin in men age <65 years (5), our results from the clinical-practice perspective were in line with the findings from the meta-analysis of clinical trials showing that statins were associated with an increased risk of newly developed diabetes (8). The absolute risk increase by statins was comparably small in both studies (0.3% in our study; 0.4% in the meta-analysis). However, most trials targeted specific CV outcomes but not primarily diabetes occurrence. Methods for diagnosing diabetes were not uniform across trials, and some adopted only physician-reporting cases or results from few occasions of fasting

Figure 4   Kaplan-Meier Survival Curves for Subjects Categorized by the Presence of Diabetes and Statin Use

(A) Estimated rates of major CV event were 11.5% for nondiabetic individuals without prior statin use, 17.0% for diabetic patients without prior statin use, 12.5% for diabetic patients with prior statin use, and 11.0% for nondiabetic individuals with prior statin use. **(B)** Estimated rates of in-hospital death from all causes were 14.1% for nondiabetic individuals without prior statin use, 20.3% for diabetic patients without prior statin use, 15.0% for diabetic patients with prior statin use, and 8.7% for nondiabetic individuals with prior statin use. DM = diabetes mellitus.

glucose. This might not reflect the true consequences in the real-world exposure of statins. Our study combined the clinical diagnoses and the confirmation from pharmacy claims. The hazard of developing diabetes was consistent across age, sex, and comorbidities. Furthermore, we explored the benefits of statin therapy in clinical practice. In general, treatment of statins prevented 1 fatal event in 202 subjects and led to 1 case of diabetes in 301 patients per year. However, the information should be reviewed with caution because the incidence of diabetes in our study was

21 per 1,000 person-years, which was relatively more than in other investigations (16,17). Ethnic differences in diabetes occurrence and susceptibility to statins were reported (17–19). Therefore, we may have overestimated the potential risk for diabetes against the benefits of statins, especially in the cohort with a lower diabetes incidence.

Statins carrying an increased risk for diabetes were also reported in postmenopausal women from the analyses of the Women's Health Initiative (19). All statins of varying potency correlated with hazards for diabetes. The women in our study shared a risk for diabetes that was similar to that for men after exposure to statins. Even though we enrolled women age ≥55 years, we could not identify whether they were menopausal or took hormone replacement therapy. In addition, a dose-dependent increment in the risk of incident diabetes after statin use was further suggested by the meta-analysis of 5 trials focusing on subjects at extremely high CV risk (10). For a mean follow-up of 4.9 years, intensive-dose regimens increased the risk of diabetes by 12% but reduced MACE by 16% compared with moderate doses. Our study did not explore the dose-dependent effect of statins because 62% of users had been exposed to ≥2 statins, as is common in clinical practice. On comparison of those who received only a single statin, the dose-dependent hazard was not found (HR: 1.01; 95% CI: 0.83 to 1.22; p = 0.938, low vs. high daily dose). Most physicians prescribed statins at medium or lower equipotency doses in routine practice (20), unlike in clinical trials. The long-term adherence was suboptimal even in high-risk subjects (21). Whether persistent high-dose statins have greater hazards than usual doses of statins among populations with lower CV risk requires further investigation.

There were 44% of subjects in the control group who had CHD as a diagnosis. Previous reports of disparities between clinical practices and trials suggested elderly persons, women, and comorbidities were negatively associated with statin use (22,23). In our subjects with CHD, the distributions of age and sex were similar, but the Charlson index was higher among controls (1.8 ± 1.6 vs. 2.0 ± 1.7, p < 0.001). After adjusting for the Charlson index, statins significantly attributed to the risk of diabetes (HR: 1.13; 95% CI: 1.03 to 1.24; p = 0.007) and the reduction of in-hospital death (HR: 0.64; 95% CI: 0.56 to 0.72; p < 0.001).

The mechanisms responsible for the increased risk of diabetes after statins were not the scope of our design. The pathway of interfering isoprenoids by statins leading to the attenuation of glucose transporter 4 expression was proposed (24,25). The evidence from the patient care database supported the cellular and animal findings that statin treatment significantly increased fasting plasma glucose in both nondiabetic and diabetic patients (26). However, there was still controversy over laboratory versus clinical results, especially whether it was the common off-target effects across all statins (27–29). Our results from 3,227 subjects who received a single statin were in agreement with the meta-analyses that incorpo-

Table 2	**Univariate and Multivariate Analyses of In-Hospital Deaths According to Status of Diabetes and Prior Exposure of Statins**			
	Nondiabetic Individuals Without Prior Statin Use	**Diabetic Patients Without Prior Statin Use**	**Diabetic Patients With Prior Statin Use**	**Nondiabetic Individuals With Prior Statin Use**
Overall cohort				
N	29,332	4,316	1,387	7,025
Crude	Reference	1.70 (1.51–1.91)	1.38 (1.10–1.73)	0.59 (0.54–0.66)
Adjusted*	Reference	1.91 (1.70–2.15)	1.54 (1.23–1.92)	0.58 (0.53–0.64)
High-risk cohort†				
N	15,481	2,206	728	3,720
Crude	Reference	1.45 (1.25–1.69)	1.11 (0.83–1.49)	0.61 (0.54–0.68)
Adjusted*	Reference	1.69 (1.45–1.96)	1.31 (0.98–1.75)	0.62 (0.55–0.70)
Secondary prevention cohort				
N	13,733	1,986	652	3,266
Crude	Reference	1.43 (1.22–1.67)	1.08 (0.79–1.47)	0.61 (0.53–0.69)
Adjusted*	Reference	1.68 (1.44–1.98)	1.28 (0.94–1.73)	0.62 (0.55–0.71)

Values are hazard ratios (95% confidence intervals). *Adjusted for age, sex, hypertension, CHD, stroke, chronic kidney disease, hemodialysis, and Charlson index. †One or more risk factor other than hypertension.

rated most available statins, suggesting statins as the class with little heterogeneity for an increased risk for diabetes (8,10). Other than rosuvastatin and fluvastatin (HR: 1.26; 95% CI: 1.00 to 1.59; p = 0.052), atorvastatin (HR: 1.58; 95% CI: 1.34 to 1.86; p < 0.001), lovastatin (HR: 1.77; 95% CI: 1.57 to 2.00; p < 0.001), pravastatin (HR: 1.69; 95% CI: 1.35 to 2.12; p < 0.001), and simvastatin (HR: 1.57; 95% CI: 1.31 to 1.86; p < 0.001) were hazards for diabetes compared with the control group.

The identification of factors attributing to new-onset diabetes after statin exposure may help physicians identify subjects who are susceptible to diabetes occurrence. Independent predictors such as age, baseline fasting glucose and triglycerides, body mass index, and hypertension were explored (5,8,9). Some of those variables were highly related to the consequences of endothelial dysfunction and insulin resistance, the precursors or markers of diabetes (30). Therefore, surveillance for abnormal glucose homeostasis should be persistent in all subjects taking statins.

Study strengths and limitations. With the use of the nationwide cohort database, the strengths of our design include the following: We provided a longer follow-up than clinical trials and helped to evaluate the long-term risk and benefit. The endpoints ascertained under the rigorous definitions may be a useful reference for clinicians. Our study was the first to investigate the risk and benefit of statins in the general population, and the robust results warrant the cautious evaluation of statin use in the low-risk population since the encouragement of primary prevention in the low-cost statin era (31). However, the findings and implications of our study should be interpreted within the context of several weaknesses. The investigation was retrospective, and subjects with established coronary events, who were mostly likely to benefit from statins, were excluded. The analyses may overlook the potentially favorable prognoses of diabetes with prior statin therapy in the secondary prevention cohort. The conclusions may not be generally applicable to other populations. However, our results were consis-

tent with the findings of published analyses across ethnicities and various CV risk groups. The mean daily dose was relatively lower than doses in clinical trials, and the dose-dependent relation between statins and diabetes could not be confirmed in our study. There was no individual information, such as family history of diabetes, tobacco use, and exact compliance to drugs, and no laboratory result was available in the claims database. Therefore, we could not extrapolate the association between incident diabetes and low-density lipoprotein cholesterol reduction and other metabolic profiles as found by other investigators. We used in-hospital all-cause mortality in this analysis because the encrypted NHIRD could not be linked to the national death registry to precisely capture all deaths. According to the health statistics of Taiwan, 20% of fatalities were due to CV diseases and in-hospital deaths accounted for 42% of overall mortality. Therefore, out-of-hospital deaths may bias our results. However, we explored the potential impacts of the unrecognized deaths with 2 sets of analyses by linking our data to the withdrawal certificate records; statin treatment showed superiority in all-cause mortality scenarios and noninferiority in the worst-case scenarios (Online Figs. 1 and 2). Finally, we enrolled subjects who received statins before 2004, when rosuvastatin and pitavastatin were not available. The odds ratio for developing diabetes was 1.18 (95% CI: 1.04 to 1.33) for rosuvastatin compared with the placebo in the pooled analysis (8). The reported phase III and IV studies that compared pitavastatin with statins had small sample sizes and short follow-ups (≤2 years) (32). The impact of pitavastatin on glucose metabolism requires further observation.

Conclusions

Statin use is associated with an increase in diabetes occurrence. However, the benefit of statin treatment overweighs the hazard in high-risk subjects and secondary prevention subjects. The outcomes of those who developed diabetes

after statin use are generally favorable in those subgroups. Therefore, continuous surveillance of signals of dysglycemia should be incorporated into the care program to optimize overall risk management.

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Key Words: diabetes ■ outcome research ■ statins.

▶ **APPENDIX**

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