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ORIGINAL RESEARCH

Evaluating Risk of Incident Diabetes Between Patients Who Used Lovastatin and Red Yeast Rice Prescriptions (LipoCol Forte): A Retrospective Cohort Study Based on a Real-World Database

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Objective: This study aimed to evaluate the risk of incident diabetes between people who used lovastatin and red yeast rice (RYR) prescriptions.

Methods: A retrospective cohort study was performed to analyze the real-world database of Taiwan's National Health Insurance. We identified the RYR cohort, which included 34,504 persons age 20 years or older who began their use of a RYR prescription in 2010–2014. A comparison cohort of 34,504 adults beginning the use of lovastatin was selected from the same dataset, which was matched by age and sex. Both cohorts had no diabetes before the use of the medications. Events of incident diabetes in 2000–2015 were ascertained from medical claims. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of incident diabetes associated with the use of RYR prescriptions were calculated.

Results: The incidences of diabetes for the RYR cohort and the lovastatin cohort were 1.01 and 2.59 per 100 person-years, respectively ($P < 0.0001$). Compared with the lovastatin cohort, the adjusted HR of incident diabetes was 0.46 (95% CI 0.43–0.50) for people who used RYR prescriptions. The association between reduced incident diabetes and use of RYR prescriptions was significant in various subgroups. There was a dose-response relationship between RYR prescriptions and the reduced risk of incident diabetes.

Conclusion: We raised the possibility that people who used RYR prescriptions may have a lower risk of incident diabetes compared with the lovastatin cohort.

Keywords: diabetes, lovastatin, red yeast rice, risk

Introduction

Due to the increasing number of diabetes patients and its economic burden all over the world,[1,2] identifying the risk factors and methods to prevent diabetes has become urgent. Although statin (hydroxymethylglutaryl-CoA reductase inhibitor) therapy is considered a relatively safe and well-tolerated method to effectively improve blood lipid levels and reduce cardiovascular events,[3] meta-analyses of randomized trials and cohort studies have suggested that statin therapy slightly increases the risk of new-onset diabetes.[4–9] An increased incidence of diabetes with statin therapy by providing evidence of a dose-dependent association has also been investigated.[5] Nevertheless, it was widely accepted that the clinical practice in patients with cardiovascular risk or existing cardiovascular disease should not change the treatment plan of using statins.[5,10]

In the clinical setting of traditional Chinese medicine, red yeast rice (RYR) has been frequently prescribed by physicians to improve blood lipid levels in patients with hyperlipidemia, and its therapeutic effects have been investigated.[11,12] Monacolin K (lovastatin) is one of the important components of scientifically processed RYR prescriptions (such as Xuezhikang, HypoCol, and LipoCol Forte) that has been proven to effectively lower levels of total cholesterol and low-density lipoprotein cholesterol.[13–15] Although the tolerance and safety of RYR use has been reviewed and studied,[16] the risk of diabetes in patients who used RYR has not been adequately evaluated.

There are many studies reporting the risk of diabetes in patients who used lovastatin, but the findings are controversial.[6,7,17–22] Some studies suggested lovastatin therapy increased the risk of incident diabetes,[6,17–19] while other studies did not find a significant association.[7,20,21] Another study suggested a reduced risk of diabetes in patients who used lovastatin.[22] However, information was unavailable on the comparison of the risk of incident diabetes between people who used lovastatin and RYR prescriptions. Using reimbursement claims data from Taiwan's National Health Insurance Program, we conducted a national retrospective cohort study with a real-world database to evaluate the risk of incident diabetes in people who used lovastatin and RYR prescriptions.

Methods
Source of Data
Our study was conducted using reimbursement claims data from Taiwan's National Health Insurance Program. This insurance program was started in 1995 and currently covers more than 99% of Taiwan's population (approximately 23 million people). The research data of Taiwan's National Health Insurance Program is a real-world database record of all the inpatient and outpatient medical services of beneficiaries as well as basic demographics, primary and secondary medical diagnoses, treatment procedures, prescribed medications and medical expenditures. This database has been evaluated previously,[23,24] and research articles based on it have been accepted in prominent scientific journals worldwide.[15,25]

Ethical Approval
For the protection of personal privacy, the reimbursement claims of insurance data used in this study were electronic information that was decoded with regard to patient identification for further academic access. Although the Health and Welfare Data Science Center, Ministry of Health and Welfare exempt such uses from informed consent, because patient identification was decoded and scrambled, this study was reviewed and approved by the Institutional Review Board of Taipei Medical University (TMU-JIRB-201905042; TMUJIRB-201902053; TMUJIRB-201710033).

Study Design
In this real-world database including a retrospective cohort of 23 million insured individuals, we identified 34,504 patients age 20 years or older, with their first use of RYR prescriptions between 2010 and 2014, and without a history of diabetes before the date of RYR use as the RYR cohort. During the same index period, 34,504 people age 20 years or older were matched by age and sex (with case-control ratio=1:1), and they had no history of diabetes before the date of lovastatin use as the lovastatin cohort. Patients with any diagnosis (including primary and secondary diagnoses during inpatient and outpatient care) of diabetes before the use of RYR prescriptions or lovastatin were excluded to ensure that all study participants were free of diabetes at the start of both cohorts. Follow-up started from the use of medication (RYR prescriptions or lovastatin) and lasted until censoring due to death, loss to follow-up, or other causes by December 31, 2015. Therefore, no immortal time bias exists in this study. Those who used RYR prescriptions and lovastatin in the same period were also excluded. We sought to evaluate the risk of incident diabetes between people who used lovastatin and RYR prescriptions during the follow-up period.

Measures and Definitions
By the definition of our previous study,[15] we defined people who visited clinics of traditional Chinese medicine and received a physician's prescription for RYR (LipoCol Forte) under the coverage of Taiwan's National Health Insurance Program. Unlike biochemical medications, the Chinese herbal medicine LipoCol Forte is an all-natural RYR extract that has been covered by Taiwan's National Health Insurance Program since 2010. Both physicians of conventional medicine and physicians of Chinese medicine can prescribe LipoCol Forte. Each capsule of LipoCol Forte contains 600 mg RYR, including the index component Monacolin K (lovastatin) 5.7 mg. Under a physician's standard directions, patients with hyperlipidemia (total cholesterol $\geq$200 mg/dl and/or low-density lipoprotein

cholesterol ≥130 mg/dl and/or triglyceride ≥200 mg/dl) take 2 capsules per day.

Patients' low income status was defined by qualifying for waived medical copayment as verified by the Ministry of Health and Welfare, Taiwan. We used physicians' diagnoses and the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) to define coexisting medical conditions and the main outcome of diabetes (ICD-9-CM 250). People who had one visit, two visits, and three visits related to outpatient care for diabetes were defined as diabetes cases in model 1, model 2, and model 3, respectively. In model 4, people admitted for inpatient care of diabetes were defined as diabetes cases. In model 5, people who used antidiabetic drugs were defined as diabetes cases. Coexisting medical conditions were determined from medical claims during the follow-up period and included hypertension (ICD-9-CM 401–405), mental disorders (ICD-9-CM 290–319), chronic obstructive pulmonary disease (ICD-9-CM 490, 491, 496), ischemic heart disease (ICD-9-CM 410–414), heart failure (ICD-9-CM 428), hyperlipidemia (ICD-9-CM 272.0, 272.1, 272.2, 272.4), stroke (ICD-9-CM 430–438), and liver cirrhosis (ICD-9-CM 571.2, 571.5, 571.6). Renal dialysis was defined by administration codes of the insurance program (D8 and D9). Charlson comorbidity index, emergency visits, and number of hospitalizations were also considered important factors of personal medical conditions in this study.

Statistical Analysis

Chi-square tests were used to compare sociodemographic characteristics and coexisting medical conditions, Charlson comorbidity index, emergency visits, and number of hospitalizations between people who used RYR prescriptions and lovastatin. We calculated the hazard ratios (HRs) with 95% CIs for risk of incidence diabetes between the RYR cohort and the lovastatin cohort by adjusting for age, sex, low income, hypertension, mental disorders, hyperlipidemia, ischemic heart disease, heart failure, liver cirrhosis, chronic obstructive pulmonary disease, and renal dialysis in the multivariate Cox proportional hazard models. We conducted sensitivity analyses with different definitions of incident diabetes to calculate the corresponding adjusted HRs of incident diabetes associated with the use of RYR prescriptions. The risk of incident diabetes between people who used RYR prescriptions and lovastatin were also calculated in the subgroups analyses by age, sex, Charlson comorbidity index,

number of medical conditions, emergency visits, and hospitalizations.

Results

The baseline characteristics of people who used RYR prescriptions and lovastatin before matching are shown in Table S1. After frequency matching, compared with the lovastatin cohort (Table 1), the RYR cohort had lower proportions of low income ($P < 0.0001$), ≥3 hospitalizations ($P < 0.0001$), ≥3 emergency visits ($P < 0.0001$), hypertension ($P < 0.0001$), ischemic heart disease ($P < 0.0001$), liver cirrhosis ($P = 0.0286$), stroke ($P < 0.0001$), heart failure ($P = 0.0023$), and renal dialysis ($P < 0.0001$). However, high proportions of mental disorders ($P < 0.0001$), chronic obstructive pulmonary disease ($P < 0.0001$), and Charlson comorbidity index scores of 0 ($P < 0.0001$) were found in the RYR cohort compared with the lovastatin cohort. The proportions of use of anti-hypertensive drug ($P < 0.0001$) and anticoagulant ($P < 0.0001$) were lower in RYR cohort than in lovastatin cohort.

In model 1 (Table 2), people who used RYR prescriptions had a lower risk of incident diabetes compared with people who used lovastatin (HR 0.51, 95% CI 0.49–0.52). The corresponding adjusted HRs of RYR prescriptions associated with incident diabetes in model 2, model 3, and model 4 were 0.49 (95% CI 0.47–0.51), 0.48 (95% CI 0.46–0.50), and 0.30 (95% CI 0.25–0.37), respectively. In model 5, a lower incidence of diabetes (use of antidiabetic drugs) was found in the RYR cohort compared with the lovastatin cohort (1.01 vs 2.59 per 100 person-years, $P < 0.0001$) during the follow-up period. People who used RYR prescriptions had a lower risk of incident diabetes than those who used lovastatin (HR 0.46, 95% CI 0.43–0.50). In Figure 1, the Kaplan-Meier model shows that the diabetes-free probability in patients who used RYR prescriptions is higher than in patients who used lovastatin (log rank test, $P < 0.0001$).

The HRs of RYR prescription associated with incident diabetes risk were 0.46 (95% CI0.43–0.50), 0.45 (95% CI 0.42–0.49), and 0.45 (95% CI 0.41–0.48) for excluding incidentdiabetes cases in the one month, three months, and six months of initial follow-up period, respectively.

Under the definition of diabetes as the use of antidiabetic drugs, Table 3 shows that the reduced HRs for incident diabetes associated with RYR prescriptions are 0.46 (95% CI 0.42–0.51) in women and 0.46 (95% CI 0.42–0.51) in men. The association between RYR prescriptions and the reduced risk of incident diabetes was significant in the following age groups: 20–39 (HR 0.32, 95% CI 0.22–0.47),

Table 1 Baseline Characteristics of People Use RYR Prescription or Lovastatin

	Lovastatin		RYR Prescription		p-value
	N=34,504		N=34,504		
Sex	n	(%)	n	(%)	1.0000
Female	19,178	(55.6)	19,178	(55.6)	
Male	15,326	(44.4)	15,326	(44.4)	
Age, years					1.0000
20–29	489	(1.4)	489	(1.4)	
30–39	2079	(6.0)	2079	(6.0)	
40–49	6739	(19.5)	6739	(19.5)	
50–59	14,407	(41.8)	14,407	(41.8)	
60–69	7723	(22.4)	7723	(22.4)	
70–79	2580	(7.5)	2580	(7.5)	
≥80	487	(1.4)	487	(1.4)	
Low income					<0.0001
No	33,288	(96.5)	33,795	(98.0)	
Yes	1216	(3.5)	709	(2.0)	
Calendar year of enrollment					<0.0001
2010	13,550	(39.3)	4866	(14.1)	
2011	10,504	(30.4)	7113	(20.6)	
2012	4120	(11.9)	8018	(23.2)	
2013	3539	(10.3)	7164	(20.8)	
2014	2791	(8.1)	7343	(21.3)	
Number of hospitalizations					<0.0001
0	28,095	(81.4)	28,852	(83.6)	
1	3670	(10.6)	3727	(10.8)	
2	1338	(3.9)	1016	(2.9)	
≥3	1401	(4.1)	909	(2.6)	
Number of emergency visits					<0.0001
0	24,586	(71.3)	24,090	(69.8)	
1	4907	(14.2)	5937	(17.2)	
2	2142	(6.2)	2188	(6.3)	
≥3	2869	(8.3)	2289	(6.6)	
Medical conditions					
Hypertension	12,531	(36.3)	9991	(29.0)	<0.0001
Mental disorders	6033	(17.5)	7079	(20.5)	<0.0001
COPD	3073	(8.9)	3372	(9.8)	<0.0001
Ischemic heart disease	3125	(9.1)	2782	(8.1)	<0.0001
Liver cirrhosis	1016	(2.9)	921	(2.7)	0.0286
Stroke	731	(2.1)	393	(1.1)	<0.0001
Heart failure	379	(1.1)	300	(0.9)	0.0023
Renal dialysis	261	(0.8)	80	(0.2)	<0.0001

(*Continued*)

Table 1 (Continued).

	Lovastatin		RYR Prescription		p-value
	N=34,504		N=34,504		
CCI, score					<0.0001
0	13,620	(39.5)	18,977	(55.0)	
1	13,112	(38.0)	6893	(20.0)	
2	3643	(10.6)	4363	(12.6)	
≥3	4129	(12.0)	4271	(12.4)	
Use of Antihypertensive drug*					<0.0001
No	27,149	(78.7)	28,923	(83.8)	
Yes	7355	(21.3)	5581	(16.2)	
Use of anticoagulants†					<0.0001
No	33,890	(98.2)	34,092	(98.8)	
Yes	614	(1.8)	412	(1.2)	

Notes: *Included beta-blocker, CCB, ACEI, and diuretics. †Included Coumadin, heparin, and enoxaparin.
Abbreviations: COPD, chronic obstructive pulmonary disease; RYR, red yeast rice.

40–49 (HR 0.34, 95% CI 0.27–0.42), 50–59 (HR 0.46, 95% CI 0.41–0.52), 60–69 (HR 0.48, 95% CI 0.42–0.55), and ≥70 (HR 0.56, 95% CI 0.48–0.66) years. RYR prescriptions were associated with a reduced risk of incident diabetes in subgroups of people with: 0 medical conditions (HR 0.52, 95% CI 0.48–0.57), 1 medical condition (HR 0.38, 95% CI 0.33–0.44), 2 medical conditions (HR 0.43, 95% CI 0.32–0.57), ≥3 medical conditions (HR 0.58, 95% CI 0.37–0.90), 0 emergency visits (HR 0.45, 95% CI 0.42–0.49), 1 emergency visit (HR 0.35, 95% CI 0.27–0.46), ≥2 emergency visits (HR 0.78, 95% CI 0.61–0.99), 0 hospitalizations (HR 0.48, 95% CI 0.44–0.52), 1 hospitalization (HR 0.27, 95% CI 0.20–0.36), and ≥2 hospitalizations (HR 0.70, 95% CI 0.55–0.91). In the subgroups of people with Charlson comorbidity index scores of 0 (HR 0.64, 95% CI 0.58–0.71), Charlson comorbidity index scores of 1 (HR 0.29, 95% CI 0.25–0.34), Charlson comorbidity index scores of 2 (HR 0.32, 95% CI 0.24–0.43), and Charlson comorbidity index scores ≥3 (HR 0.47, 95% CI 0.36–0.62), a reduced risk of incident diabetes was also associated with RYR prescriptions.

The characteristics of patients with use of RYR prescription and lovastatin before matching were shown in . The adjusted HRs of incident diabetes were associated with cumulative consumption of RYR prescriptions ≤60 capsules (HR

Table 2 Risk of Incident Diabetes Between People with Use of RYR Prescription and Lovastatin During the Follow-Up Period

Definitions of Diabetes[‡]		n	Pys	Incident Diabetes			
				Events	Incidence*	HR	(95% CI)[†]
Model 1	Lovastatin	34,504	95,633	14,426	15.1	1.00	(Reference)
	RYR	34,504	96,899	7013	7.24	0.51	(0.49–0.52)
Model 2	Lovastatin	34,504	97,376	13,631	14.0	1.00	(Reference)
	RYR	34,504	98,198	6234	6.35	0.49	(0.47–0.51)
Model 3	Lovastatin	34,504	98,474	13,157	13.4	1.00	(Reference)
	RYR	34,504	98,962	5809	5.87	0.48	(0.46–0.50)
Model 4	Lovastatin	34,504	146,753	769	0.52	1.00	(Reference)
	RYR	34,504	114,672	140	0.12	0.30	(0.25–0.37)
Model 5[‡]	Lovastatin	34,504	140,696	3642	2.59	1.00	(Reference)
	RYR	34,504	113,054	1145	1.01	0.46	(0.43–0.50)

Notes: *Per 100 person-years. [†]Adjusted for all covariates listed in Table 1; Model 1: one visit of outpatient care for diabetes; Model 2: two visits of outpatient care for diabetes; Model 3: three visits of outpatient care for diabetes; Model 4: admission to inpatient care for diabetes; Model 5: use of antidiabetic drugs. [‡]The HRs of RYR prescription associated with incident diabetes risk were 0.46 (95% CI 0.43–0.50), 0.45 (95% CI 0.42–0.49), and 0.45 (95% CI 0.41–0.48) for excluding incident diabetes cases in the one month, three months, and six months of initial follow-up period, respectively.
Abbreviations: CI, confidence interval; HR, hazard ratio; PYs, person-years; RYR, red yeast rice.

0.63, 95% CI 0.59–0.68), 61–120 capsules (HR 0.18, 95% CI 0.13–0.24), 121–180 capsules (HR 0.16, 95% CI 0.11–0.25), and ≥181 capsules (HR 0.08, 95% CI 0.05–0.11) during the follow-up period (Table S2). For people who used RYR prescriptions <500 mg, 500–999 mg, 1000–1499 mg, and ≥1500 mg per month on average during the follow-up period, the HRs of incident diabetes were 0.68 (95% CI 0.63–0.74), 0.08 (95% CI 0.05–0.13), 0.09 (95% CI 0.05–0.15), and 0.19 (95% CI 0.16–0.23), respectively, compared with the lovastatin cohort.

Discussion

This nationwide retrospective cohort study is the first study to compare the risk of incident diabetes between people who

Figure 1 Kaplan–Meier model for measuring the diabetes-free probability in patients with hyperlipidemia used lovastatin and RYR prescription (log rank test, P < 0.0001).

used RYR prescriptions and lovastatin during the follow-up period. The results showed that use of RYR was probably associated with a reduced risk of incident diabetes, with significant findings regardless of age, gender, or medical conditions. There was a dose-response relationship between RYR prescriptions and the reduced risk of incident diabetes.

In this study, we used some methods and procedures to analyze a real-world database for comparing the risk of incident diabetes in patients who used RYR prescriptions and lovastatin. To reduce the confounding bias, we used multivariate Cox proportional hazard regression to adjust for the potential confounders (age, sex, low income, medical conditions, emergency visits, hospitalizations, and Charlson comorbidity index) before validating the risk of incident diabetes between the RYR cohort and the lovastatin cohort. To validate new-onset diabetes cases, we conducted sensitivity analyses, which included various definitions of incident diabetes according to antidiabetic drugs and physician's diagnosis of diabetes during outpatient or inpatient medical visits. To evaluate reliability, the stratified analyses were performed to present the significant association between the use of RYR and reduced risk of incident diabetes in several subgroups. To avoid immortal time bias in the RYR cohort and the lovastatin cohort, we calculated the person-years start from the date of intake of medication until the end of study during the follow-up period. By calculating cumulative consumption of RYR prescriptions, we tried to evaluate the possible dose-response relationship between the use of RYR and reduced diabetes risk. However, it was possible that healthy
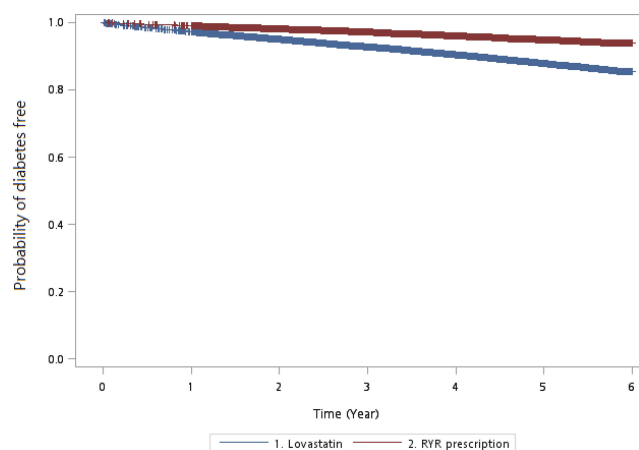
Table 3 The Stratified Analysis by Age, Sex, and Medical Conditions for the Association Between Risk of Incident Diabetes and RYR Prescription

		n	Pys	Incident Diabetes*			
				Events	Incidence†	HR	(95% CI)‡
Women	Lovastatin	19,178	78,774	1885	2.39	1.00	(Reference)
	RYR	19,178	62,334	569	0.91	0.46	(0.42–0.51)
Men	Lovastatin	15,326	61,922	1757	2.84	1.00	(Reference)
	RYR	15,326	50,719	576	1.14	0.46	(0.42–0.51)
Age, 20–39 years	Lovastatin	2568	10,706	165	1.54	1.00	(Reference)
	RYR	2568	8873	37	0.42	0.32	(0.22–0.47)
Age, 40–49 years	Lovastatin	6739	28,221	524	1.86	1.00	(Reference)
	RYR	6739	23,055	112	0.49	0.34	(0.27–0.42)
Age, 50–59 years	Lovastatin	14,407	59,535	1309	2.20	1.00	(Reference)
	RYR	14,407	47,738	383	0.80	0.46	(0.41–0.52)
Age, 60–69 years	Lovastatin	7723	30,576	1026	3.36	1.00	(Reference)
	RYR	7723	24,019	357	1.49	0.48	(0.42–0.55)
Age, ≥70 years	Lovastatin	3067	11,658	618	5.30	1.00	(Reference)
	RYR	3067	9369	256	2.73	0.56	(0.48–0.66)
Medical conditions, 0	Lovastatin	15,807	61,849	2320	3.75	1.00	(Reference)
	RYR	17,096	53,093	773	1.46	0.52	(0.48–0.57)
Medical conditions, 1	Lovastatin	12,395	50,669	1027	2.03	1.00	(Reference)
	RYR	11,597	38,632	273	0.71	0.38	(0.33–0.44)
Medical conditions, 2	Lovastatin	4563	20,121	203	1.01	1.00	(Reference)
	RYR	4399	15,845	70	0.44	0.43	(0.32–0.57)
Medical conditions, ≥3	Lovastatin	1739	8056	92	1.14	1.00	(Reference)
	RYR	1412	5484	29	0.53	0.58	(0.37–0.90)
Emergency visit0, 0	Lovastatin	24,586	96,763	3157	3.26	1.00	(Reference)
	RYR	24,090	75,222	937	1.25	0.45	(0.42–0.49)
Emergency visits, 1	Lovastatin	4907	21,061	254	1.21	1.00	(Reference)
	RYR	5937	20,795	93	0.45	0.35	(0.27–0.46)
Emergency visits, ≥2	Lovastatin	5011	22,872	231	1.01	1.00	(Reference)
	RYR	4477	17,037	115	0.68	0.78	(0.61–0.99)
Hospitalizations, 0	Lovastatin	28,095	112,725	3153	2.80	1.00	(Reference)
	RYR	28,852	92,208	983	1.07	0.48	(0.44–0.52)
Hospitalizations, 1	Lovastatin	3670	15,745	275	1.75	1.00	(Reference)
	RYR	3727	13,534	64	0.47	0.27	(0.20–0.36)
Hospitalizations, ≥2	Lovastatin	2739	12,226	214	1.75	1.00	(Reference)
	RYR	1925	7311	98	1.34	0.70	(0.55–0.91)
CCI score, 0	Lovastatin	13,620	54,368	1094	2.01	1.00	(Reference)
	RYR	18,977	58,710	785	1.34	0.64	(0.58–0.71)
CCI score, 1	Lovastatin	13,112	52,220	2117	4.05	1.00	(Reference)
	RYR	6893	23,359	203	0.87	0.29	(0.25–0.34)

(Continued)

Table 3 (Continued).

		n	Pys	Incident Diabetes*			
				Events	**Incidence[†]**	**HR**	**(95% CI)[‡]**
CCI score, 2	Lovastatin	3643	15,738	228	1.45	1.00	(Reference)
	RYR	4363	15,159	65	0.43	0.32	(0.24–0.43)
CCI score, ≥3	Lovastatin	4129	18,369	203	1.11	1.00	(Reference)
	RYR	4271	15,826	92	0.58	0.47	(0.36–0.62)

Notes: *Diabetes cases were defined as those who used antidiabetic drugs. [†]Per 100 person-years. [‡]Adjusted for all covariates listed in Table 1.
Abbreviations: CI, confidence interval; CCI, Charlson comorbidity index; HR, hazard ratio; PYs, person-years; RYR, red yeast rice.

worker effects may have existed in this dose-response relationship, and our study was an observational study that could not provide solid evidence. In previous studies,[13–15] RYR prescriptions had no dose-response effects on improving blood lipids and perioperative outcomes.

Cumulative evidence suggested a slightly increased diabetes risk in patients who used statins.[4–9] However, how statins increase the risk of diabetes is not completely understood. Some possible mechanisms were suggested by previous studies.[26–28] It was suggested that statin treatment decreased ubiquinone (CoQ10) status and cytochrome oxidase activity, which could independently alter insulin secretion.[26–28] Statins can also inhibit calcium mediated pancreatic insulin release and decrease expression of the β cell glucose transporters GLUT-2 and GLUT-4.[28] Because the therapeutic benefits of decreasing lipids are much more than the scant side effects, patients with cardiovascular risk or existing cardiovascular disease should not change a treatment plan involving the use of statins.[5] Individuals with hypercholesterolemia who fail to take their prescribed statin experience a substantially increased risk of fatal stroke.[10]

Although some studies suggested that RYR was relatively safe,[11,13,29] the potential side effects of RYR, such as muscle symptoms, central nervous system complaints, and diabetes, are essentially the same as those for statins.[30] However, the risks of diabetes or increased fasting glucose in patients who used RYR were not adequately evaluated previously. Some clinical trials used the combination of RYR and other nutraceuticals, such as garlic, berberine,[31,32] chitosan,[31] olive,[33] phytosterols,[34,35] and policosanols;[32] thus, the side effects of RYR could not be investigated independently. In addition, it is also not easy to predict or understand the side effect risks of RYR because of the high variability in monacolin content in various commercial RYR dietary supplements.[36–38] Unlike the dietary supplement, it was suggested that the content of RYR prescriptions with good manufacturing practice were relatively

stable and safe, such as Xuezhikang, HypoCol, and LipoCol Forte.[13–15,29] A clinical trial suggested that there were no differences between the HypoCol group and the placebo group with regard to glucose tolerance.[13] In a multicenter clinical trial, Xuezhikang decreased fasting blood glucose in patients with or without hyperlipidemia compared to baseline.[29] However, these two clinical trials were designed to investigate beneficial effects of lowering blood lipids and did not focus on the risk of incident diabetes in patients who used RYR.

Mechanisms regarding the lower risk of incident diabetes in patients who used RYR are still unclear. There were two possible explanations. First, people with hyperlipidemia who choose RYR prescriptions (with a visit to a traditional Chinese medicine practitioner) may have better knowledge, attitudes and practices regarding disease prevention and health promotion;[39] these factors could also contribute to the reduced incidence of diabetes. Second, RYR was effective against obesity-related inflammation, insulin resistance, and nonalcoholic fatty liver disease in mice, irrespective of monacolin K levels.[40] This animal study provided some potential evidence to support the hypothesis that the risk of incident diabetes was lower in people who used RYR prescriptions than in people who used lovastatin. However, the findings of our study could not be fully explained by the above reasons. The monacolin K in RYR prescriptions contains gamma-aminobutyric acid and various monacolins, phytosterols, and isoflavones,[11] and very little is known about the effects of these constituents on the fasting glucose. RYR prescriptions should be further evaluated carefully before their use as one of the alternative treatments for the management of dyslipidemia in the clinical setting of conventional medicine, although the evidence for the use of RYR prescriptions is in dyslipidemia versus other clinical conditions.[11–16]

Our study is mainly limited by the unavailable information of the adherence of patients to RYR prescriptions

and lovastatin. Although the high validity of Taiwan's National Health Insurance Program was evaluated,[23,24] we did not understand whether the study subjects took all of the medications. Second, because RYR prescriptions (LipoCol Forte) being covered by Taiwan's National Health Insurance Program since 2010, we could not evaluate the long-term risk of incident diabetes in people who used RYR prescriptions. Third, the incident diabetes and coexisting medical conditions were identified according to the physician's diagnosis during patients' visits for outpatient care and/or inpatient care. It is possible that people who had diabetes did not seek medical care. Therefore, we could not exclude the possibility that some people with diabetes were not identified in this study. Fourth, more than 30% of the participants are older than 60 years old who may need to take more than one medication and these medications may alter the level of blood glucose. It is also a study limitation that we could not consider all medications use of participants in this study. In addition, detailed information of socioeconomics, lifestyle (such as smoking and alcohol drinking), physical activity, eating habit, biochemical measures (such as fasting sugar and lipid level), and the severity of comorbid disease and were not available from the insurance database. Therefore, we could not evaluate the effects of these factors on the association between RYR prescriptions and reduced risk of diabetes. The unavailable data of knowledge, attitude, and practice regarding disease prevention were also limitations. Finally, while we have adjusted for various potential confounders in the multiple regression models, residual confounding could not be excluded.

In summary, we raised the possibility that people who used RYR prescriptions may have a lower risk of incident diabetes compared with people who used lovastatin. The reduced risk of incident diabetes varied within people with levels of cumulative consumption of RYR prescriptions. However, we could not infer the causality from the current results because of this study's limitations. The medication compliance of patients and undiagnosed diabetes were the main limitations that need to be cautiously considered when interpreting our data. Large multicenter trials with long-term evaluation are needed to provide solid evidence for the relationship between RYR prescriptions and incident risk of diabetes. We do not suggest that patients with hyperlipidemia use RYR prescriptions in the clinical setting of conventional medicine unless its safety is acceptable.

Abbreviations
ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; CI, confidence interval; HR, hazard ratio; RYR, red yeast rice.

Author Contributions
TLC, CCL: conception and design, analysis and interpretation of the data, drafting the article, critical revision of the manuscript for important intellectual content and final approval of the version to be published. CSL, JAL, CCY, LCS, YCC, CCS: conception and design, interpretation of the data, critical revision of the manuscript for important intellectual content and final approval of the version to be published. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure
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