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Original Research

Statin Use and the Risk for Incident Diabetes Mellitus in Patients with Acute Coronary Syndrome after Percutaneous Coronary Intervention: A Population-Based Retrospective Cohort Study in Taiwan

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ABSTRACT

Objectives: The purpose of this study was to examine the association between statin use by individuals and the risk for incident diabetes mellitus in patients with acute coronary syndrome (ACS) following percutaneous coronary intervention (PCI).
Methods: We conducted a retrospective cohort study of patients who were hospitalized for ACS between January 1, 2006, and December 31, 2010, and who had undergone PCI (n=30,665); the data were retrieved from the Taiwan National Health Insurance Research Database. A propensity score technique was used to establish a 1:1 matched cohort for statin users and non-statin users (n=9043 for each group). The risk for incident diabetes mellitus in statin users compared to non-statin users for patients with ACS after PCI was estimated by the multivariable Cox proportional hazards regression model.
Results: Statin use was associated with a significant increase of 27% in the risk for new-onset diabetes mellitus (adjusted hazard ratio [HR] 1.27, 95% CI 1.14 to 1.41) compared to non-statin use in the matched cohort. The matched cohort analysis indicated that almost all individual statins were associated with a statistically significant increase in the risk for new-onset diabetes mellitus compared to those without statin use.
Conclusions: Our study indicated an association between increased risk for new-onset diabetes mellitus and statin use. Because the benefits of statins in prevention of morbidity and mortality in patients with ACS are well-established, clinical decision making should not be changed for patients with existing cardiovascular disease in whom statin therapy is recommended.

Mots clés :
statine
diabète sucré
banque de données NHIRD (National Health Insurance Research Database)
étude de cohorte
innocuité des médicaments

RÉSUMÉ

Objectifs : L'objectif de la présente étude était d'examiner l'association entre l'utilisation des statines et le risque d'incidence du diabète sucré chez les patients souffrant d'un syndrome coronarien aigu (SCA) à la suite d'une intervention coronarienne percutanée (ICP).
Méthodes : Nous avons mené une étude de cohorte rétrospective auprès de patients qui avaient été hospitalisés pour un SCA entre le 1er janvier 2006 et le 31 décembre 2010, et qui avaient subi une ICP (n=30 665); nous avons extrait les données de la banque de données de la National Health Insurance Research de Taïwan. Nous avons utilisé une technique par score de propension pour établir une cohorte appariée 1:1 d'utilisateurs de statines et de non-utilisateurs de statines (n=9043 dans chaque groupe). Nous avons estimé le risque relatif d'incidence du diabète sucré chez les utilisateurs de statines par rapport aux non-utilisateurs de statines chez les patients souffrant d'un SCA après une ICP à l'aide du modèle de régression multivariée de Cox, soit le modèle à risques proportionnels.

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Résultats : L'utilisation de statines a été associée à une augmentation significative de 27 % du risque de diabète sucré de novo (rapport de risque [RR] ajusté 1.27, IC à 95 % 1.14 à 1.41) comparativement à la non-utilisation de statines dans la cohorte appariée. L'analyse de cohorte appariée a révélé que presque tous les individus utilisant les statines avaient montré une augmentation statistiquement significative du risque de diabète sucré de novo comparativement à ceux n'utilisant pas les statines.
Conclusions : Notre étude a montré une association entre l'augmentation du risque de diabète sucré de novo et l'utilisation des statines. Puisque les avantages des statines dans la prévention de la morbidité et de la mortalité chez les patients souffrant d'un SCA sont bien établis, il ne faudrait pas modifier la prise de décision clinique chez les patients souffrant déjà d'une maladie cardiovasculaire chez qui le traitement par statines est recommandé.

Introduction

The effectiveness of hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) in reducing the risk for cardiovascular mortality and morbidity in patients with acute coronary syndrome (ACS) has been well established (1,2). Although statins have been widely used and well tolerated in patients with ACS over the past decade, an association with increased risk for new-onset diabetes mellitus has been reported in various population groups (3–10). The U.S. Food and Drug Administration added reports of increased blood sugar and glycolated hemoglobin (A1C) levels to statin labels in 2012 (11). However, inconsistent results have been reported regarding statin use and the risk for incident diabetes mellitus. Coleman et al and Rajpathak et al have conducted meta-analyses of several statin trials, but they did not find significantly increased risks for incident diabetes mellitus with statin use (relative risk [RR] 1.03; 95% confidence interval [CI] 0.89 to 1.19; RR 1.06, 95% CI 0.93 to 1.25) (12,13). Sattar et al, Mills et al, Preiss et al and Culver et al also conducted meta-analyses of several statin trials, and they found a significantly increased risk for incident diabetes mellitus with statin use (RR 1.09; 95% CI, 1.02 to 1.17; odds ratio [OR] 1.09; 95% CI 1.02 to 1.09; OR 1.12; 95% CI 1.04 to 1.22; hazard ratio [HR] 1.48; 95% CI 1.38 to 1.59) (7,14–16).

In addition, there are inconsistent study results concerning the effects of individual statins on the risk for incident diabetes mellitus. The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) study showed that rosuvastatin use was not associated with a significantly increased risk for incident diabetes mellitus (RR 1.13; 95% CI 0.86 to 1.50) due to its small sample size. The Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study showed that rosuvastatin use significantly increased the risk for incident diabetes mellitus (RR 1.25; 95% CI 1.05 to 1.49) (17,18). The Heart Protection Study (HPS) and the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) showed that simvastatin use did not significantly increase the risk for incident diabetes mellitus (HR 1.14; 95% CI 0.98 to 1.33; RR 1.07; 95% CI 0.95 to 1.19) (19,20). The Treating to New Targets (TNT), Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) studies showed that atorvastatin use did not significantly increase the risk for incident diabetes mellitus (HR 1.10; 95% CI 0.94 to 1.29; HR 1.19; 95% CI 0.98 to 1.43; RR 1.15; 95% CI 0.91 to 1.44), but the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study showed that atorvastatin use significantly increased the risk for incident diabetes mellitus (HR 1.37; 95% CI 1.08 to 1.75) (21–24). The West of Scotland Coronary Prevention Study (WOSCOPS) suggested that pravastatin use was associated with a 30% lower risk of new-onset diabetes compared with placebo (HR 0.70; 95% CI 0.50 to 0.99), and the Long-term Intervention With Pravastatin in Ischaemic Disease (LIPID) study showed that pravastatin use did not significantly decrease the risk for incident diabetes mellitus (HR 0.95; 95% CI 0.77 to 1.16) (25,26).

There have been reports that incident diabetes mellitus associated with statin use may be more common in Asian populations, women and the elderly (14,27,28). These reports have not yet been explored in patients with ACS after percutaneous coronary intervention (PCI), especially in the Asian population, which may be at higher risk for incident diabetes. Additionally, polymorphisms of the cytochrome P450 enzyme are associated with lipid-lowering efficacy in Asian populations (29,30). Therefore, the objective of this study was to examine the association between statin use and the risk for incident diabetes mellitus in patients with ACS following PCI. Differing effects on glucose homeostasis by various statins with different lipophilicity and/or potency have been reported (31–34). Additionally, it is unclear from the effects of individual statins associated with incident diabetes mellitus in patients with ACS undergoing PCI which statins, specifically, may improve morbidity and mortality in these patients. This is the first study that used the National Health Insurance Database and propensity score matching method to assess the association between individual statin use and the risk for incident diabetes mellitus in patients with ACS following PCI.

Methods

We conducted a retrospective cohort study of patients hospitalized for ACS between January 1, 2006, and December 31, 2010. This nationwide population-based cohort study was based on patient data obtained from the Taiwan National Health Insurance Research Database (NHIRD) from 2005 to 2011 under the national health insurance system. The NHIRD includes all claims data from the National Health Insurance program in Taiwan, which covers more than 99% of the entire Taiwanese population of 23.7 million. Because the NHIRD consists of deidentified secondary data and is released to the public for research purposes, the study was exempt from full review by the Institutional Review Board.

Study Population

We identified all patients who were hospitalized for ACS between January 1, 2006, and December 31, 2010 (N=230,830) from the NHIRD. In this study, patients with ACS were defined as those who had primary discharge diagnosis codes of 410.xx, 411.xx, or 414.xx based on the International Classification of Diseases, 9th Revision (ICD-9-CM) codes. Patients who had been previously admitted to the hospital due to ACS in 2005, who were younger than 18 years of age, had unknown discharge dates for the index ACS event and had not undergone PCI and patients with histories of diabetes mellitus before or during the index ACS event were excluded from our study. Patients with PCI were identified by the ICD-9-CM procedure codes of 3601, 3605 or 3606. Patients with histories of diabetes mellitus were defined as having at least 1 NHI ambulatory claim record or 1 inpatient record of the following diagnosis code,