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Effects of metformin treatment on the risk of acute myocardial infarction

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Metformin, a cornerstone in the pharmacologic management of type 2 diabetes mellitus (T2DM), continues to be one of the most widely utilized antidiabetic agents globally. Beyond its primary role in glycemic control, metformin has demonstrated a variety of pleiotropic effects in both clinical and experimental settings. Among these, its cardiovascular protective properties have attracted considerable attention. The purpose of this study was to investigate the benefits of metformin in acute myocardial infarction (AMI) prevention in patients with T2DM. This retrospective cohort study utilized data from Taiwan's National Health Insurance Research Database, spanning the years 2000 to 2013. A total of 9186 patients with T2DM who were prescribed metformin were identified as the exposed group, while an equal number of patients with T2DM who had not received metformin served as the comparison (non-exposed) group. AMI was defined as the primary outcome of interest. To investigate the relationship between metformin use and AMI risk in patients with T2DM, hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were estimated using a Cox proportional hazards model. The analysis included 9186 metformin users and an equal number of non-users, we identified 282 and 339 AMI cases, respectively, for incidence rates of 3.36 and 4.15 per 1000 person years, respectively. Adjusted HR (95% CI) for metformin treatment and incident AMI was 0.76 (0.41–0.96). This negative association was consistently observed in both sexes [adjusted HR (95% CI) was 0.72 (0.56–0.97) for males adjusted HR (95% CI) was 0.87 (0.54–0.94) for females]. In summary, metformin treatment reduced the risk of AMI in patients with T2DM. These findings suggest that metformin may serve a dual role in both managing hyperglycemia and reducing cardiovascular risk.

Keywords Acute myocardial infarction, Cohort study, Metformin, Type 2 diabetes

Cardiovascular disease (CVD) remains the foremost cause of mortality and a leading contributor to long-term disability on a global scale. According to the Global Burden of Disease Study, CVD was responsible for an estimated 19 million deaths and 438 million disability-adjusted life years (DALYs) in 2021[1]. Among individuals with type 2 diabetes mellitus (T2DM), CVD—including myocardial infarction (MI), stroke, and ischemic heart disease—represents a major clinical complication. Poor glycemic control significantly elevates cardiovascular risk in this population and perpetuates a cycle of recurrent CVD events[2].

As a biguanide compound, metformin is currently the most widely used oral agent for managing hyperglycemia in type 2 diabetes[3]. In addition to its role in glycemic control, preclinical evidence suggests that metformin may influence mitochondrial oxidative phosphorylation and mitigate intracellular calcium imbalance within cardiovascular tissues—mechanisms that play a critical role in the development of atherosclerosis[4]. Therefore, most guidelines recommended metformin as the first-line therapy for T2DM[5] but also previous clinical trials have shown that metformin is associated with a reduction in major adverse cardiovascular events and cardiovascular mortality[6–9]. In diabetic patients, prolonged metformin therapy may improve cardiovascular outcomes by promoting weight loss, improving insulin resistance, reducing metabolic syndrome severity, and lowering both total and low-density lipoprotein (LDL) cholesterol levels[6–8,10]. Notably, in animal models of MI,

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the administration of metformin potently limits ischemia-reperfusion injury (IRI) and reduces infarct size[11]. In human populations, the UK Prospective Diabetes Study (UKPDS) showed lower risk of AMI in metformin users than in participants on diet therapy alone[12]. However, meta-analyses of randomized controlled Trials have not demonstrated a reduced frequency of cardiovascular events or death in the metformin versus non-metformin group[13–15]. Accordingly, in this article, we investigated whether metformin administration in patients with T2DM is associated with cardio protection to AMI.

Methods

Data source

The present study was a retrospective cohort study using universal health care data from the National Heath Insurance Research Database (NHIRD) in Taiwan[16,17]. NHIRD is a population-based database derived from original claims data of the National Health Insurance (NHI) program. The data in the NHIRD contain demographic data, including patients' sex, age, disease diagnoses, prescriptions, and details of each outpatient visit or their inpatient care. Disease diagnoses recorded in the database were classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Data for the present study were extracted from the Longitudinal Health Insurance Database 2000 (LHID 2000), a representative subset of the National Health Insurance Research Database (NHIRD) comprising one million individuals randomly selected from the full registry between January 1, 2000, and December 31, 2013. Previous validation studies have shown no significant differences in age, sex, or healthcare expenditures between the LHID cohort and the general NHIRD population[16].

As this study used de-identified secondary data with no direct patient contact, the requirement for informed consent was waived by the Institutional Review Board of Cathay General Hospital, Taipei, Taiwan. Ethical approval for this study was granted by the same board (IRB No. CGH-P107074). All procedures conducted adhered to applicable ethical standards and regulatory guidelines.

Study subjects

Eligible subjects were selected from the NHIRD between January 1, 2000 and December 31, 2006 and met the following criteria: (i) age ≥ 30 years; (ii) presence of T2DM, based on the record of hospital admission with a diagnostic code of T2DM (ICD-9-CM 250); and (iii) receipt of a prescription of antidiabetic drugs for a period exceeding 180 days. In the present study, patients have been prescribed antidiabetic drugs for at least two times to reduce immortal time bias[18]. In the current study, patients with T2DM who received metformin treatment were defined as the exposed cohort and patients with T2DM without prescription of metformin were characterized as the non-exposed cohort. To ensure cohort accuracy, several exclusion criteria were applied. Patients with a diagnosis of type 1 diabetes mellitus (ICD-9-CM code 250.x3), those with a T2DM diagnosis prior to the year 2000, individuals prescribed metformin for 180 days or less, and patients younger than 30 years of age were excluded from the analysis. Additionally, to minimize the risk of misclassifying pre-existing retinal disorders, we excluded individuals diagnosed with nonproliferative diabetic retinopathy, sight-threatening diabetic retinopathy, or diabetic macular edema within the first year following initiation of antidiabetic therapy.

Ascertainment of AMI

The primary outcome was defined as a first-time hospitalization with a principal diagnosis of acute myocardial infarction (AMI; ICD-9-CM codes 410–410.92) occurring between January 1, 2007 and December 31, 2013. To ensure the accuracy of the diagnosis of AMI, we further reviewed procedures (e.g., coronary artery bypass grafting) and prescriptions of antiplatelet agents (e.g. clopidogrel) during admission and at the first outpatient visit after discharge. The diagnosis of AMI in the NHIRD has been validated in previous studies[19].

Covariate adjustment

Demographic data, preexisting comorbidities, and concurrent medication prescriptions were included as covariates. To determine the presence of comorbid conditions, we reviewed inpatient and outpatient claim records during the cohort entry period. Conditions of interest included hypertension, hyperlipidemia, chronic obstructive pulmonary disease (COPD), chronic kidney disease, heart failure, and diagnoses related to alcohol use. Concomitant medications considered in the analysis included antihypertensive agents, statins, aspirin, and nonsteroidal anti-inflammatory drugs (NSAIDs). To minimize baseline differences between the two groups, we conducted a 1:1 propensity score matching (PSM) procedure. Propensity scores were estimated for each individual using a logistic regression model that incorporated age, sex, index date, and preexisting comorbidities as covariates. In this study, chronic obstructive pulmonary disease (COPD) was used as a proxy for smoking status; diagnoses related to alcoholism and alcohol use disorders were adopted as indicators of alcohol consumption; and hypertension together with hyperlipidemia served as surrogate markers for obesity. Given that chronic kidney disease and heart insufficiency are contraindications to metformin therapy[20,21], we included chronic kidney disease and heart failure to the propensity score for adjustment.

Statistical analysis

Baseline characteristics between the metformin and non-metformin groups were compared using standardized mean differences (SMD)[22]with an SMD ≥ 0.1 suggesting a meaningful imbalance between groups. To evaluate the association between metformin use and the risk of acute myocardial infarction (AMI) among patients with type 2 diabetes mellitus (T2DM), we applied Cox proportional hazards regression models adjusted for the propensity score to estimate hazard ratios (HRs) along with 95% confidence intervals (CIs). We further conducted stratified analyses by sex to assess whether the association remained consistent across gender subgroups. All statistical

Variable	Non-exposed cohort n= 9186	Exposed cohort n= 9186	SMD
Sex			0.000
Male	46.80	46.80	
Female	53.20	53.20	
Age, year			0.000
30–49	32.90	32.90	
50–69	53.90	53.90	
≥ 70	13.20	13.20	
Comorbidities			
Hypertension	66.64	71.93	0.046
Hyperlipidemia	46.33	56.65	0.006
COPD	45.57	48.31	0.012
Chronic kidney disease	14.52	12.80	0.050
Heart failure	18.48	16.03	0.048
Alcoholism or alcohol-related disorders	14.51	15.75	0.032
Use of co-medications (%)			
Statins	38.04	47.87	0.053
Aspirins	22.24	25.15	0.006
Anti-hypertensive agents	29.62	30.32	0.010
NSAIDs	6.36	7.31	0.046

Table 1. Baseline characteristics in both exposed (use of metformin) and non-exposed (non-use of metformin) cohorts. Propensity score-matched[+] cohorts. *COPD* chronic obstructive pulmonary disease, *NSAIDs* non-steroidal anti-inflammatory drugs, *SMD* standardized mean difference. †The propensity score, which represents the probability of receiving metformin treatment, was calculated for each patient by using a logistic regression model with covariates of age, sex, baseline comorbidities, including hypertension, hyperlipidemia, chronic obstructive pulmonary disease, chronic kidney disease, heart failure, and alcoholism or alcohol-related disorders, as well as use of co-medications, including antihypertensive medications, statins, aspirins, anti-hypertensive agents, and non-steroidal anti-inflammatory drugs (NSAIDs).

Variable	No. of patients	No. of PYs	No. of AMI	Incidence rate (per 1000 PYs)	Adjusted HR (95% CI)
Non-use of metformin cohort	9186	81,695.00	339	4.15	1.00 (reference)
Use of metformin cohort	9186	83,838.00	282	3.36	0.76 (0.41–0.96)

Table 2. Risk of acute myocardial infarction (AMI) associated with Metformin treatment in patients with type 2 diabetes mellitus. Hazard ratios were adjusted for the propensity score. *PYs* person-years, *HR* hazard ratio, *CI* confidence interval.

tests were two-sided, with a significance threshold set at $\alpha = 0.05$. Analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC, USA).

Results

A detailed comparison of baseline demographic factors, comorbidity profiles, and co-medication usage between the exposed cohort (metformin users) and the non-exposed cohort (non-users) is presented in (Table 1). There were no significant differences in the distributions of age and sex between the exposed and non-exposed cohorts due to the matching scheme. However, the exposed cohort had significantly higher prevalence of comorbidities of hypertension, hyperlipidemia, COPD, and alcoholism or alcohol-related disorders, and higher proportions of use of co-medications of statins, aspirins, anti-hypertensive agents, and NSAIDs than the non-exposed cohort. By contrast, the exposed cohort had lower prevalence of chronic kidney disease and heart failure than the non-exposed cohort.

As shown in Table 2, the incidence of acute myocardial infarction (AMI) was lower among patients with type 2 diabetes mellitus (T2DM) receiving metformin therapy (3.36 per 1,000 person-years) compared to those not receiving metformin (4.15 per 1,000 person-years). After adjusting for confounding factors, metformin use was associated with a reduced risk of AMI, with an adjusted hazard ratio (HR) of 0.76 (95% confidence interval [CI], 0.41–0.96).

Table 3 presents the results of stratified analyses by sex, which were consistent with the overall findings. In both male and female patients with type 2 diabetes mellitus (T2DM), metformin use was associated with a reduced risk of acute myocardial infarction (AMI) compared to non-use. The adjusted hazard ratio (HR) was 0.72 (95% CI: 0.56–0.97) in males and 0.87 (95% CI: 0.54–0.94) in females. Taken together, both primary

Variable	No. of patients	No. of PYs	No. of AMI	Incidence rate (per 1000 PYs)	Adjusted HR (95% CI)
Men					
Non-use of metformin	4887	43,499.00	220	5.06	1.00 (reference)
Use of metformin	4887	44,658.00	180	4.03	0.72 (0.56–0.97)
Women					
Non-use of metformin	4299	38,196.00	119	3.12	1.00 (reference)
Use of metformin	4299	39,180.00	102	2.60	0.87 (0.54–0.94)

Table 3. Risk of acute myocardial infarction (AMI) in relation to use of Metformin treatment stratified by sex. Hazard ratios were adjusted for the propensity score. *PYs* person-years, *HR* hazard ratios, *CI* confidence interval.

analysis and subgroup analysis demonstrated consistent findings that metforment treatment in patients with T2DM was associated with a decreased risk of AMI.

Discussion

This nationwide cohort study based on medical claims data made available by Taiwan's NHIRD demonstrated that metformin treatment in patients with T2DM had a decreased risk of AMI as compared with those without use of metformin. This cardioprotective effect to AMI associated with clinical use of metformin prescription consistently observed in both sexes.

Coronary microvascular dysfunction (CMD) is commonly observed in individuals with diabetes and is considered a key manifestation of diabetes-related microangiopathy[23]. The dysregulation of microvascular function is a persistent feature across various states of hyperglycemia and insulin resistance, primarily due to the heightened susceptibility of microvessels to oxidative stress and inflammation driven by elevated glucose levels[24]. Both systemic and localized inflammatory responses are critically involved in the pathogenesis and progression of cardiovascular disease (CVD), contributing to the transition from early endothelial dysfunction to overt clinical syndromes[25]. In addition to traditional risk factors, several acute and chronic conditions—such as psychological stress, autoimmune disorders, infections, and aging—can trigger endothelial injury and impair vascular function. The resulting low-grade vascular inflammation accelerates atherogenesis and CVD progression. In this context, metformin has shown anti-inflammatory properties, including suppression of cell adhesion molecules in individuals with dysregulated glucose metabolism. Beyond glycemic control, metformin therapy exerts beneficial effects by decreasing systemic inflammation and oxidative stress, which may underlie its observed cardioprotective effects in diabetic populations[26]. Moreover, at doses relevant to clinical practice, metformin has been associated with protective effects in a range of myocardial conditions, such as myocardial ischemic injury[27] diabetic cardiomyopathy[27] cardiotoxicity[28] and ventricular dysfunction/heart failure[29,30]. A central mechanism by which metformin confers cardioprotective benefits involves the activation of AMPK, leading to reduced inflammation and oxidative stress—both key contributors to myocardial pathologies[31,32]. With respect to cardioprotection in AMI, several preclinical studies have demonstrated that metformin treatment can induce acute infarct size reduction and improved cardiac function[33,34]. Overall, the findings of the present study are in line with findings from previous studies[6–9] that metformin was effective in reducing the risk of cardiovascular events, in particular for AMI.

This study has several notable strengths. First, we utilized a nationwide, comprehensive prescription claims database rather than relying on self-reported medication use, thereby reducing the risk of recall bias. Additionally, the NHIRD, being a population-based dataset with universal coverage under a single-payer healthcare system, captures a highly representative sample of Taiwan's general population. This enabled us to conduct analyses in a real-world context with minimal selection bias.

Nevertheless, several limitations inherent to the use of claims-based data should be acknowledged[35]. Information on key clinical risk factors for acute myocardial infarction (AMI)—including smoking habits, blood pressure levels, and measures of obesity—was unavailable in the dataset. Moreover, laboratory data such as lipid profiles were not accessible, which restricted our ability to assess important biomarkers. Consequently, the possibility of residual confounding cannot be excluded. Another limitation is that medication exposure was inferred from dispensed prescription records and may not accurately reflect actual medication adherence or over-the-counter drug use, potentially introducing exposure misclassification.

Conclusions

In summary, this population-based study revealed that metformin treatment reduced the risk of AMI in patients with T2DM. Metformin appears to exert cardiovascular protective effects in addition to its established role in glycemic control. A deeper understanding of the pathways through which metformin exerts its diverse cardiovascular and metabolic effects may enhance our insight into cardiovascular disease mechanisms and support the development of novel cardioprotective therapies or interventions.

Data availability

The data sets used in the present study are not available due to the ownership of the nationwide insurance claims dataset by the Ministry of Health and Welfare in Taiwan. Correspondence and requests for the data should be addressed to the corresponding author Prof. Chien-An Sun.

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Author contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by C-C. C., Y-C. C., C-A. S. Data analyses were conducted by J-Y. C. All authors read and approved the

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Declarations

Competing interests
The authors declare no competing interests.

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