ORIGINAL RESEARCH

Use of Spontaneous Reporting Systems to Detect Host-Medication Interactions: Sex Differences in Oral Anti-Diabetic Drug-Associated Myocardial Infarction

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***Background*—**Medical treatment should be tailored to an individual's characteristics to optimize treatment benefits. We examined whether case-only analyses from spontaneous reporting systems can detect host-medication interactions in oral antidiabetic drug-associated myocardial infarction.

***Methods and Results*—**Interaction between sex and use of oral antidiabetic drugs was mined among patients with myocardial infarction in the US Food and Drug Administration Adverse Event Reporting System from 2004 to 2014, including 55 718 males and 42 428 females. The odds ratio (OR) of multiplicative interactions was used to estimate sex-drug interaction. Detected signs of these interactions were then validated by a nested case-control study utilizing a healthcare record database, Taiwan's National Health Insurance Research Database, from 2001 to 2014, including 31 585 cases and 126 340 controls. In the US Food and Drug Administration Adverse Event Reporting System, a higher proportion of male than female patients used metformin (10.32% in males versus 7.82% in females) and sulfonylureas (4.75% in males versus 3.43% in females); after adjusting for patients' pharmacy-based chronic disease score, males had a higher risk of metformin-associated (OR=1.07; 99% confidence interval, 1.00–1.14) and sulfonylureas-associated (OR=1.21; 99% confidence interval, 1.10–1.33) myocardial infarction than females. Detected signs of sex-drug interactions were validated in the National Health Insurance Research Database (OR for metformin=1.14; 99% confidence interval, 1.03–1.26; OR for sulfonylureas=1.13; 99% confidence interval, 1.02–1.25).

***Conclusions*—**Males have a higher risk of metformin- and sulfonylureas-associated myocardial infarction than females, which suggests that sex-drug interactions are a key issue in diabetes mellitus treatment plan development. This case-only approach using information from spontaneous reporting systems may be a potential tool for screening host-medication interactions that cause adverse events. **(*J Am Heart Assoc*. 2018;7:e008959. DOI: 10.1161/JAHA.118.008959.)**

Key Words: case-only study • drug-associated adverse events • host-medication interactions • sex differences • spontaneous reporting systems

Accumulated evidence from epidemiological studies and fundamental research has demonstrated that multiple factors play a role in the development of drug-associated adverse events, including drug properties and host-drug interactions. Previous studies revealed differences in reactions to a drug among subpopulations with different characteristics.[1,2] Moreover, treatment efficacy and safety could vary across subpopulations, such as different sexes,[3] and, recently, precision medicine has received substantial attention, including precision diabetes mellitus medicine.[4,5] Medical treatment should be tailored to an individual's characteristics, such as sex, to optimize treatment benefits and minimize the risk of adverse events.

Safety profiles of drugs before marketing are limited, and hence postmarketing drug safety surveillance, are needed.

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Accompanying Datas S1, S2 and Tables S1, S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.008959

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Clinical Perspective

What Is New?

- In the US Food and Drug Administration Adverse Event Reporting System, case-only analyses showed that males have a higher risk of metformin- and sulfonylureas-associated myocardial infarction than females, and these findings were validated in Taiwan's healthcare database analyses.

What Are the Clinical Implications?

- Spontaneous reporting systems could be a potential tool for screening host-medication interactions.
- These findings from the host-medication studies could provide scientific evidence for precision medicine.
- Sex-drug interactions are a key issue in diabetes mellitus treatment plan development.

Spontaneous reporting systems have been designed for passive surveillance, such as the US Food and Drug Administration Adverse Event Reporting System (FAERS), which is a database that supports the US Food and Drug Administration postmarketing safety surveillance for approved drugs. Spontaneous reporting systems collect voluntarily submitted reports of adverse events and records of drug use by patients; therefore, the exposure of certain populations to specific drugs is unknown. Although several statistical methods have been proposed for detecting indicators of highly disproportionate reporting rates of a specific drug-event combination,[6] these methods investigated relative reporting rates, but not relative risk.

To better understand postmarketing drug safety, electronic healthcare records have been an important source of active surveillance, and these records contain detailed clinical information such as demographic characteristics of insured individuals, diagnosis, prescription, hospitalization, and medical expenditure. Data obtained from electronic healthcare records have been utilized to conduct formal drug safety studies.[7] In the big data era, pharmacoepidemiological research has combined information from multiple sources of administrative claims databases for postmarketing drug safety surveillance.[8] However, few studies have integrated the use of spontaneous reporting systems and electronic healthcare records in drug safety research.

Based on spontaneous reporting systems with case-only information, descriptive case series can be applied,[9] but it is difficult to determine whether the risk of an adverse events among users of a specific drug is higher than that among nonusers. Case-only study designs have been shown to be powerful tools for assessing the possible interactions that cause diseases under certain assumptions for independence between 2 variables of interest in a population.[10–12] Moreover, this study design has been applied to explore the gene-medication interaction for pharmacogenetic research.[13] Hence, spontaneous reporting systems are a potential source for detecting interactions between individuals' characteristics and medications. The present study proposes a novel case-only design as a potential approach to detect host-medication interactions in the pharmacoepidemiological field with 2 phases: a mining phase in a spontaneous reporting system and a validation phase in an electronic healthcare database.

The motivation behind the present study is the cardiovascular safety of antidiabetic drugs.[14] Among patients with diabetes mellitus, cardiovascular disease is the leading cause of morbidity and mortality. However, hypoglycemic drugs do not definitively reduce adverse cardiovascular events.[15–18] In addition to glycemic efficacy, cardiovascular safety is a critical determinant in preapproval of hypoglycemic drug trials and postmarketing surveillance. The sex difference in the cardiovascular safety of hypoglycemic drugs has been poorly studied, although sex differences for cardiovascular disease incidence and risk factors have been well noted.[19–21] In this study, we integrated information from spontaneous reporting systems and electronic healthcare records to explore sex differences in oral antidiabetic drug-associated myocardial infarction. Interaction between sex and the use of oral antidiabetic drugs was first detected in the FAERS and then validated in Taiwan's National Health Insurance Research Database (NHIRD).

Methods

Analytical methods have been made available to other researchers. The FAERS data are available to the public at the US Food and Drug Administration website. The NHIRD used in this study is held by the Taiwan Ministry of Health and Welfare. The Ministry of Health and Welfare approved our application to access these data. Any researcher interested in accessing the data set can submit an application form to the Ministry of Health and Welfare requesting access.

Mining Phase: Detection of Interaction in Spontaneous Reporting Systems

Interaction between sex and use of oral antidiabetic drugs were mined among patients with myocardial infarction in the FAERS from 2004 to 2014. The Standardized Medical Dictionary for Regulatory Activities (MedDRA; version 18.0) Queries (SMQs) index was used to identify myocardial infarction–related events (see Data S1 for the included search terms). A total of 55 718 males and 42 428 females were selected.

Oral antidiabetic medications were categorized into: metformin (biguanide), sulfonylureas, alpha-glucosidase inhibitors (AGIs), thiazolidinediones, meglitinides, and dipeptidyl peptidase-4 (DPP-4) inhibitors. Rosiglitazone, a thiazolidinedione agent, has been shown to increase the risk of myocardial infarction in a meta-analysis,[22] and hence rosiglitazone and pioglitazone, another thiazolidinedione agent, were separately considered.

Based on the information for drugs reportedly used by patients, we mapped drug use to 28 disease categories (including cardiac diseases, hypertension, coronary/peripheral vascular diseases, diabetes mellitus, hyperlipidemia, thyroid disorders, asthma, tuberculosis, cystic fibrosis, gastric acid disorder, inflammatory bowel disease, liver failure, renal disease, end-stage renal disease, epilepsy, Parkinson's disease, anxiety and tension, depression, psychotic illnesses, bipolar disorder, malignancies, pain, rheumatoid arthritis, pain and inflammation, gout, transplant, glaucoma, and HIV) according to the Anatomical Therapeutic Chemical classification system[23] and calculated the chronic disease score (CDS), a summary score of 28 pharmacy-based disease categories, as an index for chronic illness. The CDS was calculated using the following equation: $CDS=\sum_{28\ diseases} w_i \times D_i$, where w_i indicated the weight for the CDS disease category i, and D_i was equal to 1 if the drug of the ith disease category was dispensed (otherwise D_i was set to 0).[24] The 28 disease categories and corresponding weights are shown in Table S1. Based on a previous study, predictive performance for the subsequent-year hospitalization of the pharmacy-based comorbidity measure was better than that of diagnosis-based measures.[23] The CDS was then adjusted in the association test. Risk factors of myocardial infarction may not be adequately approached by the CDS; hence, in the sensitivity analysis, we used pharmacy-based disease categories by step-wise selection, rather than the summary CDS, in the regression model to test the robustness of our analysis.

Modeling any variable as a function of another in a case-only analysis gives the estimate of the interaction between these 2 variables. The case-only estimate of the multiplicative interaction between sex and drug was obtained by fitting a logistic regression model while adjusting for covariates[25]: $\text{logit } p(\text{Sex=male})=\alpha+\beta\times\text{Drug}+\theta\times\text{Covariates}$, when the drug variable and covariates are categorical or continuous (see Data S2 and Table S2 for a detailed description of the methodology and assumptions for detecting interactions in a case-only study). The adjusted case-only odds ratio (OR) was calculated by exp (β). If the estimated OR was significantly larger than 1, than the reported drug-associated adverse events had higher odds of being observed in males than in females.

Validation Phase in the Healthcare Database

The validation study utilized the NHIRD derived from Taiwan's single-payer compulsory National Health Insurance program, which covers up to 99% of the 23 million Taiwanese population. We applied a nested case-control study design within a diabetes mellitus cohort, defined by the use of antidiabetic drugs, to validate the interaction between sex and an indicated drug. The study was approved by the Internal Review Board of Human Studies of China Medical University Hospital. The requirement for informed consent was waived.

We assembled a cohort of new antidiabetic drug users from 2001 to 2014. The date of the first use of the antidiabetic drug was the cohort entry date. Inclusion criteria were as follows: (1) any antidiabetic drug use ever (≥20 years old) between 2001 and 2014; (2) lack of antidiabetic drug use in 2000; (3) lack of diagnosis of myocardial infarction (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] code: 410.x, 411.x, 412.x), cerebrovascular disease (*ICD-9-CM* code: 430.x-438.x), or peripheral arterial disease (*ICD-9-CM* code: 440.2, 443.9) from 1998 to 2000 or before the cohort entry date. A total of 1 603 906 new antidiabetic drug users were followed up.

For each case diagnosed with acute myocardial infarction (*ICD-9-CM* code: 410.x), we randomly selected 4 controls who did not have acute myocardial infarction at the time of the case diagnosis and who were individually matched by sex, age within a 2-year difference, and the calendar year of the cohort entry date. In total, 31 585 cases and 126 340 controls were included in this study.

Specific oral antidiabetic medications, including metformin, sulfonylureas, AGIs, thiazolidinediones, meglitinides, and DPP-4 inhibitors, for each subject before the index date of acute myocardial infarction were identified. Pattern of use was categorized as current use (a prescription termination date within 30 days before the index day) and noncurrent use.

We conducted a conditional logistic regression analysis of acute myocardial infarction on oral antidiabetic medication with adjustment for the pharmacy-based CDS, insulin use, and other oral antidiabetic drug use. Interaction terms between sex and oral antidiabetic drugs were included in the model to explore the sex difference in drug-associated acute myocardial infarction. Sensitivity analysis with adjustment for pharmacy-based disease categories was also performed.

To be consistent with signal detection phase, we did not exclude ad initio the insulin users. In addition, use of insulin reflects severity, hence including insulin users could increase generalizability. In order to study the pure effect of an oral antidiabetic drug on myocardial infarction, we restricted the study samples to noninsulin users. Individuals in the control group were matched with those in the myocardial infarction group at a 2:1 ratio, and 14 368 cases and 28 736 controls were included.

All statistical analyses were performed using the SAS statistical package (version 9.4 for Windows; SAS Institute Inc, Cary, NC). To consider multiple testing, a P value of <0.01 was considered statistically significant and the 99% confidence interval (CI) are reported.[26]

Table 1. Distribution of Oral Antidiabetic Drug Use in Myocardial Infarction Cases by Sex and Case-Only Interaction Estimate Between Sex and Drug in Causing Myocardial Infarction Using the US Food and Drug Administration Adverse Event Reporting System

Drug	Male (n=55 718) n (%)	Female (n=42 428) n (%)	Univariate Model		Adjusted Model 1*		Adjusted Model 2†	
			OR (99% CI)	*P* Value	OR (99% CI)	*P* Value	OR (99% CI)	*P* Value
Metformin	5786 (10.38)	3341 (7.87)	1.36 (1.28–1.44)	<0.0001	1.07 (1.00–1.14)	0.007	1.07 (1.00–1.14)	0.007
Sulfonylureas	3366 (6.04)	1780 (4.20)	1.47 (1.36–1.59)	<0.0001	1.21 (1.10–1.33)	<0.0001	1.26 (1.16–1.37)	<0.0001
TZDs								
Rosiglitazone	14 692 (26.37)	8101 (19.09)	1.52 (1.46–1.58)	<0.0001	1.45 (1.39–1.52)	<0.0001	1.58 (1.50–1.65)	<0.0001
Pioglitazone	73 (0.13)	33 (0.08)	1.69 (0.98–2.89)	0.01	1.53 (0.89–2.64)	0.04	1.47 (0.83–2.59)	0.08
AGIs	70 (0.13)	20 (0.05)	2.66 (1.38–5.10)	0.0001	2.52 (1.31–4.87)	0.0003	2.20 (1.12–4.31)	0.003
Meglitinides	40 (0.07)	20 (0.05)	1.52 (0.75–3.09)	0.12	1.53 (0.75–3.11)	0.13	1.63 (0.78–3.40)	0.09
DPP-4 inhibitors	101 (0.18)	44 (0.10)	1.75 (1.10–2.79)	0.002	1.78 (1.11–2.84)	0.002	1.72 (1.05–2.80)	0.004

AGIs indicates alpha-glucosidase inhibitors; CI, confidence interval; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; OR, odds ratio; TZDs, thiazolidinediones.
*Adjusted for age, insulin use, other oral antidiabetic drug use, and chronic disease score.
†Adjusted for age, insulin use, other oral antidiabetic drug use, and pharmacy-based disease category (variable selection from 28 disease categories except diabetes mellitus by a step-wise regression procedure).

Results

Detection of Interaction in the FAERS

In a case-only study using the FAERS, average age was 59.99 years (SD=12.81) in male patients with myocardial infarction and 61.23 (SD=14.01) in females. Mean chronic disease score was 0.96 (SD=0.91) in males and 0.92 (SD=0.93) in females. Distribution of oral antidiabetic drug use in myocardial infarction cases by sex is shown in Table 1. Overall, male patients had a higher reporting rate of oral antidiabetic drug use than females. Low reporting rates in the use of pioglitazone, AGIs, meglitinides, DPP-4 inhibitors, and glucagon-like peptide-1 receptor agonists may lead to relatively unstable parameter estimates. A higher proportion of male than female patients used metformin (10.38% in males versus 7.87% in females) and sulfonylureas (6.04% in males versus 4.20% in females).

After adjusting for patient age, CDS, insulin use, and other oral antidiabetic drug use, males had a higher risk of metformin-associated (case-only OR of the multiplicative interaction=1.07 with 99% CI, 1.00–1.14) and sulfonylureas-associated (case-only OR of the multiplicative interaction=1.21 with 99% CI, 1.10–1.33) myocardial infarction than females. The sensitivity analysis, with adjustment for pharmacy-based disease categories, showed grossly consistent findings (Table 1).

Validation Study in the NHIRD

In a nested case-control study using the NHIRD, distribution of demographic factors and chronic disease scores in cases and controls by sex are shown in Table 2, and the distribution of current oral antidiabetic drug use is shown in Table 3. The proportion of both males and females who used metformin, sulfonylureas, rosiglitazone, AGIs, meglitinides, and DPP-4 inhibitors was higher in cases than that in controls. The estimated crude OR between drug use and myocardial infarction from the univariate analysis for metformin and sulfonylureas was higher in males.

Results of multivariable analyses are displayed in Table 4. Parameter estimates of a specific drug indicated the effect of the drug on myocardial infarction in females. After adjusting for CDS, insulin use, and other oral antidiabetic drug use, current use of metformin, rosiglitazone, pioglitazone, and AGIs was not associated with myocardial infarction in females. However, current use of sulfonylureas, meglitinides, and DPP-4 inhibitors was associated with a higher risk of myocardial infarction in females.

Parameter estimates of the interaction between a specific drug and sex suggested a multiplicative interaction, indicating the difference between the log-OR comparing a specific drug use with no use in males and the log-OR comparing a specific drug use to no use in females. An OR for the interaction, exp (parameter estimate of the interaction term), larger than 1 indicated that males had a higher risk of drug-associated adverse events than females. After adjusting for the CDS, insulin use, and other oral antidiabetic drug use of patients, males had a higher risk of metformin-associated (OR of the multiplicative interaction=1.14 with 99% CI, 1.03–1.26) and sulfonylureas-associated (OR of the multiplicative interaction=1.13 with 99% CI, 1.02–1.25) myocardial infarction than females. For pioglitazone use, females had a higher risk of myocardial infarction than males (OR of the multiplicative interaction=0.76 with 99% CI, 0.59–0.98).

Table 2. Distribution of Demographic Factors and Chronic Disease Score in Cases With Acute Myocardial Infarction and Controls by Sex in a Validation Study, Including 31 585 Cases and 126 340 Controls, Using Taiwan's National Health Insurance Research Database

	Male		Female	
	Case (n=21 824) Mean±SD	Control (n=87 296) Mean±SD	Case (n=9761) Mean±SD	Control (n=39 044) Mean±SD
Age, y	58.52±12.78	58.45±12.72	64.79±12.77	64.66±12.69
Duration of diabetes mellitus, y	4.75±3.48	4.76±3.47	5.06±3.63	5.07±3.62
Chronic disease score	1.17±1.16	0.80±0.89	1.40±1.24	0.92±0.94

The sensitivity analysis showed grossly consistent findings with the model after adjusting for the pharmacy-based CDS (Table 4). Males still had a higher risk of metformin-associated (OR of the multiplicative interaction=1.13 with 99% CI, 1.02–1.25) and sulfonylureas-associated (OR of the multiplicative interaction=1.12 with 99% CI, 1.00–1.24) myocardial infarction than females. Results for pioglitazone use were also consistent: Females had a higher risk of myocardial infarction than males (OR of the multiplicative interaction=0.76 with 99% CI, 0.58–0.99).

Among noninsulin users, the distribution of current oral antidiabetic drug use and the results of multivariable analyses are displayed in Tables 5 and 6, respectively. For metformin use, males (OR=1.08 with 99% CI, 1.01–1.16) had a higher risk of developing myocardial infarction than females (OR=0.89 with 99% CI, 0.79–0.99), and this sex difference reached a statistical significance. For sulfonylureas use, it was associated with a higher risk of myocardial infarction in males (OR=1.21 with 99% CI, 1.12–1.30), but not in females (OR=1.11 with 99% CI, 0.98–1.25); however, this sex difference did not reach a statistical significance; this may be attributed to reduced power with reduced sample size, or indicate that the insulin use, a proxy for severity of diabetes mellitus, plays a role of effect modification on sex difference.

Discussion

This study integrated spontaneous reporting systems and electronic healthcare records to explore host-medication interactions. We first mined indicators for interaction between sex and oral antidiabetic drug-associated myocardial infarction in the FAERS, in which the included information was case-only. The detected indicators, sex-metformin interactions and sex-sulfonylureas interactions, were then further validated in the NHIRD, a healthcare claims database. This study demonstrated that the case-only approach using spontaneous reporting systems is a potential tool for screening host-medication multiplicative interactions in causing adverse events.

The case-only design has been criticized for being susceptible to bias arising from nonindependence between the 2 variables of interest in the population. No significant sex difference in the prevalence of diabetes mellitus in the United States has been reported,[27] and the associations between sex

Table 3. Distribution of Current Oral Antidiabetic Drug Use in Cases With Myocardial Infarction and Controls by Sex in a Validation Study, Including 31 585 Cases and 126 340 Controls, Using Taiwan's National Health Insurance Research Database

	Male				Female			
	Case (n=21 824) n (%)	Control (n=87 296) n (%)	Crude OR (99% CI)	*P* Value	Case (n=9761) n (%)	Control (n=39 044) n (%)	Crude OR (99% CI)	*P* Value
Metformin	10 094 (46.25)	33 973 (38.92)	1.37 (1.31–1.42)	<0.0001	4013 (41.11)	14 786 (37.87)	1.15 (1.08–1.22)	<0.0001
Sulfonylureas	11 332 (51.92)	34 430 (39.44)	1.69 (1.62–1.76)	<0.0001	4633 (47.46)	14 725 (37.71)	1.52 (1.43–1.62)	<0.0001
TZDs								
Rosiglitazone	303 (1.39)	874 (1.00)	1.40 (1.18–1.67)	<0.0001	138 (1.41)	381 (0.98)	1.47 (1.13–1.92)	0.0001
Pioglitazone	957 (4.39)	4146 (4.75)	0.92 (0.83–1.01)	0.02	391 (4.01)	1543 (3.95)	1.02 (0.87–1.18)	0.80
AGIs	2354 (10.79)	5694 (6.52)	1.75 (1.63–1.87)	<0.0001	1055 (10.81)	2465 (6.31)	1.82 (1.65–2.01)	<0.0001
Meglitinides	2662 (12.20)	3433 (3.93)	3.43 (3.20–3.68)	<0.0001	1400 (14.34)	1564 (4.01)	4.08 (3.68–4.51)	<0.0001
DPP-4 inhibitors	3001 (13.75)	7123 (8.16)	1.97 (1.85–2.11)	<0.0001	1283 (13.14)	2862 (7.33)	2.14 (1.93–2.37)	<0.0001

AGIs indicates alpha-glucosidase inhibitors; CI, confidence interval; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; OR, odds ratio; TZDs, thiazolidinediones.

Table 4. Interaction Between Sex and Current Oral Antidiabetic Drug Use in Drug-Associated Acute Myocardial Infarction in a Validation Study, Including 31 585 Cases and 126 340 Controls, Using Taiwan's National Health Insurance Research Database

	Adjusted Model 1*			Adjusted Model 2†		
	β	OR (99% CI)	*P* Value	β	OR (99% CI)	*P* Value
Metformin	−0.01	0.99 (0.91–1.08)	0.71	0.11	1.12 (1.02–1.22)	0.001
Metformin×sex	0.13	1.14 (1.03–1.26)	0.0007	0.12	1.13 (1.02–1.25)	0.003
Sulfonylureas	0.24	1.27 (1.16–1.38)	<0.0001	0.31	1.36 (1.24–1.49)	<0.0001
Sulfonylureas×sex	0.12	1.13 (1.02–1.25)	0.003	0.11	1.12 (1.00–1.24)	0.008
Rosiglitazone	0.08	1.08 (0.73–1.59)	0.61	0.10	1.11 (0.74–1.65)	0.51
Rosiglitazone×sex	−0.22	0.80 (0.51–1.25)	0.20	−0.22	0.80 (0.50–1.27)	0.22
Pioglitazone	−0.13	0.88 (0.70–1.09)	0.12	−0.10	0.91 (0.72–1.14)	0.27
Pioglitazone×sex	−0.27	0.76 (0.59–0.98)	0.006	−0.27	0.76 (0.58–0.99)	0.007
AGIs	0.06	1.06 (0.91–1.24)	0.30	0.05	1.05 (0.90–1.24)	0.39
AGIs×sex	0.04	1.04 (0.87–1.24)	0.57	0.06	1.06 (0.88–1.27)	0.43
Meglitinides	0.87	2.38 (2.04–2.78)	<0.0001	0.80	2.22 (1.89–2.61)	<0.0001
Meglitinides×sex	−0.02	0.98 (0.81–1.17)	0.73	−0.04	0.96 (0.79–1.16)	0.56
DPP-4 inhibitors	0.22	1.25 (1.08–1.45)	0.0001	0.24	1.28 (1.09–1.49)	<0.0001
DPP-4 inhibitors×sex	0.01	1.01 (0.85–1.19)	0.93	0.00	1.00 (0.84–1.19)	0.99
Chronic disease score	0.14	1.16 (1.13–1.18)	<0.0001			
Cardiac disease				1.23	3.44 (3.22–3.67)	<0.0001
Hypertension				−0.05	0.95 (0.90–1.00)	0.006
Hyperlipidemia				−0.10	0.90 (0.84–0.96)	<0.0001
Thyroid disorder				−0.35	0.71 (0.54–0.93)	0.001
Asthma				0.18	1.20 (1.14–1.27)	<0.0001
Liver failure				−0.92	0.40 (0.30–0.54)	<0.0001
End-stage renal disease				1.42	4.12 (3.55–4.78)	<0.0001
Malignancies				−0.48	0.62 (0.47–0.81)	<0.0001
Pain				0.59	1.81 (1.61–2.03)	<0.0001
Rheumatoid arthritis				0.09	1.10 (1.00–1.21)	0.01
Pain and inflammation				0.20	1.22 (1.16–1.29)	<0.0001

AGIs indicates alpha-glucosidase inhibitors; CI, confidence interval; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; OR, odds ratio.

*Adjusted for summary pharmacy-based chronic disease score, insulin use, and oral anti-diabetic drug use by performing a conditional logistic regression model.

†Adjusted for insulin use, oral anti-diabetic drug use, and pharmacy-based disease category (variable selection from 28 disease categories except diabetes mellitus and coronary/peripheral vascular disease by a step-wise regression procedure) by performing a conditional logistic regression model. Unexpected directions of the effect for some disease categories may be the result of multicollinearity among the explanatory variables.

and adherence reported were not consistent. Although 2 recent studies using large US healthcare claims databases between 2007 and 2011 observed that males have ≈14% higher adherence to oral antidiabetic medication than females in patients with diabetes mellitus,[28,29] 1 previous study using US healthcare claims data between 2001 and 2004 observed that sex exerted little influence on adherence to diabetes mellitus medication.[30] Additionally, details about prevalence of each oral antidiabetic drug are lacking and need to be further studied. To date, there are no consistent data showing that sex differences exist in rate of oral antidiabetic drug use, and thus it is reasonable to assume independence between sex and medication in the US population. If the information on the OR between sex and oral antidiabetic drug use in the general population is available, it can be considered in the case-only studies (Data S2).

Even if the 2 variables of interest are associated in the general population, it is possible to remove the bias arising from nonindependence using multivariable modeling.[25] To control for covariates that cause nonindependence between the 2 variables of interest, adjustment for the covariate, which represents a common cause if the 2 variables of interest interact or if an intermediate variable participates in the pathway between them, will remove the nonindependence

Table 5. Distribution of Current Oral Antidiabetic Drug Use in Cases With Acute Myocardial Infarction and Controls by Sex Among Noninsulin Users in a Validation Study, Including 14 368 Cases and 28 736 Controls, Using Taiwan's National Health Insurance Research Database

Male	Case (n=10 451) n (%)	Control (n=20 902) n (%)	Crude OR (99% CI)	*P* Value	Adjusted OR (99% CI)*	*P* Value
Metformin	4594 (43.96)	8013 (38.34)	1.27 (1.20–1.36)	<0.0001	1.08 (1.01–1.16)	0.004
Sulfonylureas	4808 (46.01)	8054 (38.53)	1.38 (1.29–1.47)	<0.0001	1.21 (1.12–1.30)	<0.0001
TZDs						
Rosiglitazone	119 (1.14)	225 (1.08)	1.06 (0.79–1.43)	0.61	0.82 (0.60–1.11)	0.09
Pioglitazone	324 (3.10)	894 (4.28)	0.71 (0.60–0.85)	<0.0001	0.58 (0.49–0.69)	<0.0001
AGIs	808 (7.73)	1223 (5.85)	1.35 (1.20–1.53)	<0.0001	1.11 (0.98–1.26)	0.03
Meglitinides	831 (7.95)	682 (3.26)	2.57 (2.24–2.95)	<0.0001	2.41 (2.09–2.78)	<0.0001
DPP-4 inhibitors	1007 (9.64)	1499 (7.17)	1.44 (1.28–1.62)	<0.0001	1.20 (1.06–1.36)	0.0001
Female	Case (n=3917) n (%)	Control (n=7834) n (%)	Crude OR (99% CI)	*P* Value	Adjusted OR (99% CI)*	*P* Value
Metformin	1525 (38.93)	2895 (36.95)	1.09 (0.98–1.21)	0.03	0.89 (0.79–0.99)	0.01
Sulfonylureas	1603 (40.92)	2778 (35.46)	1.28 (1.15–1.43)	<0.0001	1.11 (0.98–1.25)	0.03
TZDs						
Rosiglitazone	45 (1.15)	73 (0.93)	1.24 (0.76–2.03)	0.27	1.00 (0.60–1.68)	0.99
Pioglitazone	120 (3.06)	260 (3.32)	0.92 (0.69–1.23)	0.45	0.78 (0.57–1.06)	0.03
AGIs	273 (6.97)	436 (5.57)	1.28 (1.04–1.58)	0.002	1.02 (0.82–1.27)	0.85
Meglitinides	318 (8.12)	268 (3.42)	2.49 (1.99–3.10)	<0.0001	2.14 (1.70–2.70)	<0.0001
DPP-4 inhibitors	329 (8.40)	484 (6.18)	1.45 (1.19–1.78)	<0.0001	1.21 (0.98–1.50)	0.02

AGIs indicates alpha-glucosidase inhibitors; CI, confidence interval; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; OR, odds ratio; TZDs, thiazolidinediones.
*Adjusted for chronic disease score and other oral antidiabetic drug use.

and yield a valid estimate of interaction among cases. In this study, adjustment for covariates in multivariable modeling not only adjusted for potential confounders of main effects, but also removed the sex-medication association from the general population. In the results of the FAERS, a case-only adjusted OR significantly larger than 1 indicated that males had a higher risk of oral antidiabetic drug-associated myocardial infarction than females.

In the FAERS, rosiglitazone was the most common drug among patients with myocardial infarction, and this may be linked to the fact that the US Food and Drug Administration released a boxed warning of cardiovascular safety for this drug, which increased the willingness to submit reports on the adverse events among rosiglitazone users. In recent years, use of rosiglitazone in Taiwan declined after reports that rosiglitazone was associated with an increased risk of myocardial infarction and cardiovascular-related mortality.[31] The results of the NHIRD analysis indicated that there was no elevated risk of acute myocardial infarction in patients being treated with rosiglitazone, which was consistent with the RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes) clinical trial.[32] Consistent with a meta-analysis of randomized trials, our results showed that pioglitazone is associated with a low risk of myocardial infarction in female and male patients.[33]

Among noninsulin users, metformin and sulfonylureas use were both associated with a 10% to 20% increase in risk of myocardial infarction in males, but were not harmful to females. However, other studies showed that there was no harmful effect of metformin or sulfonylureas on cardiovascular risk, but no sex difference was observed in such cases.[34,35] There has been no long-term cardiovascular outcome data for AGIs,[14] and this retrospective cohort study based on the NHIRD indicated that AGIs increased the risk of myocardial infarction in male noninsulin users. For meglitinides, a randomized trial showed that these drugs did not increase the risk of core cardiovascular outcomes among patients with impaired glucose tolerance,[36] but this study observed that these drugs increased the risk of myocardial infarction among patients with diabetes mellitus. Additionally, meglitinides-treated patients had higher risks for myocardial infarction than patients treated with DPP-4 inhibitors as well as other oral antidiabetic drug users.[37]

In this study, results showed that males have a higher risk of metformin- and sulfonylureas-associated myocardial

Table 6. Interaction Between Sex and Current Oral Antidiabetic Drug Use in Drug-Associated Acute Myocardial Infarction Among Noninsulin Users in a Validation Study, Including 14 368 Cases and 28 736 Controls, Using Taiwan's National Health Insurance Research Database

	Adjusted Model 1*			Adjusted Model 2†		
	β	OR (99% CI)	*P* Value	β	OR (99% CI)	*P* Value
Metformin	−0.10	0.90 (0.81–1.01)	0.02	0.09	1.10 (0.97–1.24)	0.04
Metformin×sex	0.17	1.19 (1.04–1.35)	<0.0001	0.16	1.18 (1.02–1.35)	<0.0001
Sulfonylureas	0.12	1.13 (1.01–1.27)	0.01	0.30	1.35 (1.20–1.53)	<0.0001
Sulfonylureas×sex	0.05	1.06 (0.92–1.21)	0.30	0.03	1.03 (0.89–1.19)	0.57
Rosiglitazone	0.01	1.01 (0.60–1.69)	0.95	0.06	1.06 (0.62–1.83)	0.78
Rosiglitazone×sex	−0.22	0.81 (0.44–1.47)	0.35	−0.24	0.79 (0.42–1.48)	0.33
Pioglitazone	−0.25	0.78 (0.58–1.06)	0.04	−0.19	0.83 (0.60–1.15)	0.14
Pioglitazone×sex	−0.30	0.74 (0.52–1.06)	0.03	−0.26	0.77 (0.53–1.12)	0.07
AGIs	0.03	1.03 (0.83–1.28)	0.73	−0.01	0.99 (0.78–1.25)	0.90
AGIs×sex	0.07	1.07 (0.83–1.38)	0.46	0.13	1.14 (0.87–1.49)	0.23
Meglitinides	0.78	2.18 (1.74–2.75)	<0.0001	0.81	2.25 (1.76–2.88)	<0.0001
Meglitinides×sex	0.09	1.09 (0.84–1.43)	0.39	0.02	1.02 (0.76–1.37)	0.86
DPP-4 inhibitors	0.20	1.22 (0.99–1.51)	0.01	0.30	1.34 (1.07–1.69)	<0.0001
DPP-4 inhibitors×sex	−0.02	0.98 (0.76–1.25)	0.79	−0.09	0.92 (0.71–1.19)	0.40
Chronic disease score	0.34	1.41 (1.37–1.45)	<0.0001			
Cardiac disease				1.43	4.18 (3.82–4.59)	<0.0001
Asthma				0.32	1.38 (1.25–1.52)	<0.0001
Gastric acid disorder				0.18	1.20 (1.05–1.36)	<0.0001
Renal disease				0.69	2.00 (1.33–3.02)	<0.0001
End-stage renal disease				1.56	4.74 (3.74–6.01)	<0.0001
Anxiety and tension				0.12	1.12 (1.02–1.24)	<0.0001
Psychotic illness				0.30	1.35 (1.14–1.61)	<0.0001
Malignancies				−0.46	0.63 (0.44–0.92)	<0.0001
Pain				1.08	2.95 (2.46–3.53)	<0.0001
Rheumatoid arthritis				0.23	1.26 (1.10–1.44)	<0.0001
Pain and inflammation				0.21	1.24 (1.15–1.34)	<0.0001

AGIs indicates alpha-glucosidase inhibitors; CI, confidence interval; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; OR, odds ratio.

*Adjusted for summary pharmacy-based chronic disease score and oral antidiabetic drug use by performing a conditional logistic regression model.

†Adjusted for oral antidiabetic drug use and pharmacy-based disease category (variable selection from 28 disease categories except diabetes mellitus and coronary/peripheral vascular disease by a step-wise regression procedure) by performing a conditional logistic regression model. Unexpected direction of effect for some disease categories may be resulted from multicollinearity among explanatory variables.

infarction than females. One multicenter observational study showed that women had a significantly higher reduction in body weight after treatment with metformin or sulfonylurea drugs.[38] However, this study also showed that men had significantly higher hemoglobin A1c reductions after treatment with lifestyle or metformin.[38] Although the underlying mechanism for the sex-drug interaction remains unclear, the mechanism might be associated with the influence of endogenous sex hormones, such as protective effects of estrogen or harmful effects of testosterone.[39]

The strengths of this study include the novelty of using case-only analyses to detect host-medication interactions that cause adverse events based on spontaneous reporting systems and validation using a nation-wide cohort assembled from healthcare databases and the adjustment for comorbidity measured as pharmacy-based chronic disease score in spontaneous reporting systems and healthcare databases. However, several limitations should be considered. First, the indicator detection study and validation study were from different countries, and ancestral heterogeneity may have

impacted the pattern of association between sex, drugs, and adverse events. Second, the validity of spontaneous reporting systems could be limited. The data could be affected by selection bias, because these systems may not receive all adverse event reports that occur with a specific drug.[40] Furthermore, whether the under-reporting varies by sex as well as its impact on the case-only approach needs to be explored further. Additionally, the data could be affected by information bias because these systems may not receive all drug reports for a specific adverse event. Moreover, certain reported adverse events may not be directly caused by the drug. Third, well-known examples of sex-drug interactions in cardiovascular adverse events lack testing in the novel case-only design; hence, we evaluated it by analyzing the cardiovascular safety of antidiabetic drugs during the validation phase. Case-only analyses should be evaluated in other scenarios. Fourth, the validation study using the NHIRD defined the use of an oral antidiabetic drug as current use at the index date and thus did not consider the influence of switching. Fifth, some potential confounding factors, such as education years, alcohol use, smoking, body weight, and exercise, were not available from the FAERS and NHIRD. The association between the drugs and myocardial infarction reported in this study should be considered with caution, because these risk factors are associated with myocardial infarction[41] and were not considered in this analysis. The roles of these factors on the associations between antidiabetic medication and myocardial infarction warrant further investigation.

Conclusions

This study indicated that the case-only approach using information from spontaneous reporting systems may be a potential tool for screening host-medication multiplicative interaction in causing adverse events. Using antidiabetic drug-associated myocardial infarction as an example, the results indicated that males have a higher risk of metformin- and sulfonylureas-associated myocardial infarction than females, which suggests that the sex-drug interaction is a key issue in diabetes mellitus treatment plan.[42]

This case-only approach should be further applied to other domains of drug safety to explore host-medication interactions. The findings from these studies would provide scientific evidence for precision medicine.

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Disclosures

None.

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