Journal of Food and Drug Analysis

Volume 31 | Issue 4 Article 13

Application of the US Food and Drug Administration's Sentinel Routine Querying Tools to the Taiwan Sentinel Data Model-formatted National Health Insurance Research Database

ORIGINAL ARTICLE

Application of the U.S. Food and Drug Administration's Sentinel Routine Querying Tools to the Taiwan Sentinel Data Model-formatted National Health Insurance Research Database

Fang-Ju Lin [a,b,c], Ling-Ya Huang [b], Chi-Chuan Wang [a,b,c,*], Sengwee Toh [d]

[a] Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University Hospital, Taipei, Taiwan
[b] School of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan
[c] Department of Pharmacy, National Taiwan University Hospital, Taipei, Taiwan
[d] Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA

Abstract

The U.S. Food and Drug Administration's Sentinel System is a leading distributed data network for drug safety surveillance in the world. The National Health Insurance Research Database (NHIRD) in Taiwan was converted into the Taiwan Sentinel Data Model (TSDM) based on the Sentinel Common Data Model (SCDM) version 6.0.2. The goal of this study was to investigate the feasibility of applying the same study designs, analytic choices, and analytic tools as used by the U.S. Sentinel System to examine the same drug−outcome associations in the TSDM-formatted NHIRD. Four known drug−outcome associations previously examined by the U.S. Sentinel System were selected as the use cases: (1) use of angiotensin-converting enzyme inhibitors (ACEIs) and risk of angioedema, (2) use of warfarin and risk of gastrointestinal bleeding, (3) use of oral clindamycin and risk of *Clostridioides difficile* infection (CDI), and (4) use of glyburide and risk of serious hypoglycemia. We followed the same study designs and analytic choices used by the U.S. Sentinel System and applied the Sentinel Routine Querying Tools to answer the same study questions within the TSDM-formatted NHIRD. The results showed that ACEIs were associated with a non-significant increase in risk of angioedema compared to beta-blockers (hazard ratio [HR]: 1.21; 95% confidence interval [CI]: 0.89−1.64); warfarin was associated with a higher risk of gastrointestinal bleeding compared to statins (HR: 1.72; 1.50−1.98); glyburide was associated with an increased risk of hypoglycemia compared to glipizide (HR: 1.61, 1.30−2.00). We were unable to evaluate the association between oral clindamycin and risk of CDI due to the low event number. Our study demonstrated that it was feasible to directly apply the publicly available Sentinel Routine Querying Tools within the TSDM-formatted NHIRD. However, sources of heterogeneity other than design and analytic differences should be carefully considered when comparing the results between the two systems.

Keywords: Pharmacovigilance, Routine Querying Tools, Sentinel Initiative, Taiwan Sentinel Data Model

1. Introduction

In 2016, the U.S. Food and Drug Administration (FDA) officially launched the Sentinel System, an active surveillance system to monitor the post-market safety of medical products [1−3]. The Sentinel System is a distributed data network of more than a dozen data partners, all of whom have converted their source data into the Sentinel Common Data Model (SCDM) to allow large-scale assessment of medical product safety across multiple databases [4]. To facilitate rapid query and analysis across the databases, the Sentinel System has developed a suite of Routine Querying Tools that can be run against the SCDM [5]. The Routine Querying Tools include semi-automated analytic programs that can be customized according to specific study designs, exposures, outcomes, and covariates. These tools can

Received 15 November 2022; revised 27 August 2023; accepted 25 October 2023.
Available online 15 December 2023

* Corresponding author at: School of Pharmacy, National Taiwan University, Room 202, No.33, Linsen S. Rd., Zhongzheng Dist., Taipei City 100, Taiwan.
E-mail address: chicwang@ntu.edu.tw (C.-C. Wang).

https://doi.org/10.38212/2224-6614.3482

be used for cohort identification, descriptive analysis, and complex confounding-adjusted inferential analysis. Currently, there are four levels of analyses available: signal identification, descriptive analysis, retrospective inferential analysis, and prospective sequential inferential analysis [6].

To test the validity of the Routine Querying Tools, four known positive drug exposure-outcome associations were selected as use cases within Mini-Sentinel (the pilot program of the Sentinel System established in 2009): (1) use of angiotensin-converting enzyme inhibitors (ACEIs) and risk of angioedema [7], (2) use of warfarin and risk of gastrointestinal (GI) bleeding [8], (3) use of oral clindamycin and risk of *Clostridioides difficile* infection (CDI) (*C. difficile* was formerly known as *Clostridium difficile*) [9], and (4) use of glyburide and risk of serious hypoglycemia [10]. The Cohort Identification and Descriptive Analysis (CIDA) and the Propensity Score Analysis (PSA) modules from the Routine Querying Tools were tested in these four use cases.

Following the SCDM structure, we previously built the Taiwan Sentinel Data Model (TSDM) using the longitudinal data from the National Health Insurance Research Database (NHIRD) [11]. This is a U.S. Sentinel System-compatible platform which allows us to directly adapt the U.S. Sentinel Routine Querying Tools and run them against the data in Taiwan. The goal of this study was to investigate the feasibility of applying the same study designs, analytic choices, and analytic tools as used by the U.S. Sentinel System to examine the same drug exposure-outcome associations in the TSDM-formatted NHIRD. All four known positive drug exposure-outcome associations tested in the Mini-Sentinel program were tested in the present study.

2. Methods

2.1. Data source

The TSDM-formatted NHIRD between 1 January 2011 and 31 December 2017 served as the data source for this study. Details of the TSDM are described elsewhere [11]. Briefly, the TSDM contains 11 tables: Enrollment, Demographic, Dispensing, Encounter, Diagnosis, Procedure, Death, Cause of Death, Laboratory Result, Vital Signs, and Inpatient Pharmacy. Laboratory results, vital signs, and inpatient pharmacy data are available only in a subset of population with linked electronic health records.

2.2. Use cases

Because data for specific time periods used in the original Sentinel analyses were not available in the NHIRD at the time we conducted the study, we modified the study period for each use case. The first use case (ACEI exposure and risk of angioedema) was conducted with data from 1 January 2011 to 31 December 2017 in the NHIRD (versus 1 January 2001 to 31 December 2011 in the Sentinel study [7]). We used data from 1 January 2012 to 31 December 2015 for the second use case (warfarin exposure and risk of GI bleeding), which was roughly consistent with the study period of the original Sentinel analysis (1 January 2012 to 30 September 2015) [8]. The third use case (use of oral clindamycin and risk of CDI) was conducted with data from 1 January 2012 to 31 December 2015 (versus 1 January 2006 to 31 December 2013 in the Sentinel analysis [9]), and the fourth use case (use of glyburide and risk of hypoglycemia) was conducted with data from 1 January 2012 to 31 December 2015 (versus 1 January 2008 to 30 September 2014 in the Sentinel study [10]).

Details of these four use cases have been published elsewhere [7–10,12–15]. We followed the same designs of the four use cases used by the U.S. Sentinel System [7–10]. In brief, these four cases were retrospective cohort studies with a new-user, active-comparator design. We applied the codes and definitions described in the publicly available Sentinel reports to identify exposure, outcome, and covariates, with modifications as appropriate. For example, instead of using the National Drug Codes, we used Taiwan's National Health Insurance (NHI) Drug Codes to identify medications in the TSDM-formatted NHIRD. Because the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes have been used for reimbursement in Taiwan since 1 January 2016, both the Ninth Revision of the ICD Clinical Modification codes (ICD-9-CM) and the ICD-10-CM codes were used to define diseases and conditions in the first use case. We only used ICD-9-CM codes for the other three use cases as the study period ended in or before 2015.

We also followed the outcome definitions provided by the U.S. Sentinel System. Angioedema was defined by an inpatient or outpatient diagnosis at any position; GI bleeding was defined by an inpatient diagnosis at the primary position; CDI was defined as a hospitalization with a diagnosis of CDI in any position; hypoglycemia events were defined

by emergency department visits with a diagnosis of hypoglycemia at any position or admissions with a primary diagnosis of hypoglycemia. The complete lists of codes can be found in the Sentinel reports and publications [7–10,12–15]. Codes that were mapped or modified based on the Sentinel reports are provided in Tables S1-S4 (https://www.jfda-online.com/journal/vol31/iss4/13/).

Propensity score (PS) methods were applied to all four use cases to balance baseline characteristics. PS stratification (by quantile) was applied in the first use case, while 1:1 PS matching was applied in the second, third, and fourth use cases. Following the analytical approach in the Sentinel study, we also performed 1: up to 10 variable matching in the second use case. Covariate balance was assessed by absolute standardized differences (aSD), where a value <0.1 generally indicated no considerable difference between the two groups.

2.3. Sentinel Routine Querying Tools

Two modules from the Sentinel Routine Querying Tools were used in this project: the CIDA module and the PSA module, which consisted of SAS macros that allowed users to identify the study cohort and pre-specify the statistical analysis [16]. We were able to apply the Sentinel tools directly to TSDM, with one major modification. While the column length for drug code is 11 digits in the SCDM version 6.0.2, the Sentinel routine querying macro program "ms_extractdrugs.sas" was set to read drug codes with either 9 or 11 digits. Although the column length of the drug codes was set to be 11 digits in the TSDM (per SCDM version 6.0.2 specification), the NHI Drug Codes only contained 10 digits. We therefore modified the SAS macro "ms_extractdrugs.sas" to read 10-digit drug codes in the TSDM.

To mimic the distributed data network of the Sentinel System and improve computational efficiency, we randomly divided the TSDM-formatted NHIRD into eight subsamples (i.e., "sites") for analysis. For the first use case, the pooled result was generated from a Cox proportional hazards model stratified by PS quantile and site. For the second, third, and fourth use cases, the pooled results were generated from Cox models with two analytical approaches. We first performed the analysis stratified solely by site for samples with 1:1 PS matching. We next stratified the Cox models by both site and matched pair for 1: up to 10 variable matching in the second use case and for 1:1 matching in the third and fourth use cases. All statistical procedures were performed in the Health and Welfare Data Science Center using SAS software version 9.4 (SAS Institute, Cary, North Carolina, USA).

3. Results

3.1. Use of ACEIs and risk of angioedema

In the first use case, we identified 533,237 ACEI initiators and 2,181,246 beta-blocker initiators after applying the same inclusion and exclusion criteria used in the U.S. Sentinel System analysis [7]. Table 1 shows the baseline characteristics of the ACEI and beta-blocker initiators. ACEI initiators tended to be older than beta-blocker initiators (mean age: 62.1 versus 52.1 years). Approximately 46% of the ACEI initiators were female, compared to 59% in the beta-blocker initiators. A higher proportion of ACEI initiators had diabetes (24% versus 10%), heart failure (5% versus 2%) and ischemic heart disease (11% versus 7%) than beta-blocker initiators.

The incidence rate of angioedema was 70.7 per 100,000 person-years for ACEI initiators and 74.9 per 100,000 person-years for beta-blocker initiators, with

Table 1. Baseline characteristics for angiotensin-converting enzyme inhibitors and beta-blocker initiators.

N (%)	ACEI initiators N = 533,237	Beta-blocker initiators N = 2,181,246	Absolute standardized difference
Age, year			
Mean (std)	62.05 (21.69)	52.12 (15.66)	**0.525**
18–44	66,782 (12.52)	760,279 (34.86)	**0.584**
45–54	104,698 (19.63)	465,061 (21.32)	
55–64	139,097 (26.09)	452,078 (20.73)	
65+	222,660 (41.76)	503,828 (23.10)	
Female	243,212 (45.61)	1,297,133 (59.47)	**0.280**
Diagnosis of:			
Allergic reactions	74,660 (14.00)	343,123 (15.73)	0.049
Diabetes	125,981 (23.63)	226,473 (10.38)	**0.358**
Heart failure	27,410 (5.14)	47,748 (2.19)	**0.158**
Ischemic heart disease	57,725 (10.83)	152,088 (6.97)	**0.136**
Use of prescription NSAIDs	264,525 (49.61)	1,099,989 (50.43)	0.016

ACEI: angiotensin-converting enzyme inhibitor; NSAIDs: non-steroidal anti-inflammatory drugs; std: standard deviation.

Table 2. Crude and adjusted results in angiotensin-converting enzyme inhibitors and beta-blocker initiators, with a maximum follow-up of 365 days.

	Number of events	Number of initiators	Person-years	Risk per 100,000 initiators	Incidence rate per 100,000 person-years (95%CI)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
ACEI initiators	65	533,237	91,946	12.19	70.69 (55.44–90.15)	0.98 (0.75–1.29)	1.21 (0.89–1.64)
Beta-blocker initiators	245	2,181,246	326,917	11.23	74.94 (66.12–84.94)	Reference	

ACEI: angiotensin-converting enzyme inhibitor; HR: hazard ratio; CI: confidence interval.
[a] Adjusted hazard ratio was generated from a site- and propensity score-stratified Cox model.

an adjusted HR of 1.21 (95% confidence interval [CI]: 0.89–1.64) (Table 2).

3.2. Use of warfarin and risk of GI bleeding

In the second use case, 58,788 warfarin initiators and 1,398,317 statin initiators were included in the final sample (Table 3). Compared to statin initiators, warfarin initiators were older (mean age: 67.6 versus 60.5 years) and more likely to have comorbid conditions and receive other classes of medications. Warfarin initiators tended to have a higher mean number of emergency room and inpatient hospital encounters but a lower mean number of ambulatory encounters, number of generics, and unique drug classes than statin initiators. Most of the baseline characteristics were well-balanced after PS matching, except for baseline antiplatelet and aspirin use. We therefore included baseline antiplatelet and aspirin use as covariates in the final Cox proportional hazards model after PS matching. Note that race is 100% Asian in Taiwan, which was correctly reflected in Table 3, and therefore race was not adjusted in the PS model.

Table 4 shows the incidence rate and HRs of GI bleeding between warfarin and statin initiators. The crude incidence rate of GI bleeding was 25.7 per 1,000 person-years for warfarin initiators and 5.5 per 1,000 person-years for statin initiators, which corresponded to a crude HR of 4.70 (95% CI: 4.29–5.15). The incidence rate in the 1:1 PS-matched cohort was 25.6 per 1,000 person-years for warfarin initiators and 15.2 per 1,000 person-years for statin initiators, with a HR of 1.72 (95% CI: 1.50–1.98). Similar results were observed in the 1:10 variable PS-matched analysis. The incidence rate was 25.6 per 1,000 person-years for warfarin initiators and 10.0 per 1,000 person-years for statin initiators, with a HR of 2.56 (95% CI: 2.32–2.82).

3.3. Use of oral clindamycin and risk of C. difficile infection

The baseline characteristics of oral clindamycin and oral penicillin initiators are presented in Table 5. There were 1,570,359 oral clindamycin initiators and 9,411,950 oral penicillin initiators. Compared to oral penicillin initiators, a higher proportion of oral clindamycin initiators were female (57.8% versus 51.0%), received first-generation cephalosporins (18.2% versus 14.4%) and tetracyclines (4.9% versus 2.6%), but a lower proportion of clindamycin initiators received macrolides (1.3% versus 4.0%) and proton pump inhibitors (1.7% versus 3.8%). A slightly lower number of inpatient hospital encounters and prescription refills was observed among those who initiated oral clindamycin than those who initiated oral penicillins. No meaningful differences were found after PS matching.

Table 6 shows the incidence rates of CDI among the oral clindamycin and oral penicillin initiators. In the unmatched analysis, 94 events were found in the penicillin initiators, but less than three events were found in the clindamycin initiators. Due to the low event numbers, we were unable to obtain a reliable effect estimate from the matched analysis.

3.4. Use of glyburide and risk of serious hypoglycemia

We identified 56,216 glyburide initiators and 52,073 glipizide initiators in the fourth use case (Table 7). Compared to glipizide users, glyburide users were younger (mean age: 59.9 versus 62.4 years), less likely to have chronic kidney disease, less likely to use insulin or non-secretagogue antidiabetic drugs, and had a slightly lower comorbidity score at baseline. A slightly higher mean number of emergency room encounters was observed in glyburide users compared to glipizide users, but a slightly lower health services utilization intensity was observed in glyburide users for inpatient encounters, prescription fills, and number of generic drugs used. All covariates were well-balanced after PS matching.

Incidence rates and HRs of hypoglycemia are presented in Table 8. The crude incidence rate of hypoglycemia was 11.4 per 1,000 person-years for glyburide users and 9.9 per 1,000 person-years for glipizide users, which corresponded to a crude HR of 1.15 (95% CI: 0.95–1.39). Similar incidence rates

Table 3. Baseline characteristics of warfarin and statin initiators.

Demographics, n (%)	Unmatched			1:1 Propensity score matching			1:10 Variable propensity score matching		
	Warfarin initiators N = 58,788	Statin initiators N = 1,398,317	Absolute standardized difference	Warfarin initiators N = 58,624	Statin initiators N = 58,624	Absolute standardized difference	Warfarin initiators N = 58,624	Statin initiators N = 407,254	Absolute standardized difference
Age, year									
mean (std)	67.58 (20.29)	60.47 (10.08)	**0.444**	67.57 (13.90)	68.68 (17.11)	0.072	67.57 (13.90)	68.72 (12.68)	0.032
18–64	26,554 (37.90)	1,045,718 (62.77)	**0.611**	22,199 (37.87)	20,914 (35.67)	0.068	22,199 (37.87)	145,118 (35.63)	0.068
65–74	17,982 (25.66)	392,371 (23.55)		15,075 (25.71)	17,189 (29.32)		15,075 (25.71)	118,736 (29.16)	
75+	25,536 (36.44)	227,899 (13.68)		21,350 (36.42)	20,521 (35.00)		21,350 (36.42)	143,400 (35.21)	
Sex									
Male	36,376 (51.91)	799,271 (47.98)	0.079	30,456 (51.95)	31,156 (53.15)	0.024	30,456 (51.95)	216,207 (53.09)	0.023
Female	33,696 (48.09)	866,717 (52.02)		28,168 (48.05)	27,468 (48.85)		28,168 (48.05)	191,047 (46.91)	
Race (Asian)	70,072 (100.0)	1,665,988 (100.0)		58,624 (100.00)	58,624 (100.00)	–	58,624 (100.00)	407,254 (100.00)	–
Recorded history of:									
Advanced liver disease	277 (0.40)	1,015 (0.06)	0.070	238 (0.41)	222 (0.38)	0.004	238 (0.41)	1,476 (0.36)	0.007
Alcohol abuse or dependence	667 (0.95)	9,952 (0.60)	0.040	564 (0.96)	621 (1.06)	0.010	564 (0.96)	4,103 (1.01)	0.005
End stage renal disease	0 (0.00)	0 (0.00)		0 (0.00)	0 (0.00)	–	0 (0.00)	0 (0.00)	–
Gastritis or gastroenteritis	12,730 (18.17)	287,560 (17.26)	0.024	10,759 (18.35)	10,721 (18.29)	0.002	10,759 (18.35)	74,339 (18.25)	0.003
Helicobacter pylori infection	280 (0.40)	6,460 (0.39)	0.002	226 (0.39)	206 (0.35)	0.006	226 (0.39)	1,557 (0.38)	0.001
Peptic ulcer	219 (0.31)	1,460 (0.09)	0.050	180 (0.31)	198 (0.34)	0.005	180 (0.31)	1,292 (0.32)	0.002
Inflammatory bowel disease	372 (0.53)	7,600 (0.46)	0.011	318 (0.54)	289 (0.49)	0.007	318 (0.54)	2,230 (0.55)	0.001
Intestinal infections	1,794 (2.56)	37,424 (2.25)	0.021	1,545 (2.64)	1,495 (2.55)	0.005	1,545 (2.64)	10,570 (2.60)	0.003
Obesity	302 (0.43)	10,568 (0.63)	0.028	251 (0.43)	232 (0.40)	0.005	251 (0.43)	1,680 (0.41)	0.002
Other GI diverticula	239 (0.34)	2,355 (0.14)	0.041	196 (0.33)	207 (0.35)	0.003	196 (0.33)	1,335 (0.33)	0.001
Other GI ulcer disease	9,624 (13.73)	158,097 (9.49)	**0.133**	8,107 (13.83)	8,204 (13.99)	0.005	8,107 (13.83)	56,957 (13.99)	0.005
Other non-GI bleeding	2,638 (3.76)	38,867 (2.33)	0.083	2,230 (3.80)	2,216 (3.78)	0.001	2,230 (3.80)	15,361 (3.77)	0.002
Renal disease	4,115 (5.87)	55,810 (3.35)	**0.121**	2,497 (5.97)	3,545 (6.05)	0.003	2,497 (5.97)	25,008 (6.14)	0.007
Sepsis	3,600 (5.14)	11,916 (0.72)	**0.265**	2,999 (5.12)	2,647 (4.52)	0.028	2,999 (5.12)	18,413 (4.52)	0.028
Shock	1,141 (1.63)	3,525 (0.21)	**0.149**	963 (1.64)	856 (1.46)	0.015	963 (1.64)	6,025 (1.48)	0.013
Tobacco use	394 (0.56)	11,520 (0.69)	0.016	351 (0.60)	400 (0.68)	0.011	351 (0.60)	2,605 (0.64)	0.005
History of use of:									
Antiplatelets and aspirin	35,136 (50.14)	469,248 (28.17)	**0.462**	29,528 (50.37)	33,042 (56.36)	**0.120**	29,528 (50.37)	228,383 (56.08)	**0.115**
COX-2 inhibitors	8,121 (11.59)	93,662 (5.62)	**0.214**	6,853 (11.69)	7,509 (12.81)	0.034	6,853 (11.69)	52,471 (12.88)	0.036
H2RAs and sucralfate	15,708 (22.42)	285,587 (17.14)	**0.133**	13,044 (22.25)	13,148 (22.43)	0.004	13,044 (22.25)	91,466 (22.46)	0.005
Heparins	4,892 (6.98)	15,022 (0.90)	**0.316**	4,106 (7.00)	3,901 (6.65)	0.014	4,106 (7.00)	27,091 (6.65)	0.014
Methotrexate	425 (0.61)	4,447 (0.27)	0.052	361 (0.62)	421 (0.72)	0.013	361 (0.62)	2,789 (0.68)	0.009
NSAIDs	36,764 (52.47)	834,385 (50.08)	0.048	30,770 (52.49)	31,137 (53.11)	0.013	30,770 (52.49)	215,275 (52.86)	0.008
Opioids	10,356 (14.78)	81,471 (4.89)	**0.337**	8,601 (14.67)	8,629 (14.72)	0.001	8,601 (14.67)	59,829 (14.69)	0.001
Oral glucocorticoids	14,710 (20.99)	213,066 (12.79)	**0.220**	12,308 (20.99)	12,372 (21.10)	0.003	12,308 (20.99)	86,025 (21.12)	0.003
Proton pump inhibitors	6,439 (9.19)	84,195 (5.05)	**0.161**	5,346 (9.12)	5,229 (8.92)	0.007	5,346 (9.12)	35,823 (8.80)	0.011
SSRIs or SNRIs	2,763 (3.94)	59,247 (3.56)	0.020	2,333 (3.98)	2,391 (4.08)	0.005	2,333 (3.98)	16,732 (4.11)	0.007
Respiratory opioids	18,623 (26.58)	359,126 (21.56)	**0.118**	15,510 (26.46)	15,528 (26.49)	0.001	15,510 (26.46)	108,376 (26.61)	0.004
Health service utilization intensity, mean (std)									
Ambulatory encounters[a]	13.09 (5.64)	10.13 (12.60)	**0.303**	13.09 (10.07)	13.47 (13.48)	0.031	13.09 (10.07)	13.44 (10.03)	0.017

Other ambulatory encounters[a]	0.44 (1.83)	0.51 (1.09)	0.047	0.43 (0.78)	0.42 (1.06)	0.011	0.43 (0.78)	0.42 (0.92)	0.005
Emergency room encounters	0.85 (1.16)	0.23 (0.47)	**0.700**	0.84 (1.49)	0.79 (1.14)	0.038	0.84 (1.49)	0.79 (2.08)	0.023
Inpatient hospital encounters	0.81 (0.77)	0.14 (0.29)	**1.143**	0.80 (1.44)	0.72 (0.92)	0.065	0.80 (1.44)	0.72 (1.20)	0.037
Non-acute institutional encounters	0.00 (0.02)	0.00 (0.02)	0.015	<0.01 (0.03)	<0.01 (0.04)	0.006	<0.01 (0.03)	<0.01 (0.04)	0.003
Prescription fills	37.44 (25.59)	24.86 (33.73)	**0.420**	37.38 (27.30)	38.55 (42.07)	0.033	37.38 (27.30)	38.44 (32.41)	0.020
Generics[b]	14.96 (6.92)	10.31 (10.53)	**0.521**	14.93 (7.45)	15.26 (10.60)	0.036	14.93 (7.45)	15.24 (10.34)	0.018
Unique drug classes	14.91 (6.91)	10.28 (10.62)	**0.517**	13.58 (6.31)	13.88 (9.04)	0.040	13.58 (6.31)	13.87 (8.74)	0.020

GI: gastrointestinal; H2RAs: H2 receptor antagonists; NSAIDs: non-steroidal anti-inflammatory drugs; SSRI: selective serotonin reuptake inhibitors; SNRI: Serotonin and norepinephrine reuptake inhibitors; std: standard deviation. Bold numbers indicate the absolute standardized difference between the two groups >0.1.

[a] Ambulatory encounters included visits at outpatient clinics, urgent care visits, and other same-day ambulatory hospital encounters, but exclude emergency department encounters; other ambulatory encounters included other non-overnight ambulatory encounters such as home health visits, rehabilitations and nursing facility visits.

[b] The number of drug generic names (i.e., the number of active pharmaceutical ingredients).

were observed after we applied 1:1 PS matching without stratifying on matched pair, with a HR of 1.61 (95% CI: 1.30−2.00). Slightly higher incidence rates were observed in the analysis stratified on matched pair (22.8 per 1,000 person-years for glyburide users and 12.7 per 1,000 person-years for glipizide users), but the HR remained the same as in the unstratified analysis (HR: 1.61; 95% CI: 1.30−2.00).

4. Discussion

To our knowledge, this study is the first direct application of the U.S. Sentinel Routine Querying Tools on the NHIRD in Taiwan. We demonstrated the feasibility of applying the same study designs, analytic choices, and analytic tools as used by the U.S. Sentinel System to examine the same drug exposure-outcome associations in the TSDM-formatted NHIRD. We observed two known associations: (1) warfarin use and risk of GI bleeding, and (2) glyburide use and risk of serious hypoglycemia in the TSDM-formatted NHIRD. An elevated risk of angioedema associated with ACEI use was observed in our analysis, but the 95% CI included the null. We did not have enough event numbers to examine the association between oral clindamycin and risk of CDI. It is therefore important to note that being able to apply the same design and analytic approaches does not mean the results would be comparable between data sources. Instead, it allows us to remove modifiable sources of heterogeneity and focus on other more meaningful differences, as we discuss below.

There were some notable differences in study samples between our analyses and the U.S. Sentinel System analyses. Our samples tended to be older than the samples from the U.S. Sentinel System studies. The reason for age difference could be the inclusion of primarily privately insured populations in the U.S. Sentinel System studies, in which approximately two-thirds of individuals were between 18 and 65 years old [12]. A considerably higher utilization of ambulatory services and prescription drugs was observed in our samples compared to the Sentinel samples in all four use cases. The high utilization rate was mainly attributed to the easy access and low costs of ambulatory services and prescription drugs under the NHI program in Taiwan.

A lower number of ACEI initiators was identified in our study than that in the prior reports from the Sentinel System [12]. The low utilization rate of ACEIs in Taiwan may reflect the concern about ACEI-induced cough [17]. In addition to the

Table 4. Effect estimates for gastrointestinal bleeding between warfarin and statin initiators.

Medical product	Number of initiators	Person-year	Average person-days	Number of events	**Incidence rate per 1,000 person-year**	**Incidence rate difference per 1,000 person-years**	HR (95% CI)
Unmatched analysis (site adjusted only)							
Warfarin	58,788	21,729.30	135.00	558	25.68 (23.64–27.90)	20.17	4.70 (4.29–5.15)
Statins	1,398,317	490,137.08	128.03	2,698	5.51 (5.30–5.72)		Reference
1:1 propensity score-matched analysis (Cox model NOT stratified by matched pair and adjusted for site and antiplatelet and aspirin use)[a]							
Warfarin	58,624	21,687.59	135.122	555	25.59 (23.55–27.81)	10.35	1.72 (1.50–1.98)
Statins	58,624	21,723.33	135.345	331	15.24 (13.68–16.97)		Reference
1:10 propensity score-matched analysis (Cox model stratified by matched pair and adjusted for site and antiplatelet and aspirin use)[a]							
Warfarin	58,624	21,687.59	135.122	555	25.59 (23.55–27.81)	15.59	2.56 (2.32–2.82)
Statins	407,254	151,401.86	135.786	1,514	10.00 (9.51–10.52)		Reference

HR: hazard ratio; CI: confidence interval.

[a] Baseline antiplatelet and aspirin exposure was included in the final model because it remained imbalanced after matching.

Table 5. Baseline characteristics of oral clindamycin and penicillin initiators.

Demographics, n (%)	Unmatched			1:1 Propensity score matching		
	Oral clindamycin initiators N = 1,570,359	Oral penicillin initiators N = 9,411,950	Absolute standardized difference	Oral clindamycin initiators N = 1,569,188	Oral penicillin initiators N = 1,569,188	Absolute standardized difference
Sex, female	907,104 (57.76)	4,797,309 (50.97)	**0.137**	906,280 (57.75)	903,298 (57.56)	0.004
Mean age (std)	37.97 (18.58)	38.78 (9.04)	0.055	37.97 (18.60)	38.72 (20.40)	0.009
Recorded use of:						
Aminoglycosides	13,468 (0.86)	90,755 (0.96)	0.011	13,090 (0.83)	12,795 (0.82)	0.002
Beta Lactam inhibitors	331 (0.02)	3,475 (0.04)	0.009	327 (0.02)	352 (0.02)	0.001
Cephalosporins-1st generation	285,492 (18.18)	1,350,413 (14.35)	**0.104**	285,056 (18.17)	286,155 (18.24)	0.002
Cephalosporins-2nd generation	22,650 (1.44)	128,438 (1.36)	0.007	22,573 (1.44)	22,959 (1.46)	0.002
Cephalosporins-3rd generation	5,397 (0.34)	42,291 (0.45)	0.017	5,376 (0.34)	5,418 (0.35)	0.001
Cephalosporins-4th and 5th generation	62 (0.00)	889 (0.01)	0.007	62 (0.00)	74 (0.00)	0.001
Fluoroquinolones	22,220 (1.41)	128,996 (1.37)	0.004	22,152 (1.41)	22,598 (1.44)	0.002
H2Ras	208,643 (13.29)	953,304 (10.13)	0.098	208,445 (13.28)	215,053 (13.70)	0.012
Injectable clindamycin	3,325 (0.21)	2,184 (0.02)	0.055	2,154 (0.14)	2,010 (0.13)	0.003
Injectable penicillin	1,004 (0.06)	27,282 (0.29)	0.054	1,004 (0.06)	1,030 (0.07)	0.001
Macrolides	19,928 (1.27)	377,418 (4.01)	**0.172**	19,928 (1.27)	19,861 (1.27)	0.000
Other antimicrobials	3,473 (0.22)	23,788 (0.25)	0.007	3,469 (0.22)	3,434 (0.22)	0.001
Proton pump inhibitors	26,188 (1.67)	358,171 (3.81)	**0.131**	26,175 (1.67)	25,073 (1.60)	0.006
Sulfonamides	31,635 (2.01)	181,036 (1.92)	0.007	31,597 (2.01)	31,700 (2.02)	0.001
Tetracyclines	76,288 (4.86)	247,673 (2.63)	**0.118**	75,944 (4.84)	71,199 (4.54)	0.014
Recorded history of:						
Chemotherapy administration	3,133 (0.20)	28,460 (0.30)	0.021	3,130 (0.20)	3,196 (0.20)	0.001
Diabetes	80,868 (5.15)	686,221 (7.29)	0.089	80,783 (5.15)	80,155 (5.11)	0.002
Dialysis	3,514 (0.22)	34,792 (0.37)	0.027	3,509 (0.22)	3,609 (0.23)	0.001
Immunocompromised state	22,027 (1.40)	179,116 (1.90)	0.039	22,006 (1.40)	22,449 (1.43)	0.002
Inflammatory bowel disease	11,357 (0.72)	69,466 (0.74)	0.002	11,350 (0.72)	11,384 (0.73)	<0.001
Health service utilization intensity, mean (std)						
Ambulatory encounters[a]	6.09 (7.47)	6.57 (5.47)	0.073	6.09 (7.37)	6.02 (6.29)	0.008
Other ambulatory encounters[a]	0.26 (0.75)	0.29 (1.06)	0.024	0.26 (0.76)	0.26 (0.78)	0.004
Emergency room encounters	0.14 (0.59)	0.19 (0.86)	0.065	0.14 (0.58)	0.14 (0.79)	0.001
Inpatient hospital encounters	0.06 (0.18)	0.08 (0.21)	**0.131**	0.06 (0.18)	0.06 (0.36)	0.002
Non-acute institutional encounters	0.00 (0.02)	0.00 (0.04)	0.002	0.00 (0.02)	0.00 (0.02)	0.001
Prescription fills	11.25 (14.26)	13.04 (17.68)	**0.111**	11.25 (14.02)	11.22 (15.96)	0.002
Generics[b]	5.93 (5.80)	6.19 (8.07)	0.037	5.93 (5.68)	5.89 (5.60)	0.003

H2Ras: H2 receptor antagonists; std: standard deviation. Bold numbers indicate the absolute standardized difference between the two groups >0.1.

[a] Ambulatory encounters included visits at outpatient clinics, urgent care visits, and other same-day ambulatory hospital encounters, but exclude emergency department encounters; other ambulatory encounters included other non-overnight ambulatory encounters such as home health visits, rehabilitations and nursing facility visits.

[b] The number of drug generic names (i.e., the number of active pharmaceutical ingredients).

Table 6. Effect estimates for inpatient admission and emergency visits of Clostridioides difficile infection.

Exposure	Number of Initiators	Person-years	Number of events	Incidence rate per 1,000 person-years	Incidence rate difference per 1,000 person-years
Unmatched analysis (site adjusted only)					
Oral clindamycin	1,570,359	77,288.75	NA	0.03	−0.17
Oral penicillins	9,411,950	484,387.82	94	0.19	

NA: not available. Per the Health and Welfare Data Science Center's rule, statistical tables with variable classifications yielding fewer than three units or numbers cannot be exported. Due to the low number of events, we were unable to obtain a reliable effect estimate from the matched analysis.

differences in the baseline characteristics, the incidence rates of angioedema were lower in the present study compared to the results from the U.S. Sentinel System analysis [12]. The magnitude of the relative risk of angioedema was also different, with a lower and non-significant HR found in our study compared to the HRs reported from the Sentinel System. One potential explanation for these differences is that the risk of angioedema may differ by race. Compared to beta-blocker initiators, lower incidence rate and risk of angioedema was reported in ACEI initiators of Asians compared to those of Whites in a U.S. study [18].

We identified less than 100 CDI cases in our third use case, which prevented us from further evaluating the association between oral clindamycin and risk of CDI. Several factors may have contributed to the low event number. First, the prevalence of CDI

Table 7. Baseline characteristics of glyburide and glipizide users.

	Unmatched			1:1 Propensity score matching		
	Glyburide users N = 56,216	Glipizide users N = 52,073	Absolute standardized difference	Glyburide users N = 44,685	Glipizide users N = 44,685	Absolute standardized difference
Sex, female, n (%)	24,999 (44.47)	23,336 (44.81)	0.007	19,992 (44.74)	19,959 (44.67)	0.002
Mean age (std)	59.91 (14.60)	62.40 (18.86)	**0.148**	61.27 (17.03)	61.19 (14.71)	0.005
Recorded history of, n (%)						
Chronic kidney disease	2,725 (4.85)	6,588 (12.65)	**0.279**	2,724 (6.10)	2,724 (6.10)	0.005
Serious hypoglycemia	968 (1.72)	1418 (2.72)	0.068	892 (2.00)	892 (2.00)	0.002
Insulin	5,087 (9.05)	7,655 (14.70)	**0.175**	4,944 (11.06)	4,944 (11.06)	0.001
Metformin	37,724 (67.11)	33,978 (62.25)	0.039	30,500 (68.26)	30,500 (68.26)	0.006
Non-secretagogue antidiabetic drugs	13,005 (23.13)	15,549 (29.86)	**0.153**	12,175 (27.25)	12,175 (27.25)	0.012
Combined Charlson/ Elixhauser comorbidity score (std)	0.28 (1.06)	0.65 (2.12)	**0.224**	0.38 (1.01)	0.38 (0.72)	<0.001
Health service utilization intensity, mean (std)						
Ambulatory encounters[a]	9.95 (4.27)	10.62 (13.28)	0.069	10.11 (12.31)	10.11 (12.31)	0.001
Other ambulatory encounters[a]	0.46 (1.41)	0.48 (0.91)	0.018	0.46 (0.92)	0.46 (0.92)	0.007
Emergency room encounters	0.46 (1.64)	0.31 (0.87)	**0.114**	0.35 (1.08)	0.35 (1.08)	0.007
Inpatient hospital encounters	0.23 (0.87)	0.39 (1.07)	**0.169**	0.27 (0.86)	0.27 (0.86)	0.009
Non-acute institutional encounters	0.00 (0.03)	0.00 (0.02)	0.005	0.00 (0.02)	0.00 (0.02)	0.008
Prescription fills	25.43 (20.81)	29.66 (32.26)	**0.156**	27.06 (26.36)	27.06 (26.36)	0.003
Generics[b]	10.24 (8.43)	11.69 (10.81)	**0.149**	10.78 (8.81)	10.78 (8.81)	0.004

std: standard deviation. Bold numbers indicate the absolute standardized difference between the two groups >0.1.

[a] Ambulatory encounters included visits at outpatient clinics, urgent care visits, and other same-day ambulatory hospital encounters, but exclude emergency department encounters; other ambulatory encounters included other non-overnight ambulatory encounters such as home health visits, rehabilitations and nursing facility visits.

[b] The number of drug generic names (i.e., the number of active pharmaceutical ingredients).

Table 8. Effect estimates for inpatient admission and emergency department visit for hypoglycemia.

Exposure	Number of initiators	Person-years	Number of events	Incidence rate per 1,000 person-years	Incidence rate difference per 1,000 person-years	Hazard ratio (95% CI)
Unmatched analysis (site adjusted only)						
Glyburide	56,216	20,638.84	236	11.43	1.49	1.15 (0.95, 1.39)
Glipizide	52,073	19,415.75	193	9.94	Reference	
1:1 propensity score-matched analysis (Cox model NOT stratified by matched pair and adjusted for site)						
Glyburide	44,685	16,448.18	216	13.13	4.98	1.61 (1.30, 2.00)
Glipizide	44,685	16,674.90	136	8.16	Reference	
1:1 propensity score-matched analysis (Cox model stratified by matched pair and adjusted for site)						
Glyburide	44,685	6,542.97	149	22.77	10.09	1.61 (1.30, 2.00)
Glipizide	44,685	6,542.97	83	12.69	Reference	

was low (estimated 4%) in Taiwan [19]. In addition, because the diagnosis of CDI requires patient symptoms, positive stool culture for *C. difficile* and positive test for toxin A or toxin B, CDI may be underdiagnosed during our study period as the test for *C. difficile* toxin A and B was not reimbursed by the NHI until 1 March 2017. Finally, as there are only three diagnoses available for outpatient claims and five diagnoses available for inpatient claims in the NHI, less severe CDI events might not have been recorded.

The crude and adjusted HRs from the present study were comparable to the HRs from the U.S. Sentinel study in the second use case (HR_{TSDM}: 1.72–2.56 and HR_{SCDM}: 2.22–3.10) and the fourth use case (HR_{TSDM}: 1.61 and HR_{SCDM}: 1.35–1.36). The lower magnitude of GI bleeding risk found in the TSDM may be explained by the fact that physicians tended to maintain an international normalized ratio within a lower range for warfarin users in Taiwan due to the concerns about bleeding [20,21]. Regardless of the difference in magnitude of risk, the results from the TSDM and SCDM support the two known associations between warfarin exposure and risk of GI bleeding and between glyburide exposure and risk of hypoglycemia; therefore, these results would likely lead to the same conclusion for regulatory decision making [22].

Although we showed the feasibility of direct application of the Sentinel Routine Querying Tools within the TSDM-formatted NHIRD, there are several issues that need to be considered. First, direct application of certain study specifications may not be practicable given the potential differences in clinical practice and healthcare systems. For example, we did not identify any patients with a history of end-stage renal disease (ESRD) in the present study. This is mainly because the diagnosis codes used to identify ESRD (ICD-9-CM 585.6 and 585.6x) are not commonly used in Taiwan. Most physicians only use the code 585 for chronic kidney disease without specifying the stage, making it difficult to identify ESRD using only diagnosis codes. Additional information from the Registry of Catastrophic Illness is often required to identify ESRD in the NHIRD.

Different coding systems or access to medical products among the countries is another issue. An example is the mapping between the Current Procedural Terminology/Healthcare Common Procedure Coding System codes and the NHI procedure codes. Given that procedure codes are often designed for reimbursement purposes, the structure and granularity of procedure codes may differ between different healthcare systems. For instance, a parenterally administered chemotherapy could be captured as a procedure in one country but as a dispensing in another. Moreover, as information captured in claims databases is heavily influenced by insurance coverage policies, we might not be able to capture treatments that are covered in the U.S. but not in Taiwan. For example, none of the patients in our study had bariatric surgery because bariatric surgery was not covered by the NHI program before 2020. New medical products may also enter the U.S. and Taiwanese markets at different times, which could affect the practicability of running parallel analyses between the two countries. Given these challenges, caution is required when considering direct application of the study designs and analytic choices used in the U.S. Sentinel System to the TSDM-formatted NHIRD. A thorough investigation of the definitions and codes before direct application of the Sentinel analytic package is recommended.

In conclusion, the TSDM provides a platform that allows direct application of the Sentinel Routine Querying Tools with minor modifications. However, sources of heterogeneity other than design and analytic differences should be carefully considered

when interpreting and comparing the results between the two systems.

Conflicts of interest

None.

Acknowledgments

This study is supported by National Science and Technology Council of Taiwan (MOST-109-2636-B-002-002). The sponsors had no role in the preparation of the manuscript or analysis of the study results. No payment was received for writing this article.

References

[1] Behrman RE, Benner JS, Brown JS, McClellan M, Woodcock J, Platt R. Developing the Sentinel System–a national resource for evidence development. N Engl J Med 2011;364:498–9 [In eng].
[2] Platt R, Carnahan RM, Brown JS, Chrischilles E, Curtis LH, Hennessy S, et al. The U.S. Food and Drug Administration's Mini-Sentinel program: status and direction. Pharmacoepidemiol Drug Saf 2012;21:1–8.
[3] Ball R, Robb M, Anderson SA, Dal Pan G. The FDA's sentinel initiative—a comprehensive approach to medical product surveillance. Clin Pharmacol Ther 2016;99:265–8.
[4] Curtis LH, Weiner MG, Boudreau DM, Cooper WO, Daniel GW, Nair VP, et al. Design considerations, architecture, and use of the Mini-Sentinel distributed data system. Pharmacoepidemiol Drug Saf 2012;21:23–31.
[5] Sentinel Operations Center. Routine querying system. August 2, 2021. Available at: https://www.sentinelinitiative.org/methods-data-tools/routine-querying-tools/routine-querying-system. [Accessed 12 August 2021].
[6] Sentinel operations center. Available Routine Querying Tools. Available at: https://www.sentinelinitiative.org/methods-data-tools/routine-querying-tools. [Accessed 12 August 2021].
[7] Sentinel Operations Center. Testing routine querying tools with known positive exposure-outcome associations: angioedema events after use of angiotensin-converting enzyme (ACE) inhibitors versus beta-blockers. August 22, 2016. Available at: https://www.sentinelinitiative.org/methods-data-tools/methods/testing-routine-querying-tools-known-positive-exposure-outcome-0. [Accessed 23 March 2020].
[8] Sentinel Operations Center. Testing routine querying tools with known positive exposure-outcome associations: gastrointestinal (GI) bleeding following new use of warfarin compared with statins. February 23, 2018. Available at: https://www.sentinelinitiative.org/methods-data-tools/methods/testing-routine-querying-tools-known-positive-exposure-outcome-2. [Accessed 23 March 2020].
[9] Sentinel Operations Center. Testing routine querying tools with known positive exposure-outcome associations: Clostridium difficile events after use of oral clindamycin versus penicillins. March 27, 2018. Available at: https://www.sentinelinitiative.org/methods-data-tools/methods/testing-routine-querying-tools-known-positive-exposure-outcome-1. [Accessed 23 March 2020].
[10] Sentinel Operations Center. Testing routine querying tools with known positive exposure-outcome associations: hypoglycemia events after use of glyburide versus glipizide. July 18, 2017. Available at: https://www.sentinelinitiative.org/methods-data-tools/methods/testing-routine-querying-tools-known-positive-exposure-outcome. [Accessed 23 March 2020].
[11] Huang K, Lin F-J, Ou H-T, Hsu C-N, Huang L-Y, Wang C-C, et al. Building an active medical product safety surveillance system in Taiwan: adaptation of the U.S. Sentinel System common data model structure to the National Health Insurance Research Database in Taiwan. Pharmacoepidemiol Drug Saf 2021;30:97–101.
[12] Gagne JJ, Han X, Hennessy S, Leonard CE, Chrischilles EA, Carnahan RM, et al. Successful comparison of US food and drug administration sentinel analysis tools to traditional approaches in quantifying a known drug-adverse event association. Clin Pharmacol Ther 2016;100:558–64.
[13] Carnahan RM, Gagne JJ, Hampp C, Leonard CE, Toh S, Fuller CC, et al. Evaluation of the US food and drug administration sentinel analysis tools using a comparator with a different indication: comparing the rates of gastrointestinal bleeding in warfarin and statin users. Pharmaceut Med 2019;33:29–43.
[14] Carnahan RM, Kuntz JL, Wang SV, Fuller C, Gagne JJ, Leonard CE, et al. Evaluation of the US Food and Drug Administration sentinel analysis tools in confirming previously observed drug-outcome associations: the case of clindamycin and Clostridium difficile infection. Pharmacoepidemiol Drug Saf 2018;27:731–9.
[15] Zhou M, Wang SV, Leonard CE, Gagne JJ, Fuller C, Hampp C, et al. Sentinel modular program for propensity score-matched cohort analyses: application to glyburide, glipizide, and serious hypoglycemia. Epidemiology 2017;28:838–46.
[16] Atlassian Bitbucket. Sentinel Routine Querying System: how to execute an analytic request package using the query request package (QRP). December 17, 2020. Available at: https://dev.sentinelsystem.org/projects/QA/repos/qa_package/browse. [Accessed 23 January 2021].
[17] Liang L, Kung JY, Mitchelmore B, Gill J, Cave A, Banh HL. Angiotensin-converting enzyme inhibitor induced cough in Chinese patients: a systematic review and meta-analysis. J Pharm Pharmaceut Sci 2021;24:137–47. https://doi.org/10.18433/jpps31632.
[18] Reichman ME, Wernecke M, Graham DJ, Liao J, Yap J, Chillarige Y, et al. Antihypertensive drug associated angioedema: effect modification by race/ethnicity. Pharmacoepidemiol Drug Saf 2017;26:1190–6.
[19] Wei HL, Wei SH, Huang CW, Shih CH, Huang YW, Lu MC, et al. Molecular typing and epidemiology of Clostridium difficile in respiratory care wards of central Taiwan. J Microbiol Immunol Infect 2015;48:65–71.
[20] Kuo LN, Liou JP, Chen HY, Chiang YC, Wu MT. Evaluation of the safety and efficacy of warfarin in Taiwanese patients. Int J Clin Pharmacol Ther 2013;51:106–13.
[21] Chiang CE, Wang KL, Lip GY. Stroke prevention in atrial fibrillation: an Asian perspective. Thromb Haemostasis 2014;111:789–97. https://doi.org/10.1160/TH13-11-0948. Epub 2014 Feb 6.
[22] Franklin JM, Pawar A, Martin D, Glynn RJ, Levenson M, Temple R, et al. Nonrandomized real-world evidence to support regulatory decision making: process for a randomized trial replication project. Clin Pharmacol Ther 2020;107:817–26.