Received: 1 March 2018 | Revised: 26 June 2018 | Accepted: 23 July 2018

DOI: 10.1002/pds.4642

ORIGINAL REPORT

WILEY

Modafinil and the risk of cardiovascular events: Findings from three US claims databases

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Funding information
Teva Pharmaceutical Industries Ltd

Abstract

Purpose: This study examined the potential risk of cardiovascular (CV) events associated with modafinil and the consistency of the risk estimates across databases.

Methods: A retrospective, inception cohort design of patients who initiated treatment with modafinil between 2006 and 2008 was used in three US health care claims databases. Modafinil users were matched with nonusers. Patients were further divided into two cohorts of obstructive sleep apnea (OSA) and non-OSA (NOSA) cohorts. Endpoints of interest, including myocardial infarction (MI), stroke, CV hospitalizations, and all-cause death, were assessed using incidence rates and Cox proportional hazard ratios (HRs), adjusted for potential confounding factors.

Results: The cohorts included a total of 175 524 patients in MarketScan CM; 77 266—in IMS LifeLink; and 8174—in MarketScan Medicaid. No increased risk for MI in the OSA and NOSA cohorts was observed across all three databases. The risks of CV hospitalization in the OSA and NOSA cohorts were not different between the modafinil users and nonusers, except for IMS LifeLink database where the HR was lower than one in the modafinil users compared with the nonusers (HR, 0.69; 95% confidence interval [CI], 0.54 to 0.87). For OSA patients with prior stroke, an adjusted HR of 1.96 (95% CI, 1.02 to 3.76) was observed for stroke among modafinil users compared with nonusers. Among the NOSA, the HRs for all-cause death in the OSA were inconsistent across databases.

Conclusions: Except for few CV outcomes, applying one common protocol generated consistent risk estimates of CV events following modafinil use across cohorts and databases.

KEYWORDS

administrative claims databases, cardiovascular events, modafinil, pharmacoepidemiology, safety

1 | INTRODUCTION

Modafinil is a wakefulness-promoting agent sharing some pharmacologic properties of sympathomimetic agents including amphetamine and methylphenidate, although its pharmacologic profile is not identical to that of the sympathomimetic amines. In the US, it is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea (OSA), or shift work disorder.[1] In the European Union (EU), the labeling for modafinil has been restricted to the treatment of excessive sleepiness associated with narcolepsy with or without cataplexy.

The cardiovascular (CV) profile of modafinil is of particular interest in OSA patients given their already elevated baseline CV risk. CV adverse events, such as hypertension and arrhythmias, have been

documented in association with modafinil in clinical studies.[2,3] However, accumulating evidence suggested that hypoxemia and sleep disruption contribute to the development of CV abnormalities in OSA.[4-6] As part of the risk management plan in the EU, epidemiologic CV safety study for modafinil has been conducted in three administrative health care databases.

The purpose of this study was to examine the potential risk of CV events of interest associated with modafinil and the consistency of the risk estimates in real-world settings across three health care databases using a common study protocol. In addition, the influence of the underlying baseline characteristics across populations on the observed differences CV risk was evaluated as well.

KEY POINTS

- Risk estimates for various cardiovascular (CV) outcomes across three US claims databases were generally consistent using a common study protocol.
- The results of only few risk estimates of CV events varied and were inconsistent.
- One of the three databases suggested an increased risk of stroke in modafinil users compared with nonusers. However, the lack of consistency of the risks across cohorts and databases does not support a causal relationship between modafinil and stroke.
- Findings from these studies are likely affected by unmeasured confounding due to the inherent non-randomized design and the use of claims databases.

2 | METHODS

2.1 | Study design

A retrospective cohort study was conducted in three US health care system databases: (1) Truven Health MarketScan Commercial and Medicare Supplemental Database (MarketScan CM),[7] (2) IMS LifeLink Health Plan Claims Database (IMS LifeLink, AKA PharMetrics),[8] and (3) MarketScan Medicaid Multi-State Database (MarketScan Medicaid). These integrated commercial health plan claims data sources provide de-identified longitudinal data on patient enrollment, demographics, outpatient and inpatient medical claims, diagnoses and procedures, and pharmacy claims.

All patients prescribed modafinil between 1 January 2006 and 31 December 2008 were identified. The pre-specified primary cohort consisted of modafinil new users, defined as those who had (1) at least one prescription claim for modafinil between 1 January 2006 and 31 December 2008; (2) at least 12 months of continuous enrollment (baseline period) prior to the date of their first modafinil prescription (index date); and (3) no prior prescription for modafinil during the baseline period; and matched comparison subjects who did not use modafinil ("nonusers"). Patients were assigned to OSA and non-OSA (NOSA) cohorts, based on OSA diagnosis identified in the patient record, because OSA is an independent CV risk factor.[9,10] Each modafinil user in the OSA or NOSA groups was matched to up to three nonusers in the respective group by age, gender, and geographic region (for MarketScan CM and IMS LifeLink) and race (for MarketScan Medicaid). Nonusers were assigned the same index date as their matched modafinil users and were required to have at least 12 months of continuous enrollment prior to the index date.

During the 12-month period preceding modafinil initiation (baseline period), data were extracted on patient's characteristics, comorbidities, and drug-related therapy. The following potential risk factors were examined: hypertension, CV disease, hyperlipidemia, obesity, stroke, diabetes, smoking, number of prior hospitalizations, modified Charlson Comorbidity Index score, and illicit drug use. The Charlson Comorbidity Index was calculated by mapping the diagnosis codes in a patient's profile to the relevant score.[11-14] A pre-defined set of International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes were used to identify chronic medical conditions and comorbidities in the patient records. In addition, prescription claims filled during the baseline period for the treatment of chronic medical conditions such as hypertension, CV disease, hyperlipidemia, and diabetes were extracted and used as a proxy to identify these comorbid conditions. Additional medication classes of interest were used to account for confounding effect on the outcomes, including amphetamine stimulants (excluding modafinil), antidepressants, sympathomimetic agents; hormone replacement therapy, antiplatelet agents, and non-steroidal anti-inflammatory drugs.

2.2 | Study outcomes

Study outcomes of interest included (1) myocardial infarction (MI), (2) stroke, (3) CV hospitalization, and (4) all-cause death (MarketScan databases only) during the post-index follow-up. Myocardial infarction was defined as first occurrence of ICD-9 diagnosis code 410 recorded in the primary diagnosis field in the hospital discharge claim. This code had a high positive predictive value (92% to 96%) when located as the primary diagnosis field in the hospital discharge claim in various US health care databases.[15-18] For the MI outcome, patients with a pre-index inpatient MI were excluded and were not stratified due to their small numbers.

Stroke was defined as first occurrence of inpatient hemorrhagic or ischemic stroke. These types of stroke were combined due to the small number of events, although the majority of strokes were of ischemic nature. Stroke was identified by ICD-9 hospital discharge primary diagnosis codes of cerebral infarctions 430, 431,433.x1, 434.0, 434.1, 434.x1, 434.9, and 436. These codes had a high positive predictive value (85% to 96%) when located as the primary diagnosis in the hospital discharge claim in various US health care databases.[18-21] Inpatient stroke outcomes were stratified by the presence or absence of previous inpatient stroke recorded at baseline. In patients with a history of stroke occurring prior to the index date (pre-index stroke), a new stroke event was counted only if the time lapse between the pre-index stroke and the new stroke was more than 15 days. In these patients, any stroke occurring in less than 15 days was considered an event related to the pre-index stroke and thus

TABLE 1 Demographic and baseline characteristics of obstructive sleep apnea (OSA) and non-OSA (NOSA) cohorts stratified by modafinil treatment across databases

Characteristics	MarketScan CM Database				LifeLink Database				MarketScan Medicaid Database			
	OSA		NOSA		OSA		NOSA		OSA		NOSA	
	Modafinil users Number (%)	Nonusers Number (%)	Modafinil users Number (%)	Nonusers Number (%)	Modafinil users Number (%)	Nonusers Number (%)	Modafinil users Number (%)	Nonusers Number (%)	Modafinil users Number (%)	Nonusers Number (%)	Modafinil users Number (%)	Nonusers Number (%)
Total patients	**16 807**	**46 769**	**30 420**	**81 528**	**7 112**	**19 645**	**13 841**	**36 668**	**618**	**1742**	**1564**	**4250**
Age groups, years												
<18	242 (1.4)	654 (1.4)	1002 (3.3)	2673 (3.3)	144 (2.0)	388 (2.0)	636 (4.6)	1670 (4.6)	75 (12.1)	222 (12.7)	344 (22.0)	982 (23.1)
18-64	14 534 (86.5)	40 203 (86.0)	25 041 (82.3)	66 323 (81.3)	6 869 (96.6)	19 006 (96.7)	13 034 (94.2)	34 522 (94.1)	542 (87.7)	1519 (87.2)	1201 (76.8)	3219 (75.7)
64+	2031 (12.1)	5912 (12.6)	4377 (14.4)	12 532 (15.4)	99 (1.4)	251 (1.3)	171 (1.2)	476 (1.3)	1 (0.2)	1 (0.1)	19 (1.2)	49 (1.2)
Mean age, years (SD)	50.3 (13.7)	50.8 (13.6)	48.3 (16.7)	49.0 (16.7)	45.3 (11.6)	45.6 (11.5)	41.8 (13.0)	42.1 (13.0)	38.6 (14.2)	38.6 (14.2)	32.6 (15.6)	32.6 (15.7)
Gender												
Male	8790 (52.3)	24 472 (52.3)	10 896 (35.8)	29 516 (36.2)	3555 (50.0)	9839 (50.1)	4702 (34.0)	12 482 (34.0)	185 (30.0)	518 (30.0)	474 (30.0)	1322 (31.0)
Female	8017 (47.7)	22 297 (47.7)	19 524 (64.2)	52 012 (63.8)	3557 (50.0)	9806 (49.9)	9139 (66.0)	24 186 (66.0)	433 (70.0)	1224 (70.0)	1090 (70.0)	2928 (69.0)
Region												
Northeast	1223 (7.3)	3347 (7.2)	2733 (9.0)	7265 (8.9)	1242 (17.5)	3432 (17.5)	2978 (21.5)	8001 (21.8)	N/A	N/A	N/A	N/A
North central	4746 (28.2)	13 284 (28.4)	7373 (24.2)	19 883 (24.4)	3003 (42.2)	8397 (42.7)	4308 (31.1)	11 764 (32.1)				
South	8578 (51.0)	23 819 (50.9)	15 493 (50.9)	41 227 (50.6)	1922 (27.0)	5135 (26.1)	5172 (37.4)	13 050 (35.6)				
West	2207 (13.1)	6167 (13.2)	4713 (15.5)	12 875 (15.8)	945 (13.3)	2681 (13.6)	1383 (10.0)	3853 (10.5)				
Unknown	53 (0.3)	152 (0.3)	108 (0.4)	278 (0.3)								
Race												
White	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	412 (66.7)	1162 (66.7)	1196 (76.5)	3250 (76.5)
Black									147 (23.8)	413 (23.7)	165 (10.5)	460 (10.8)
Hispanic									6 (1.0)	15 (0.9)	26 (1.7)	68 (1.6)
Other									53 (8.6)	152 (8.7)	177 (11.3)	472 (11.1)
Mean follow-up (SD), days	681 (364.7)	689 (365.0)	676 (392.0)	767 (378.5)	606 (348.5)	613 (346.8)	566 (356.4)	670 (358.0)	574 (398.9)	591 (403.2)	506 (415.6)	579 (450.2)
History of medical risk factors												
Hypertension	9662 (57.5)	26 466 (56.6)	12 747 (41.9)	31 587 (38.7)	3658 (51.4)	9587 (48.8)	4480 (32.4)	10 066 (27.5)	363 (58.7)	947 (54.4)	480 (30.7)	1119 (26.3)
Cardiovascular disease	1313 (7.8)	3541 (7.6)	1682 (5.5)	3632 (4.5)	1227 (17.3)	3261 (16.6)	1675 (12.1)	4013 (10.9)	80 (12.9)	184 (10.6)	72 (4.6)	134 (3.2)
Hyperlipidemia	8551 (50.9)	23 293 (49.8)	10 116 (33.3)	26 708 (32.8)	3245 (45.6)	8535 (43.4)	3799 (27.4)	9106 (24.8)	241 (39.0)	668 (38.3)	299 (19.1)	737 (17.3)
Obesity	1291 (7.7)	3122 (6.7)	659 (2.2)	1479 (1.8)	1094 (15.4)	2531 (12.9)	549 (4.0)	1099 (3.0)	158 (25.6)	446 (25.6)	98 (6.3)	224 (5.3)
Stroke[a]	491 (2.9)	824 (1.8)	1114 (3.7)	1514 (1.9)	145 (2.0)	166 (0.8)	269 (1.9)	269 (0.7)	16 (2.6)	29 (1.7)	45 (2.9)	60 (1.4)
Inpatient stroke	150 (0.9)	228 (0.5)	523 (1.7)	453 (0.6)	15 (0.2)	18 (0.1)	45 (0.3)	22 (0.1)	7 (1.1)	16 (0.9)	22 (1.4)	10 (0.2)
Diabetes	3934 (23.4)	11 020 (23.6)	3760 (12.4)	9962 (12.2)	1508 (21.2)	3854 (19.6)	1269 (9.2)	3060 (8.3)	186 (30.1)	513 (29.4)	191 (12.2)	467 (11.0)
Smoking	609 (3.6)	1217 (2.6)	1157 (3.8)	2399 (2.9)	455 (6.4)	862 (4.4)	904 (6.5)	1898 (5.2)	131 (21.2)	284 (16.3)	199 (12.7)	551 (13.0)

(Continues)

TABLE 1 (Continued)

Characteristics	MarketScan CM Database				LifeLink Database				MarketScan Medicaid Database			
	OSA		NOSA		OSA		NOSA		OSA		NOSA	
	Modafinil users Number (%)	Nonusers Number (%)	Modafinil users Number (%)	Nonusers Number (%)	Modafinil users Number (%)	Nonusers Number (%)	Modafinil users Number (%)	Nonusers Number (%)	Modafinil users Number (%)	Nonusers Number (%)	Modafinil users Number (%)	Nonusers Number (%)
Total patients	**16 807**	**46 769**	**30 420**	**81 528**	**7 112**	**19 645**	**13 841**	**36 668**	**618**	**1742**	**1564**	**4250**
Illicit drug use	31 (0.2)	25 (0.1)	167 (0.5)	187 (0.2)	20 (0.3)	10 (0.1)	132 (1.0)	168 (0.5)	12 (1.9)	15 (0.9)	44 (2.8)	78 (1.8)
Amphetamine stimulants	1505 (9.0)	1327 (2.8)	3731 (12.3)	1441 (1.8)	738 (10.4)	573 (2.9)	1837 (13.3)	761 (2.1)	80 (12.9)	72 (4.1)	329 (21.0)	235 (5.5)
Antidepressants	10 577 (62.9)	16 048 (34.3)	20 040 (65.9)	18 016 (22.1)	4330 (60.9)	6871 (35.0)	8774 (63.4)	7882 (21.5)	415 (67.2)	903 (51.8)	1085 (69.4)	1561 (36.7)
Sympathomimetic agents	4272 (25.4)	9331 (20.0)	6115 (20.1)	12 153 (14.9)	1708 (24.0)	3740 (19.0)	2514 (18.2)	5162 (14.1)	280 (45.3)	758 (43.5)	434 (27.7)	1060 (24.9)
HRT- estrogens	1644 (9.8)	3220 (6.9)	3828 (12.6)	7263 (8.9)	614 (8.6)	1177 (6.0)	1410 (10.2)	2587 (7.1)	53 (8.6)	101 (5.8)	127 (8.1)	231 (5.4)
Antiplatelet agents	955 (5.7)	2395 (5.1)	1199 (3.9)	2838 (3.5)	217 (3.1)	505 (2.6)	211 (1.5)	415 (1.1)	35 (5.7)	77 (4.4)	44 (2.8)	91 (2.1)
Non-steroidal/anti-inflammatory	5776 (34.4)	12 579 (26.9)	9233 (30.4)	25 322 (31.1)	2307 (32.4)	4918 (25.0)	4026 (29.1)	9593 (26.2)	310 (50.2)	829 (47.6)	643 (41.1)	1798 (42.3)
One hospitalization	1927 (11.5)	4954 (10.6)	3964 (13.0)	6463 (7.9)	642 (9.0)	1701 (8.7)	1279 (9.2)	2394 (6.5)	103 (16.7)	269 (15.4)	219 (14.0)	505 (11.9)
Two hospitalizations	757 (4.5)	1434 (3.1)	1865 (6.1)	1587 (1.9)	322 (4.5)	521 (2.7)	659 (4.8)	650 (1.8)	70 (11.3)	185 (10.6)	144 (9.2)	173 (4.1)
Charlson comorbidity score												
0	10 988 (65.4)	33 587 (71.8)	21 350 (70.2)	65 800 (80.7)	4626 (65.0)	14 083 (71.7)	10 217 (73.8)	30 152 (82.2)	327 (52.9)	871 (50.0)	1060 (67.8)	3108 (73.1)
1	3517 (20.9)	8125 (17.4)	4805 (15.8)	9506 (11.7)	1623 (22.8)	3820 (19.4)	2191 (15.8)	4312 (11.8)	193 (31.2)	577 (33.1)	318 (20.3)	830 (19.5)
2+	2302 (13.7)	5057 (10.8)	4265 (14.0)	6222 (7.6)	863 (12.1)	1742 (8.9)	1433 (10.4)	2204 (6.0)	98 (15.9)	294 (16.9)	186 (11.9)	312 (7.3)

Abbreviations: HRT, hormone replacement therapy; N/A, not available; NOS, non-OSA; OSA, obstructive sleep apnea; SD, standard deviation.

[a]Inpatient and outpatient stroke.

precluding potential selection bias arising from misclassification of stroke events.

Cardiovascular hospitalization was defined as a composite of CV events recorded in the hospital discharge claim and recorded in the primary diagnosis field. CV events were identified by ICD diagnosis codes, diagnosis-related group codes, or Current Procedural Terminology codes, based on previously published CV outcome codes.[22-29]

All-cause death was defined as death from any cause identified in inpatient hospital settings. Since administrative databases may not reliably capture death, an additional method was used as a proxy to identify death cases.[30] The proxy procedure included identification of patients for whom there was no claim recorded in the post-index period for ≥6 months until end of the patient's enrollment or end of the study period. Death was determined when the events likely to be fatal (eg, cardiac arrest, resuscitation, or hospitalization) occurred during the last month of activity. All-cause death was captured only in the MarketScan CM and Medicaid Databases and evaluated as a rough indicator for CV death since CV disease is the leading cause of death in older adults.[31,32]

2.3 | Follow-up and analysis

Patients in the OSA and NOSA cohorts were followed up from the index date until the earliest occurrence of one of the following events: study outcome, end of membership enrollment, or end of the study period (31 December 2009). Incidence rates of outcomes of interest with 95% confidence intervals (CIs) between modafinil users and nonusers in the OSA and NOSA cohorts were calculated as the number of events divided by cumulative cohort follow-up time (person-time). Survival analysis plots were generated showing time to event for all end points. Hazard ratios (HRs) with 95% CIs were calculated for each of the study endpoints using Cox proportional hazards models adjusted for covariates. The following covariates were used in the multivariate models: history of hypertension, history of CV disease (MI, unstable angina, stroke, coronary bypass surgery, coronary angioplasty), diabetes, hyperlipidemia, obesity, illicit drug use, and therapeutic class drugs used as proxy indicators for the presence of disease. Additional covariates included Charlson comorbidity score (0, 1, 2+), number of hospitalizations, medication classes: amphetamine stimulants (excluding modafinil), antidepressants, sympathomimetic agents, hormone replacement therapy, antiplatelet agents, and non-steroidal anti-inflammatory drugs. Age, gender, region (for MarketScan CM and IMS LifeLink), and race (for MarketScan Medicaid) were controlled by matching. Analyses were performed using SAS version 9.2.

3 | RESULTS

3.1 | Baseline characteristics

During the 3-year study period, the cohorts included a total of 175 524 patients (63 576 OSA and 111 948 NOSA) in MarketScan CM; 77 266 (26 757 OSA and 50 509 NOSA)—in IMS LifeLink; and 8174 (2360 OSA and 5814 NOSA)—patients in MarketScan Medicaid. The characteristics of OSA and NOSA cohorts stratified by modafinil use for all three databases are shown in Table 1.

After matching for baseline characteristics, the modafinil users and nonusers were similar with respect to age, gender, with the exception of a slight imbalance in prior medical history (for example, stroke), and medication use. The study population was younger in the MarketScan CM than in the IMS LifeLink (mean age 45 vs 50 years in the OSA modafinil users, respectively, and 42 vs 48 years in the NOSA modafinil users, respectively). In the MarketScan Medicaid, the mean age of patients was 39 (SD = 14.2) and 33 (SD = 15.6) years for OSA and NOSA groups, respectively. In the MarketScan CM, patients aged 65 years or older accounted for approximately 12% and 15% of the OSA and NOSA cohorts, respectively, whereas in the IMS LifeLink and MarketScan Medicaid Databases, less than 2% of the patients were aged 65 years or older. In the MarketScan Medicaid, the study population consisted mostly of women (70%), and a substantial proportion of the population was <18 years of age (>10% and > 20% in the OSA and NOSA groups, respectively).

3.2 | Crude incidence rates

The crude incidence rates of the outcomes of interest for the modafinil users and nonusers in the OSA and NOSA cohorts in each of the databases are shown in Table 2.

3.2.1 | MI

For OSA patients, the unadjusted incidence rate of MI ranged from 1.6 to 4.6/1000 person-years and was higher in modafinil users than nonusers in the MarketScan CM but not in the IMS LifeLink and MarketScan Medicaid. In the NOSA cohort, a similar pattern was seen where the unadjusted incidence rate of MI ranged from 0.9 to 3.6/1000 person-years and was higher in modafinil users than nonusers in MarketScan CM but not in the IMS LifeLink and MarketScan Medicaid.

3.2.2 | CV hospitalization

The unadjusted incidence rate of CV hospitalization in OSA patients was higher in modafinil users than nonusers in IMS LifeLink but not in the MarketScan CM and MarketScan Medicaid. In the NOSA cohort, the unadjusted incidence rate of CV hospitalization was higher in modafinil users than nonusers in MarketScan CM but not in IMS LifeLink and MarketScan Medicaid.

3.2.3 | Stroke

For OSA patients with prior stroke or those without prior stroke, the unadjusted incidence rate of stroke was higher in modafinil users than nonusers in MarketScan CM but not in IMS LifeLink and MarketScan Medicaid. The crude stroke rate was generally higher in patients with prior stroke than in patients without prior stroke. In the NOSA cohort, similar patterns were seen.

3.2.4 | All-cause death

For OSA patients, the unadjusted incidence rate of all-cause death was higher in modafinil users than nonusers in MarketScan Medicaid but not in MarketScan CM. In the NOSA cohort, the unadjusted

TABLE 2 Cardiovascular incidence events among modafinil users and nonusers with obstructive sleep apnea (OSA) and non-OSA (NOSA), by database: 1 January 2006 to 31 December 2009

Cohort	Database	Modafinil Users			Nonusers		
		Events/persons	Events/1000 PY	95% CI	Events/persons	Events/1000 PY	95% CI
		Myocardial infarction					
OSA	MarketScan CM	140/16 748	4.5	3.7-5.2	320/46 577	3.6	3.2-4.0
	IMS LifeLink	22/7104	1.9	1.1-2.6	53/19 606	1.6	1.2-2.0
	MarketScan Medicaid	3/615	3.1	0.0-6.6	13/1734	4.6	2.1-7.1
NOSA	MarketScan CM	200/30 315	3.6	3.1-4.0	477/81 294	2.8	2.5-3.0
	IMS LifeLink	19/13 829	0.9	0.5-1.3	67/36 626	1	0.8-1.2
	MarketScan Medicaid	6/1560	2.8	0.6-5.0	9/4240	1.3	0.5-2.2
		CV hospitalization					
OSA	MarketScan CM	643/16 807	20.9	19.3-22.5	1747/46 769	20.2	19.2-21.1
	IMS LifeLink	164/7112	14.1	11.9-16.2	379/19 645	11.6	10.5-12.8
	MarketScan Medicaid	25/618	26.7	16.2-37.1	96/1742	35.2	28.1-42.2
NOSA	MarketScan CM	802/30 420	14.4	13.4-15.4	2083/81 528	12.3	11.8-12.8
	IMS LifeLink	106/13 841	5	4.0-5.9	389/36 668	5.8	5.2-6.4
	MarketScan Medicaid	18/1564	8.3	4.5-12.2	55/4250	8.2	6.0-10.4
		Stroke (with baseline stroke)					
OSA	MarketScan CM	27/150	113.1	70.5-155.8	20/228	48.4	27.2-69.6
	IMS LifeLink	1/15	49.9	0.0-147.6	0/18	0	0.0-0.0
	MarketScan Medicaid	2/7	194.1	0.0-463.0	1/16	72.4	0.0-214.3
NOSA	MarketScan CM	81/523	103.2	80.7-125.7	51/453	61.5	44.6-78.4
	IMS LifeLink	2/45	32.8	0.0-78.4	2/22	68.2	0.0-162.6
	MarketScan Medicaid	2/22	79.2	0.0-189.0	0/10	0	0.0-0.0
		Stroke (without baseline stroke)					
OSA	MarketScan CM	162/16 657	5.2	4.4-6.0	372/46 541	4.2	3.8-4.7
	IMS LifeLink	15/7097	1.3	0.6-1.9	34/19 627	1	0.7-1.4
	MarketScan Medicaid	4/611	4.2	0.1-8.2	18/1726	6.4	3.5-9.4
NOSA	MarketScan CM	320/29 897	5.8	5.1-6.4	621/81 075	3.6	3.4-3.9
	IMS LifeLink	7/13 796	0.3	0.1-0.6	38/36 646	0.6	0.4-0.7
	MarketScan Medicaid	10/1542	4.7	1.8-7.6	27/4240	4	2.5-5.5
		All-cause death					
OSA	MarketScan CM	62/16 807	2	1.5-2.5	169/46 769	1.9	1.6-2.2
	IMS LifeLink	N/A			N/A		
	MarketScan Medicaid	0/618	0	0.0-0.0	24/1742	8.5	5.1-11.9
NOSA	MarketScan CM	232/30 420	4.1	3.6-4.6	248/81 528	1.4	1.3-1.6
	IMS LifeLink	N/A			N/A		
	MarketScan Medicaid	4/1564	1.8	0.8-4.3	16/4250	2.4	0.0-3.6

*P-value <0.05 and is statistically significant.

Abbreviations: CI, confidence interval; CV, cardiovascular; N/A, not available; NOSA, non-OSA; OSA, obstructive sleep apnea; PY, patient-years.

incidence rate of all-cause death was higher in modafinil users than nonusers in MarketScan CM but not in the MarketScan Medicaid.

3.3 | Adjusted hazard ratios

The adjusted HRs of outcomes of interest for the modafinil users and nonusers in the OSA and NOSA cohorts in each of the databases are shown in Figure 1.

3.3.1 | MI

The adjusted HRs for MI in the OSA cohorts were not statistically different across all databases suggesting comparable MI incidence rate between modafinil users and nonusers. Similar patterns were reported in the NOSA across all databases. The HRs in the OSA and NOSA varied slightly around the threshold of one for all databases except for MarketScan Medicaid. In the latter, the HR estimates were above or below one but were not different than one due to the wide CIs.

3.3.2 | CV hospitalization

Similar to the MI outcome, the adjusted HRs of CV hospitalization in the OSA cohorts were not statistically different across all databases, suggesting that the rate of CV hospitalization was similar between modafinil users and nonusers. Similar patterns were found in the NOSA across all databases, but for IMS LifeLink where the HR was lower than one in the modafinil users compared with the nonusers (HR, 0.69; 95% CI, 0.54 to 0.87).

3.3.3 | Stroke

Due to the small sample size for OSA patients with prior stroke, the adjusted HRs were calculated only in the MarketScan CM. For OSA patients with prior stroke, an adjusted HR of 1.96 (95% CI, 1.02 to 3.76) was observed for stroke among modafinil users compared with nonusers.

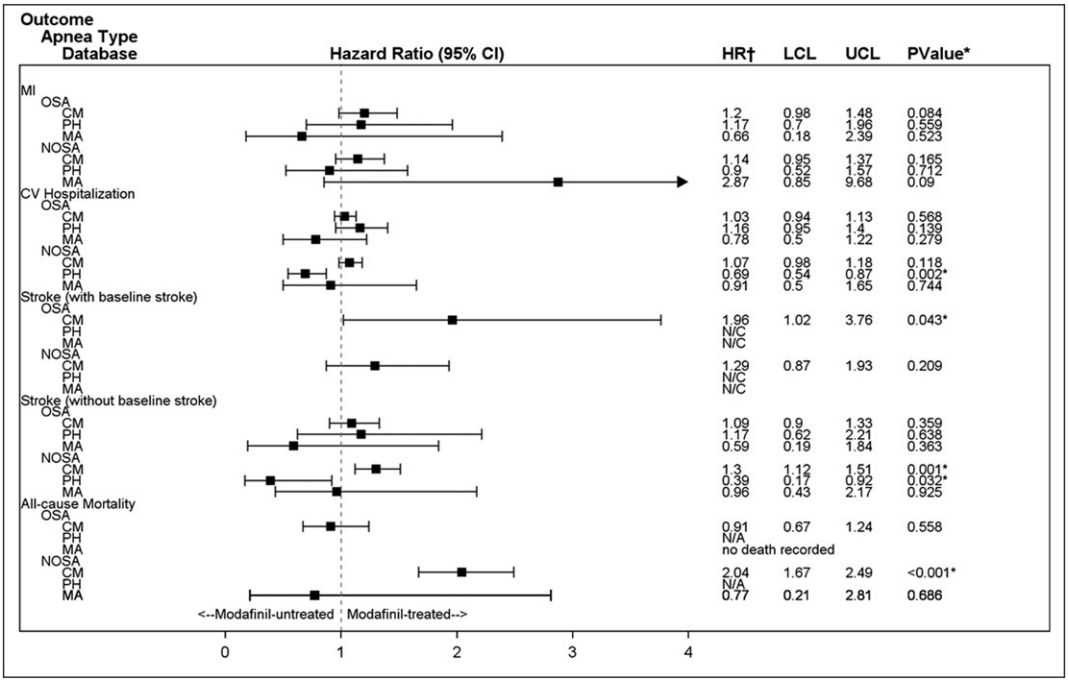

FIGURE 1 Adjusted hazard ratios for outcomes of interest among modafinil users and nonusers with obstructive sleep apnea (OSA) and non-OSA (NOSA), across databases: 1 January 2006 to 31 December 2009† hazard ratios for outcomes are referenced to modafinil exposure, adjusted for covariates.* *P*-value <0.05 is considered statistically significantOSA = obstructive sleep apnea; NOSA = non-OSA; CM = MarketScan Commercial Claims and Encounters Database; PH = IMS LifeLink Database, AKA PharMetrics; MA = MarketScan Multi-State Medicaid Database; HR = hazard ratio; CI = confidence interval; UCL = upper confidence limit; LCL = lower confidence limit CV = cardiovascular; N/C = not calculated (number of cases too small); N/A = not available.

In NOSA patients without a prior history of stroke, the HR for stroke was inconsistent across databases, showing an increased risk in MarketScan CM (HR, 1.30; 95% CI, 1.12 to 1.51), a decreased risk in IMS LifeLink (HR, 0.39; 95% CI, 0.17 to 0.92), and no difference in MarketScan Medicaid.

3.3.4 | All-cause death

All-cause death in the OSA was calculated only in the MarketScan CM showing no difference between modafinil users and nonusers. Among the NOSA cohort, the HRs for all-cause death in the NOSA were inconsistent between the databases, showing an increased risk in MarketScan CM (HR, 2.04; 95% CI, 1.67 to 2.49), and no difference in MarketScan Medicaid.

4 | DISCUSSION

In the context of a modafinil CV safety study, the incidence rates and the risk estimates of various CV events between modafinil users and nonusers were compared across three US administrative health care databases, applying a standardized methodology. The risk estimates for CV events between modafinil users and nonusers were not consistent and varied. For most events, there was no indication for increased risk across the three databases. For stroke, though, results suggested an increased stroke rate in modafinil users compared with nonusers. Specifically, modafinil was associated with nearly doubling the rate of stroke in a subgroup of OSA patients with prior stroke. However, the lack of increased risk of stroke among NOSA with prior stroke does not support causal relationship. Similarly, in NOSA patients with no prior stroke, modafinil exposure appeared to display divergent results between the three databases, with one showing an increased risk of stroke and the other—a decreased risk. Similarly, the inconsistencies across cohorts and databases do not support a causal relationship between modafinil and stroke. In addition, all-cause death rate was higher among modafinil users compared with nonusers but only among NOSA suggesting the possibility that modafinil was prescribed to the frailest patients, who might have had a greater risk of all-cause death not accounted for due to unmeasured confounding.

The study results are generally consistent with a case-control study conducted to evaluate CV outcomes in patients with OSA prescribed stimulant, including modafinil.[33] The study found that stimulant medications were not associated with elevated risk of mortality, implantable cardioverter-defibrillator, or pacemaker insertion. In addition, the incidence rates of CV outcomes in our study are generally within the range reported for the US population. The incidence of MI and first stroke in the general US population aged 35 to 64 years ranges from 0.2 to 5.5 (and up to 11.5 through age of 84 years) cases/1000 patient-years (PY), and 1.0 to 5.3 cases/1000 PY (and up to 32.1 through age of 85 years) cases/1000 patient-years (PY), respectively, and varied by age, race, and gender.[32] The proportions of recurrent stroke observed in the three databases were within, or slightly above, the range reported in the general US population aged 45 years and older (ranging from 6% to 25%).[32] Given possible

differences in demography and clinical characteristics between the study population and the general US population, the study rates and the reference rates are largely comparable.

The potential source of variation across databases should be mentioned. Some of the inconsistencies in the results can be explained by the database size and the underlying population characteristics that were examined as part of the secondary objective of this study. The MarketScan CM Database consists of a relatively large sample size with representation of the elderly population. IMS LifeLink Database has a somewhat smaller sample size, and it includes a relatively younger population with a lower baseline rate of CV events. MarketScan Medicaid Database, on the other hand, consists of a much younger, low-income population, the majority of which is female (usually pregnant women), but also families with children, and elderly or chronically disabled persons. Thus, the MarketScan CM and the IMS LifeLink databases appear to be more suitable to assess the study objectives.

An important limitation of the study is the potential for unmeasured confounding due to the inherent non-randomized design and the use of claims databases. Administrative data lack the clinical details that may be used as potential confounders, such as indication, disease severity, smoking, and blood pressure measurements. Indeed, the results suggested that modafinil users had generally more comorbidities and used more medications to treat underlying comorbidities. Accordingly, modafinil may have been prescribed to the frailest population among the NOSA who might have had a greater risk of all-cause death. Moreover, it was not possible to adjust for the reason for which modafinil was prescribed, severity of OSA, and other comorbidities. Other explanation could be misclassification of the underlying condition, OSA. It could be possible that patient classified as NOSA had undiagnosed OSA, especially since it is not clear if OSA patients were treated adequately. Therefore, even after adjusting for potential confounders, confounding by indication and by disease severity cannot be ruled out and the risks reported might be artificially elevated to an unknown magnitude.

Misclassification of exposure or outcome is another potential limitation of observational studies. In this study, subjects were classified as modafinil initiators at cohort entry and were considered exposed throughout the follow-up. This method is the observational analog of an intention-to-treat clinical trial design. As in clinical trials, this approach may misclassify users and nonusers once therapy is discontinued, but it has the advantage of preserving the between-group balance obtained by the cohort matching process at baseline. To minimize misclassification of outcome, CV outcome diagnoses were identified solely from inpatient claims using codes that have been consistently well-validated in previous studies since an independent case validation could not be performed.[15-21,34] Still misclassification of stroke outcome could have been occurred as it is possible that in modafinil users with OSA and a history of stroke, the outcome of incident stoke was not a new stroke but rather event related to previous stroke.

Deaths from any cause were identified from inpatient hospital settings. Nonetheless, the outcome measure of death should be regarded with caution as the validity of death status in these studies has not been assessed. Of note, CV disease accounts for only 30% of all global deaths.[32] Thus, it is not clear whether the increased risk of deaths observed is indeed CV related, especially given that the risk was not elevated for other CV outcomes.

Another limitation is the stratified analyses for stroke that resulted in low event rate and, consequently, limited precision. Furthermore, multiplicity could account for the statistically significant results in some of the stratified analyses, especially given the number of databases, cohorts, and outcomes.

Finally, the potential for information bias due to differentiation in the medical care and follow-up between the groups is noteworthy. Nonusers were subjects who did not receive a modafinil prescription throughout the study period and thus may be subject to less surveillance for detecting adverse outcomes, although the study outcomes are unlikely to be overlooked. Moreover, in the United States, modafinil is classified as a schedule IV-controlled substance and has restricted availability and use due to potential addiction concerns. As a result, it is possible that modafinil users would be followed up more closely compared with nonusers. However, given the severity and the expected high positive predictive value of the outcomes of interest, information bias for the primary endpoints seems unlikely.

5 | CONCLUSIONS

Using one common protocol showed an overall consistency in the risk estimates of CV events across all three databases. However, there were few risk estimates that were not consistent. The lack of consistency of the risks across cohorts and databases does not support a causal relationship between modafinil and stroke.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

ACKNOWLEDGEMENTS

We would like to acknowledge Angel Angelov, MD, for reviewing the manuscript and Varinder P Singh, MS, for his assistance in analyzing the datasets.

CONFLICT OF INTEREST

Sigal Kaplan, Sigal Melamed-Gal, and Helena Knebel are employees of Teva Pharmaceutical Industries Ltd. and/or its affiliates. Earl L. Goehring Jr., Bao-Anh Nguyen-Khoa, and Judith K Jones are employees of The Degge Group, Ltd., which received financial support from Teva to conduct this research.

FUNDING

This study was funded by Teva Pharmaceutical Industries Ltd.

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How to cite this article: Kaplan S, Goehring Jr. EL, Melamed-Gal S, Nguyen-Khoa B-A, Knebel H, Jones JK. Modafinil and the risk of cardiovascular events: Findings from three US claims databases. *Pharmacoepidemiol Drug Saf*. 2018;1–9. https://doi.org/10.1002/pds.4642