# Incidence of Cardiovascular Outcomes and Diabetes Mellitus Among Users of Second-Generation Antipsychotics

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**ABSTRACT**

***Objective:*** To examine the risk of cardiovascular outcomes and diabetes mellitus in patients prescribed second-generation antipsychotics.

***Method:*** From the MarketScan claims database, nondiabetic adults prescribed aripiprazole between July 2003 and March 2010 were propensity score–matched with patients prescribed olanzapine, quetiapine, risperidone, and ziprasidone. Patients were followed through the claims for *International Classification of Diseases, Ninth Revision* codes indicating myocardial infarction, stroke, heart failure, coronary bypass/angioplasty procedures, and incident diabetes. Incidence rates of each outcome were calculated and compared between aripiprazole and the other second-generation antipsychotics using Cox models.

***Results:*** Aripiprazole initiators were matched 1:1 to 9,917 olanzapine, 14,935 quetiapine, 10,192 risperidone, and 5,696 ziprasidone initiators. Increased risk was found with olanzapine for stroke (hazard ratio = 1.43; 95% confidence interval, 1.05–1.95) and any cardiovascular event (1.28; 1.05–1.55); with quetiapine for stroke (1.58; 1.19–2.09), heart failure (1.55; 1.15–2.11), and any cardiovascular event (1.50; 1.25–1.79); and with risperidone for stroke (1.54; 1.12–2.12), heart failure (1.43; 1.02–1.99), and any cardiovascular event (1.49; 1.21–1.83). Ziprasidone showed no significant difference in risk from aripiprazole for any outcome. Incidence of diabetes ranged from 18 to 21 events per 1,000 person-years in each cohort and did not differ significantly between second-generation drugs.

***Conclusions:*** This analysis of real-world data found lower risk of some cardiovascular events with aripiprazole than with olanzapine, quetiapine, or risperidone, but no differences were found with ziprasidone. There were no significant differences in risk of diabetes. Limitations include use of claims data and inability to adequately control for differential prescribing of second-generation antipsychotics to patients at higher risk of diabetes.

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Second-generation antipsychotics are used to treat schizophrenia and bipolar disorder; some are also indicated for adjunctive use in major depressive disorder. Although second-generation antipsychotics have generally demonstrated improved tolerability with respect to extrapyramidal adverse effects relative to conventional (or typical, first-generation) antipsychotics, there is evidence that some second-generation antipsychotics are associated with adverse metabolic events.[1,2]

Research to date has demonstrated considerable variation in metabolic outcomes among different second-generation antipsychotics, potentially indicating the absence of a specific class effect.[1–4] For example, in a large effectiveness study[5] that randomly assigned 1,493 persons with schizophrenia to receive double-blind olanzapine, quetiapine, risperidone, ziprasidone, or perphenazine for up to 18 months, the group receiving olanzapine experienced marked weight gain and metabolic sequelae. This was not observed for patients randomly assigned to ziprasidone. Aripiprazole was not yet approved for use when this study began and was therefore not included, but results from other clinical trials have indicated the presence of a neutral metabolic profile for aripiprazole as well.[6] The American Diabetes Association/American Psychiatric Association consensus statement on antipsychotic drugs and obesity and diabetes notes that aripiprazole and ziprasidone are the 2 second-generation antipsychotic agents with the lowest risk for metabolic disturbances, although data are limited.[7] Current recommendations include monitoring weight and metabolic variables for all patients receiving second-generation antipsychotics not only to screen for potential adverse effects of the drugs but also because patients with schizophrenia and other serious mental disorders have a higher baseline risk for cardiometabolic problems.[7–11] Yet, despite the observed risk of cardiometabolic disorders seen with some second-generation antipsychotics, some studies have demonstrated no increase in risk of death from cardiovascular disease compared to patients with serious mental illness who are not receiving antipsychotics.[10,11]

Pharmacoepidemiologic approaches have been used to estimate the risk of diabetes developing among patients exposed to antipsychotics.[4,12–16] Challenges include the retrospective nature of the available data, variability in data quality and quantity, absence of information regarding actual adherence, differing criteria for identifying incident diabetes, and inconsistent identification in use of non-psychotropic diabetogenic medications.[17] Antipsychotics may be preferentially prescribed to patients with particular diagnoses or disease severity levels, which can impact risk estimates. Differing diabetes surveillance rates can also be a confounder, if such surveillance decisions are made on the basis of choice of antipsychotic being prescribed or baseline risk factors present in a given individual.[16,18]

Studies comparing the rates of metabolic events among the different second-generation antipsychotics have used data that are

**Clinical Points**

- Some second-generation antipsychotics are associated with risk of adverse metabolic effects.
- Aripiprazole and ziprasidone may be associated with lower risk of some cardiovascular events than olanzapine, quetiapine, and risperidone.

now several years old, with few follow-up data regarding aripiprazole or ziprasidone, and have been particularly lacking in examination of cardiovascular outcomes. The present study examined the risk associated with use of aripiprazole compared to other individual second-generation antipsychotic agents for major cardiovascular outcomes including myocardial infarction, stroke, heart failure, and coronary artery bypass grafting/percutaneous transluminal coronary angioplasty (CABG/PTCA), as well as new-onset diabetes mellitus, using one of the largest claims databases in the United States.

## METHOD

### Data Source

This retrospective cohort study employed a purchased data extract from the Truven Health MarketScan claims database (Truven Health Analytics, Inc, Ann Arbor, Michigan; http://marketscan.truvenhealth.com), which constitutes an integrated set of fully adjudicated medical and pharmaceutical claims for all covered services. It includes inpatient and outpatient diagnoses and procedures and both retail pharmacy and mail-order prescription records. MarketScan is a Health Insurance Portability and Accountability Act of 1996–compliant, fully integrated patient-level database containing inpatient, outpatient, and prescription drug information from a commercial population. The data reflect real-world treatment patterns and costs of treatment in more than 20 million patients across the United States. Rigorous validation methods applied by the vendor ensure that claims and enrollment data are complete, accurate, and reliable. Research studies of MarketScan data have been published in more than 100 peer-reviewed journals over the past 5 years.[19–23]

### Cohort Selection

From the database, all patients who received a first dispensing of a second-generation antipsychotic (aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone) from July 2003 to March 2010 were selected. Clozapine was originally included in the analysis but was dropped because of insufficient sample size. Each patient was assigned an index date corresponding to the date of first dispensing of a qualifying antipsychotic medication. Included patients were 18–64 years old on the index date, were continuously enrolled in the health plan for ≥ 6 months before and after the index date, and had ≥ 2 pharmacy claims or a 60-day supply of the second-generation antipsychotic agent during the first 6 months after the index date. Patients were excluded if they had claims for any second-generation antipsychotic during the 6 months prior to the index date, if they received more than 1 of the study drugs on the index date, or if they had evidence of diabetes (defined as a diabetes diagnosis or pharmacotherapy for diabetes) during the 6 months prior to the index date. Additionally, because diabetes that is first diagnosed very shortly after drug initiation is likely to reflect a prevalent condition rather than new-onset diabetes mellitus associated with drug exposure, patients whose first diagnosis of new-onset diabetes mellitus occurred during the first 45 days of follow-up were excluded from the analyses.

### Outcomes

Each patient was followed from the index date to the earliest event of a switch or discontinuation of the index second-generation antipsychotic, disenrollment from the health plan, or the end of the study period (September 30, 2010) to search for outcomes; only the first occurrence of each outcome type was identified. Medication switching was defined as a first fill of a different second-generation antipsychotic from the index drug, and discontinuation was defined as a gap in supply time of the index drug > 30 days. The following outcomes were sought from the medical claims during their entire exposure period:

- New-onset or recurrent myocardial infarction, defined as ≥ 1 primary inpatient *International Classification of Diseases*, *Ninth Revision* (*ICD-9*) code for myocardial infarction;
- New-onset or recurrent stroke, defined as ≥ 1 primary inpatient *ICD-9* code for stroke;
- New-onset or recurrent heart failure, defined as ≥ 1 primary inpatient *ICD-9* code for heart failure;
- New-onset or recurrent CABG/PTCA, defined as ≥ 1 primary inpatient procedure code for CABG or PTCA;
- Any cardiovascular event, defined as the first of any of the above 4 events; and
- New-onset diabetes mellitus, defined as ≥ 1 inpatient or outpatient, primary or secondary *ICD-9* diagnosis code for type II diabetes mellitus or 1 National Drug Code identifier for the following antidiabetic medications: insulin, biguanides, thiazolidinediones, sulfonylureas, non-sulfonylurea secretagogues (including meglitinides), α-glucosidase inhibitors, and peptide analogs (which included glucagon-like peptide agonists and dipeptidyl peptidase-4 inhibitors).

### Baseline Covariates

Each patient was classified with respect to age on the index date, gender, geographic region, health plan type, and year of index date. Medical history included the type of psychiatric diagnosis (bipolar disorder, major depressive disorder, schizophrenia, and all other mental health conditions), history of major comorbid conditions (hyperlipidemia, hypertension, obesity, and peripheral vascular disease), and

history of each of the cardiovascular outcome events. The Charlson Comorbidity Index, a measure of a patient's overall comorbidity burden that has been found to predict numerous clinical outcomes,[24] was calculated from medical claims in the 6-month baseline period. The number of psychiatric diagnosis groups,[25] which include mental disorders not included in the Charlson Comorbidity Index, was also computed for each patient. Patients' pre-index claims for pharmacotherapy, including antiarrhythmics, anticonvulsants, antidepressants, antihypertensives, antithrombotic agents, cholesterol-lowering agents, corticosteroids, lithium, oral contraceptives, and phenytoin, were noted. Dose of the index antipsychotic drug was categorized as low, medium, or high on the basis of the dose ranges indicated in the product labels, where low dose is defined as below the lowest indicated dose, medium is within the labeled dose range, and high is above the highest labeled dose.

### Statistical Analysis

Because random assignment to treatment groups is not possible in real-world retrospective settings, certain drugs may be preferentially prescribed if, for example, one drug is seen as having a lower chance of promoting cardiovascular disease than another. Propensity score matching is a technique that allows the creation of groups that are similar on the identified patient characteristics, thereby permitting appropriate comparisons of outcomes even if the full population of users of a given drug is substantially different on average than users of a comparator drug. Using propensity score matching, 4 pairs of balanced groups were created, with patients receiving aripiprazole used as the reference group and patients receiving each of the other 4 drugs selected into comparator groups. First, a logistic regression model was constructed for each pair of drugs (aripiprazole vs other second-generation antipsychotic), where receipt of aripiprazole versus the comparator drug was the outcome and all of the baseline characteristics, including dose of the index drug, were used as predictors. From these models, each patient received a propensity score indicating the probability, given their baseline characteristics, of having received aripiprazole as opposed to the comparator treatment. Each aripiprazole user was matched on these scores to a user of the given comparator drug, using a "greedy" match algorithm with a caliper (ie, maximum difference between scores in pairs) of 0.01, which produces a sufficient number of appropriately matched pairs in order to conduct our analyses.[26]

Taking only the matched pairs of aripiprazole users and users of each comparator drug, the incidence rate of each outcome was calculated as the number of patients with the event divided by the total person-time at risk. Each patient's time at risk was the number of days of follow-up before medication switch/discontinuation, disenrollment, or study end; for patients with an outcome, follow-up was truncated on the day of the event. The risk of each outcome event was compared between groups using Cox proportional hazards models. All of the baseline characteristics described above were included as covariates in the Cox models. Hazard ratios (HRs) with 95% confidence intervals (CIs) were computed for each pairwise drug comparison (ie, each of the 4 comparator drugs vs aripiprazole).

### Sensitivity Analyses

The following sensitivity analyses were performed. First, to investigate whether any drug effects differed across time, drug-by-year interaction terms were added to the Cox models. Second, the new-onset diabetes mellitus outcome was redefined using only pharmacotherapy for diabetes in place of pharmacotherapy or a diagnosis code. Third, an approximation of an intent-to-treat analysis was conducted, in which patients were censored only at loss to follow-up (ie, disenrollment from the health plan or end of the study period) rather than upon discontinuation of the index drug. Finally, the dose categories for aripiprazole were modified to include doses up to 5 mg instead of 2 mg in the low-dose group. The Cox models of each outcome were rerun using each of these sensitivity definitions.

## RESULTS

A total of 138,523 patients qualified for the study, including 32,890 aripiprazole users, 17,428 olanzapine users, 58,807 quetiapine users, 22,357 risperidone users, and 6,753 ziprasidone users (Table 1). The propensity score matching achieved good balance on nearly all baseline characteristics other than year of index date (Table 2). As different subsets of aripiprazole users were matched to each of the comparator drug groups, their characteristics varied in the different comparisons. Mean ages for the matched groups were 43 years for olanzapine, 41 years for quetiapine and risperidone, and 42 years for ziprasidone (41 for the aripiprazole users matched to ziprasidone initiators). In each of the matched cohorts, major depressive disorder was the most common psychiatric diagnosis, followed by bipolar disorder; 5.5% or fewer of patients in each cohort had a schizophrenia diagnosis. Mean (standard deviation) duration of follow-up, in days, on the index drug and matched aripiprazole comparators was as follows: olanzapine, 317 (384)/matched aripiprazole, 379 (441); quetiapine, 401 (416)/matched aripiprazole, 340 (378); risperidone, 343 (408)/matched aripiprazole, 363 (422); and ziprasidone, 370 (423)/matched aripiprazole 359 (410). All patients treated with aripiprazole received the drug within the medium dose range (2–30 mg). With the inclusion of dose in the propensity score model, after matching, all patients had only medium-level doses of the index drugs.

Rates of each of the cardiovascular events among all matched patients, including myocardial infarction, stroke, heart failure, and CABG/PTCA, were considerably lower than the rates of new-onset diabetes mellitus and were typically higher in the comparator drug users than in the aripiprazole users, with the exception of ziprasidone. The incidence rates of new-onset diabetes mellitus per 1,000 person-years for aripiprazole and matched comparators, respectively, were 19.8 and 17.8 for olanzapine, 19.7 and 20.5 for quetiapine, 18.9 and 18.1 for risperidone, and 19.8 and 20.6 for ziprasidone (Table 3). The Cox models of

**Table 1. Baseline Patient Demographic and Clinical Characteristics[a]**

| Characteristic | Aripiprazole (n = 32,890) | Olanzapine (n = 17,428) | Quetiapine (n = 58,807) | Risperidone (n = 22,357) | Ziprasidone (n = 6,753) |
|---|---|---|---|---|---|
| Gender | | | | | |
| Male | 10,440 (31.7) | 7,867 (45.1)* | 22,010 (37.4)* | 9,977 (44.6)* | 2,102 (31.1) |
| Female | 22,450 (68.3) | 9,561 (54.9) | 36,797 (62.6) | 12,380 (55.4) | 4,651 (68.9) |
| Age category at index date | | | | | |
| 18–24 y | 4,243 (12.9) | 1,944 (11.2)* | 7,219 (12.3) | 3,535 (15.8)* | 805 (11.9) |
| 25–34 y | 5,051 (15.4) | 2,307 (13.2) | 9,305 (15.8) | 3,343 (15.0) | 1,132 (16.8) |
| 35–44 y | 8,015 (24.4) | 3,924 (22.5) | 14,397 (24.5) | 5,131 (23.0) | 1,779 (26.3) |
| 45–54 y | 9,372 (28.5) | 5,199 (29.8) | 17,005 (28.9) | 5,956 (26.6) | 1,933 (28.6) |
| 55–64 y | 6,209 (18.9) | 4,054 (23.3) | 10,881 (18.5) | 4,392 (19.6) | 1,104 (16.3) |
| Plan type | | | | | |
| Missing/unknown | 690 (2.1) | 265 (1.5)* | 1,180 (2.0)* | 349 (1.6)* | 141 (2.1)* |
| CDHP | 739 (2.3) | 248 (1.4) | 1,188 (2.0) | 422 (1.9) | 140 (2.1) |
| COMP | 1,568 (4.8) | 1,655 (9.5) | 4,122 (7.0) | 1,842 (8.3) | 454 (6.7) |
| EPO | 291 (0.9) | 99 (0.6) | 409 (0.7) | 161 (0.7) | 33 (0.5) |
| HMO | 5,574 (17.0) | 3,693 (21.2) | 10,574 (18.0) | 5,043 (22.6) | 1,109 (16.4) |
| POS without capitation | 3,225 (9.8) | 1,664 (9.6) | 5,851 (10.0) | 2,174 (9.7) | 662 (9.8) |
| POS with capitation | 274 (0.8) | 312 (1.8) | 653 (1.1) | 375 (1.7) | 68 (1.0) |
| PPO | 20,387 (62.3) | 9,466 (54.4) | 34,691 (59.1) | 11,948 (53.5) | 4,136 (61.3) |
| Index year | | | | | |
| 2003–2005 | 3,929 (10.7) | 9,337 (48.9)* | 15,796 (24.2)* | 9,841 (39.1)* | 2,085 (27.1)* |
| 2006–2008 | 15,701 (42.7) | 7,148 (37.4) | 34,721 (53.2) | 10,860 (43.2) | 4,257 (55.3) |
| 2009–2010 | 17,159 (46.6) | 2,610 (13.7) | 14,789 (22.6) | 4,445 (17.7) | 1,362 (17.7) |
| US geographic region | | | | | |
| Northeast | 4,094 (12.4) | 1,892 (10.9)* | 6,352 (10.8)* | 2,746 (12.3)* | 545 (8.1)* |
| North central | 9,420 (28.6) | 4,841 (27.8) | 15,665 (26.6) | 6,344 (28.4) | 1,777 (26.3) |
| South | 13,686 (41.6) | 6,316 (36.2) | 26,254 (44.6) | 8,381 (37.5) | 3,282 (48.6) |
| West | 5,549 (16.9) | 4,289 (24.6) | 10,207 (17.4) | 4,741 (21.2) | 1,114 (16.5) |
| Unknown | 141 (0.4) | 90 (0.5) | 329 (0.6) | 145 (0.6) | 35 (0.5) |
| Psychiatric diagnoses | | | | | |
| Schizophrenia | 690 (2.1) | 751 (4.3)* | 766 (1.3)* | 1,137 (5.1)* | 353 (5.2)* |
| Dementia | 56 (0.2) | 141 (0.8)* | 253 (0.4)* | 172 (0.8)* | 26 (0.4)* |
| Bipolar disorder | 5,359 (16.3) | 2,989 (17.2) | 8,501 (14.5)* | 3,386 (15.1)* | 1,806 (26.7) |
| Major depressive disorder | 18,059 (54.9) | 7,014 (40.2)* | 28,435 (48.4)* | 10,346 (46.3)* | 3,225 (47.8)* |
| All other mental health conditions | 11,239 (34.2) | 8,078 (46.4) | 25,267 (43.0) | 9,345 (41.8) | 2,248 (33.3) |
| No. of psychiatric diagnosis groups | | | | | |
| Mean | 1.3 | 1.2 | 1.3 | 1.3 | 1.5 |
| SD | 1.1 | 1.2 | 1.3 | 1.2 | 1.2 |
| Median | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Major comorbid conditions | | | | | |
| Hypertension | 4,717 (14.3) | 2,722 (15.6)* | 9,298 (15.8)* | 3,250 (14.5) | 978 (14.5) |
| Peripheral vascular disease | 88 (0.3) | 58 (0.3) | 207 (0.4) | 60 (0.3) | 15 (0.2) |
| Hyperlipidemia | 3,448 (10.5) | 1,657 (9.5)* | 5,396 (9.2)* | 1,915 (8.6)* | 621 (9.2) |
| Obesity | 845 (2.6) | 210 (1.2)* | 1,045 (1.8)* | 379 (1.7)* | 183 (2.7) |
| Charlson Comorbidity Index[b] | | | | | |
| 0 | 27,965 (85.0) | 14,039 (80.6)* | 48,031 (81.7)* | 18,594 (83.2)* | 5,723 (84.8) |
| 1–2 | 3,590 (10.9) | 2,232 (12.8) | 7,532 (12.8) | 2,668 (11.9) | 742 (11.0) |
| 3–4 | 1,045 (3.2) | 721 (4.1) | 2,507 (4.3) | 815 (3.6) | 236 (3.5) |
| > 4 | 281 (0.9) | 430 (2.5) | 720 (1.2) | 269 (1.2) | 50 (0.7) |
| Prior cardiovascular events | | | | | |
| Myocardial infarction | 50 (0.2) | 74 (0.4)* | 162 (0.3)* | 76 (0.3)* | 13 (0.2) |
| Stroke | 194 (0.6) | 286 (1.6)* | 786 (1.3)* | 357 (1.6)* | 77 (1.1)* |
| Heart failure | 122 (0.4) | 142 (0.8)* | 324 (0.6)* | 160 (0.7)* | 23 (0.3) |
| Dose of antipsychotic | | | | | |
| High | 0 (0) | 0 (0) | 0 (0) | 2,916 (13.1) | 0 (0) |
| Medium | 32,720 (100.0) | 13,187 (76.1) | 15,563 (26.6) | 11,543 (52.0) | 5,699 (85.1) |
| Low | 0 (0) | 4,144 (23.9) | 42,962 (73.4) | 7,752 (34.9) | 1,000 (14.9) |

[a]All variables except number of psychiatric diagnosis groups are expressed as n (%).
[b]A weighted composite measure that considers the presence of 16 diagnoses present in claims data.
*$P \leq .001$ vs aripiprazole.
Abbreviations: CDHP = consumer-driven health plan, COMP = comprehensive, EPO = exclusive provider organization, HMO = health maintenance organization, POS = point of service, PPO = preferred provider organization.

each outcome are summarized in Table 4. Compared with aripiprazole, there was a significant increase in risk with olanzapine for stroke (HR = 1.43; 95% CI, 1.05–1.95) and any cardiovascular event (HR = 1.28; 95% CI, 1.05–1.55). Quetiapine was associated with an increased risk of stroke (HR = 1.58; 95% CI, 1.19–2.09), heart failure (HR = 1.55; 95% CI, 1.15–2.11), and any cardiovascular event (HR = 1.50; 95% CI, 1.25–1.79). Similar findings were obtained with risperidone: increased risk of stroke (HR = 1.54; 95% CI, 1.12–2.12), heart failure (HR = 1.43; 95% CI, 1.02–1.99), and any cardiovascular event (HR = 1.49; 95% CI, 1.21–1.83). Ziprasidone showed no significant difference in risk from aripiprazole for any outcome; for any cardiovascular event, the HR for ziprasidone was 1.15 (95% CI, 0.87–1.54). There

**Table 2. Matched Baseline Patient Demographic and Clinical Characteristics[a]**

| Characteristic | Aripiprazole (n = 9,917) | Olanzapine (n = 9,917) | Aripiprazole (n = 14,935) | Quetiapine (n = 14,935) | Aripiprazole (n = 10,192) | Risperidone (n = 10,192) | Aripiprazole (n = 5,696) | Ziprasidone (n = 5,696) |
|---|---|---|---|---|---|---|---|---|
| Gender | | | | | | | | |
| Male | 4,328 (43.6) | 4,345 (43.8) | 5,743 (38.5) | 5,800 (38.8) | 4,468 (43.8) | 4,512 (44.3) | 1,762 (30.9) | 1,805 (31.7) |
| Female | 5,589 (56.4) | 5,572 (56.2) | 9,192 (61.5) | 9,135 (61.2) | 5,724 (56.2) | 5,680 (55.7) | 3,934 (69.1) | 3,891 (68.3) |
| Age category at index date | | | | | | | | |
| 18–24 y | 1,302 (13.1) | 1,241 (12.5) | 2,017 (13.5) | 1,947 (13.0) | 1,649 (16.2) | 1,589 (15.6) | 713 (12.5) | 673 (11.8) |
| 25–34 y | 1,390 (14.0) | 1,443 (14.6) | 2,542 (17.0) | 2,535 (17.0) | 1,604 (15.7) | 1,586 (15.6) | 993 (17.4) | 979 (17.2) |
| 35–44 y | 2,291 (23.1) | 2,278 (23.0) | 3,822 (25.6) | 3,858 (25.8) | 2,383 (23.4) | 2,412 (23.7) | 1,485 (26.1) | 1,517 (26.6) |
| 45–54 y | 2,885 (29.1) | 2,887 (29.1) | 4,191 (28.1) | 4,218 (28.2) | 2,710 (26.6) | 2,712 (26.6) | 1,599 (28.1) | 1,618 (28.4%) |
| 55–64 y | 2,049 (20.7) | 2,068 (20.9) | 2,363 (15.8) | 2,377 (15.9) | 1,846 (18.1) | 1,893 (18.6) | 906 (15.9) | 909 (16.0) |
| Plan Type | | | | | | | | |
| Missing/unknown | 177 (1.8) | 168 (1.7) | 324 (2.2) | 346 (2.3) | 182 (1.8) | 156 (1.5) | 128 (2.3) | 117 (2.1) |
| CDHP | 170 (1.7) | 165 (1.7) | 272 (1.8) | 279 (1.9) | 186 (1.8) | 193 (1.9) | 128 (2.3) | 123 (2.2) |
| COMP | 756 (7.6) | 753 (7.6) | 872 (5.9) | 873 (5.9) | 723 (7.1) | 747 (7.4) | 356 (6.3) | 395 (6.9) |
| EPO | 75 (0.8) | 67 (0.7) | 108 (0.7) | 98 (0.7) | 84 (0.8) | 73 (0.7) | 33 (0.6) | 27 (0.5) |
| HMO | 1,859 (18.8) | 1,865 (18.8) | 2,582 (17.4) | 2,605 (17.5) | 2,166 (21.3) | 2,188 (21.5) | 977 (17.2) | 944 (16.6) |
| POS without capitation | 967 (9.8) | 967 (9.8) | 1,430 (9.6) | 1,411 (9.5) | 1,068 (10.5) | 1,067 (10.5) | 575 (10.1) | 562 (9.9) |
| POS with capitation | 127 (1.3) | 139 (1.4) | 121 (0.8) | 129 (0.9) | 133 (1.3) | 134 (13.0) | 56 (1.0) | 61 (1.1) |
| PPO | 5,764 (58.3) | 5,772 (58.3) | 9,164 (61.6) | 9,160 (61.5) | 5,627 (55.3) | 5,603 (55.1) | 3,431 (60.4) | 3,457 (60.8) |
| Index year | | | | | | | | |
| 2003–2005 | 3,278 (33.1) | 3,331 (33.6)* | 2,708 (18.1) | 2,792 (18.7)* | 3,063 (30.1) | 3,200 (31.4)* | 1,497 (26.3) | 1,590 (27.9)* |
| 2006–2008 | 4,965 (50.1) | 4,777 (48.2) | 8,547 (57.2) | 8,318 (55.7) | 5,223 (51.2) | 4,904 (48.1) | 3,277 (57.5) | 3,088 (54.2) |
| 2009–2010 | 1,674 (16.9) | 1,809 (18.2) | 3,680 (24.6) | 3,825 (25.6) | 1,906 (18.7) | 2,088 (20.5) | 922 (16.2) | 1,018 (17.9) |
| US geographic region | | | | | | | | |
| Northeast | 1,091 (11.0) | 1,103 (11.1) | 1,454 (9.7) | 1,445 (9.7) | 1,253 (12.3) | 1,252 (12.3) | 498 (08.7) | 460 (8.1) |
| North central | 2,777 (28.0) | 2,758 (27.8) | 4,033 (27.0) | 4,005 (26.8) | 2,918 (28.6) | 2,906 (28.5) | 1,526 (26.8) | 1,547 (27.2) |
| South | 3,842 (38.7) | 3,833 (38.7) | 6,785 (45.4) | 6,821 (45.7) | 3,895 (38.2) | 3,914 (38.4) | 2,704 (47.5) | 2,722 (47.8) |
| West | 2,152 (21.7) | 2,170 (21.9) | 2,598 (17.4) | 2,603 (17.4) | 2,058 (20.2) | 2,060 (20.2) | 936 (16.4) | 939 (16.5) |
| Unknown | 55 (0.6) | 53 (0.5) | 65 (0.4) | 61 (0.4) | 68 (0.7) | 60 (0.6) | 32 (0.6) | 28 (0.5) |
| Psychiatric diagnoses | | | | | | | | |
| Schizophrenia | 442 (4.5) | 456 (4.6) | 408 (2.7) | 405 (2.7) | 406 (4.0) | 412 (4.0) | 286 (5.0) | 316 (5.5) |
| Bipolar disorder | 1,923 (19.4) | 1,837 (18.5) | 3,170 (21.2) | 3,130 (21) | 1,771 (17.4) | 1,668 (16.4) | 1,565 (27.5) | 1,543 (27.1) |
| Major depressive disorder | 3,506 (35.4) | 3,502 (35.3) | 5,583 (37.4) | 5,621 (37.6) | 3,957 (38.8) | 4,058 (39.8) | 2,032 (35.7) | 2,006 (35.2) |
| All other mental health conditions | 4,046 (40.8) | 4,122 (41.6) | 5,774 (38.7) | 5,779 (38.7) | 4,058 (39.8) | 4,054 (39.8) | 1,813 (31.8) | 1,831 (32.1) |
| No. of psychiatric diagnosis groups | | | | | | | | |
| Mean | 1.30 | 1.27 | 1.45 | 1.46 | 1.35 | 1.34 | 1.51 | 1.53 |
| SD | 1.15 | 1.25 | 1.22 | 1.31 | 1.18 | 1.21 | 1.22 | 1.26 |
| Median | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Major comorbid conditions | | | | | | | | |
| Hypertension | 1,506 (15.2) | 1,498 (15.1) | 2,250 (15.1) | 2,312 (15.5) | 1,412 (13.9) | 1,442 (14.2) | 824 (14.5) | 834 (14.6) |
| Peripheral vascular disease | 30 (0.3) | 30 (0.3) | 45 (0.3) | 48 (0.3) | 24 (0.2) | 22 (0.2) | 15 (0.3) | 14 (0.2) |
| Hyperlipidemia | 969 (9.8) | 956 (9.6) | 1,437 (9.6) | 1,438 (9.6) | 913 (9.0) | 904 (8.9) | 512 (9.0) | 520 (9.1) |
| Obesity | 132 (1.3) | 134 (1.4) | 293 (2.0) | 302 (2.0) | 191 (1.9) | 181 (1.8) | 156 (2.7) | 151 (2.7) |
| Charlson Comorbidity Index[b] | | | | | | | | |
| 0 | 8,133 (82.1) | 8,178 (82.5) | 12,490 (83.7) | 12,480 (83.6) | 8,586 (84.3) | 8,596 (84.4) | 4,825 (84.7) | 4,823 (84.7) |
| 1–2 | 1,234 (12.5) | 1,178 (11.9) | 1,763 (11.8) | 1,762 (11.8) | 1,119 (11.0) | 1,133 (11.1) | 640 (11.2) | 636 (11.2) |
| 3–4 | 375 (3.8) | 374 (3.8) | 553 (3.7) | 561 (3.8) | 366 (3.6) | 348 (3.4) | 194 (3.4) | 200 (3.5) |
| >4 | 168 (1.7) | 183 (1.8) | 122 (0.8) | 125 (0.8) | 114 (1.1) | 110 (1.1) | 35 (0.6) | 37 (0.6) |
| Prior cardiovascular events | | | | | | | | |
| Myocardial infarction | 27 (0.3) | 31 (0.3) | 24 (0.2) | 24 (0. 2) | 26 (0.3) | 27 (0.3) | 7 (0.1) | 8 (0.1) |
| Stroke | 111 (1.1) | 118 (1.2) | 130 (0.9) | 138 (0.9) | 114 (1.1) | 112 (1.1) | 64 (1.1) | 66 (1.2) |
| Heart failure | 60 (0.6) | 63 (0.6) | 54 (0.4) | 54 (0.4) | 54 (0.5) | 51 (0.5) | 18 (0.3) | 20 (0.4) |
| Dose of antipsychotic | | | | | | | | |
| Medium | 9,917 (100.0) | 9,917 (100.0) | 14,935 (100.0) | 14,935 (100.0) | 10,192 (100.0) | 10,192 (100.0) | 5,696 (100.0) | 5,696 (100.0) |

[a]All variables except number of psychiatric diagnosis groups are expressed as n (%).
[b]A weighted composite measure that considers the presence of 16 diagnoses present in claims data.
*$P \leq .001$ vs aripiprazole.
Abbreviations: CDHP = consumer-driven health plan, COMP = comprehensive, EPO = exclusive provider organization, HMO = health maintenance organization, POS = point of service, PPO = preferred provider organization.

were no significant differences in new-onset diabetes mellitus between aripiprazole and any comparator drug.

The sensitivity analyses adding the drug-by–index year interaction terms revealed only 1 statistically significant interaction, for olanzapine and risk of heart failure. Results suggested a trend of increasing risk of heart failure with olanzapine compared to aripiprazole across the years of the study, with an HR (95% CI) for olanzapine of 0.76 (0.47–1.24) in 2003–2005, 1.28 (0.79–2.06) in 2006–2008, and 2.83 (0.98–8.14) in 2009–2010. Use of the pharmacotherapy definition of new-onset diabetes mellitus reduced the overall number of events but had no impact on the lack of difference observed in risk of new-onset diabetes mellitus between aripiprazole and the other second-generation antipsychotics.

**Table 3. Outcomes Following Second-Generation Antipsychotic Initiation**

| | Aripiprazole | | | Comparator Drug | | |
|---|---|---|---|---|---|---|
| Comparison and Outcome | Group n | n (%) With Event | Incidence Rate per 1,000 Patient-Years | Group n | n (%) With Event | Incidence Rate per 1,000 Patient-Years |
| Olanzapine comparison | 9,917 | | | 9,917 | | |
| Acute myocardial infarction | | 44 (0.4) | 2.0 | | 59 (0.6) | 2.5 |
| Stroke | | 71 (0.7) | 3.2 | | 99 (1.0) | 4.3 |
| Heart failure | | 72 (0.7) | 3.2 | | 85 (0.9) | 3.7 |
| CABG/PTCA | | 29 (0.3) | 1.3 | | 34 (0.3) | 1.5 |
| New-onset diabetes mellitus | | 429 (4.3) | 19.8 | | 403 (4.1) | 17.8 |
| Quetiapine comparison | 14,935 | | | 14,935 | | |
| Acute myocardial infarction | | 53 (0.4) | 1.8 | | 66 (0.4) | 2.2 |
| Stroke | | 81 (0.5) | 2.8 | | 126 (0.8) | 4.2 |
| Heart failure | | 72 (0.5) | 2.4 | | 106 (0.7) | 3.6 |
| CABG/PTCA | | 33 (0.2) | 1.1 | | 38 (0.3) | 1.3 |
| New-onset diabetes mellitus | | 563 (3.8) | 19.7 | | 592 (4.0) | 20.5 |
| Risperidone comparison | 10,192 | | | 10,192 | | |
| Acute myocardial infarction | | 38 (0.4) | 1.7 | | 50 (0.5) | 2.1 |
| Stroke | | 64 (0.6) | 2.9 | | 100 (1.0) | 4.3 |
| Heart failure | | 61 (0.6) | 2.7 | | 91 (0.9) | 3.9 |
| CABG/PTCA | | 24 (0.2) | 1.1 | | 40 (0.4) | 1.7 |
| New-onset diabetes mellitus | | 409 (4.0) | 18.9 | | 410 (4.0) | 18.1 |
| Ziprasidone comparison | 5,696 | | | 5,696 | | |
| Acute myocardial infarction | | 21 (0.4) | 1.7 | | 15 (0.3) | 1.2 |
| Stroke | | 31 (0.5) | 2.5 | | 48 (0.8) | 3.7 |
| Heart failure | | 37 (0.7) | 3.0 | | 39 (0.7) | 3.0 |
| CABG/PTCA | | 13 (0.2) | 1.1 | | 13 (0.2) | 1.0 |
| New-onset diabetes mellitus | | 237 (4.2) | 19.8 | | 258 (4.5) | 20.6 |

Abbreviations: CABG = coronary artery bypass graft, PTCA = percutaneous transluminal coronary angioplasty.

**Table 4. Cox Proportional Hazard Analysis of Outcomes Among Matched Aripiprazole and Olanzapine Initiators (aripiprazole used as reference)**

| | Acute Myocardial Infarction | | Stroke | | Heart Failure | | CABG/PTCA | | Any Cardiovascular Event | | Diabetes Mellitus | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Comparison | Hazard Ratio | 95% CI | Hazard Ratio | 95% CI | Hazard Ratio | 95% CI | Hazard Ratio | 95% CI | Hazard Ratio | 95% CI | Hazard Ratio | 95% CI |
| Olanzapine | 1.26 | 0.85–1.87 | 1.43 | 1.05–1.95 | 1.11 | 0.81–1.53 | 1.11 | 0.67–1.83 | 1.28 | 1.05–1.55 | 0.90 | 0.79–1.03 |
| Quetiapine | 1.24 | 0.86–1.78 | 1.58 | 1.19–2.09 | 1.55 | 1.15–2.11 | 1.12 | 0.70–1.79 | 1.50 | 1.25–1.79 | 1.03 | 0.92–1.15 |
| Risperidone | 1.26 | 0.82–1.92 | 1.54 | 1.12–2.12 | 1.43 | 1.02–1.99 | 1.60 | 0.96–2.66 | 1.49 | 1.21–1.83 | 0.97 | 0.85–1.11 |
| Ziprasidone | 0.68 | 0.35–1.33 | 1.51 | 0.96–2.40 | 0.98 | 0.62–1.56 | 1.03 | 0.47–2.27 | 1.15 | 0.87–1.54 | 1.05 | 0.88–1.25 |

Abbreviations: CABG = coronary artery bypass graft, PTCA = percutaneous transluminal coronary angioplasty.

The intent-to-treat analysis, in which patients were censored at end of follow-up rather than upon drug discontinuation, also did not affect the results. Redefining the low dose of aripiprazole to include doses up to 5 mg instead of 2 mg led to 1 important change, in that the comparison of olanzapine to aripiprazole on risk of new-onset diabetes mellitus now showed a small but statistically significant reduction in risk with olanzapine (HR = 0.85; 95% CI, 0.74–0.98).

## DISCUSSION

The present study examined the risk of cardiometabolic events among large cohorts of patients initiating treatment with aripiprazole or another second-generation antipsychotic. The results show an increased risk of heart failure and stroke ranging from 28% to 58% associated with use of some of the comparator drugs as measured using the hazard ratio, a relative measure of effect size compared with aripiprazole. Some of these observed effects may be considered small in magnitude and, given the low incidence rates, are not likely to be clinically meaningful on an individual practice level but nevertheless represent a potentially relevant impact on disease burden for the population exposed.[27] There was no significant difference in the risk of developing diabetes between aripiprazole and any of the comparator drugs. Ziprasidone showed no difference in risk profile compared to aripiprazole. Previous studies[12–15] examining the incidence of diabetes in individuals taking second-generation antipsychotics using real-world data have found variations in event rates across the different agents. Olanzapine and clozapine have been consistently associated with the greatest effects on diabetes, and aripiprazole and ziprasidone have been associated with the smallest.[7,15] While diabetes has been investigated in patients taking second-generation antipsychotics, the literature on cardiovascular outcomes in this population is sparse, providing no adequate basis for comparison with the present study results. Missing from our analysis are 4 additional second-generation antipsychotics that have become recently available: asenapine, iloperidone, lurasidone, and paliperidone; data regarding their metabolic profiles are promising.[28,29]

Clinical guidelines[7] published in 2004 highlight the importance of frequent weight monitoring and metabolic testing in patients taking second-generation antipsychotics.

Although metabolic testing rates in this population have remained lower than recommended,[30–33] additional awareness of the problem of diabetes may be changing prescribing patterns. Patients perceived as being at higher risk of developing diabetes because of weight or prediabetic blood glucose levels, for example, may have been preferentially prescribed either aripiprazole or ziprasidone, which were indicated in the guidelines as potentially carrying a lower risk of diabetes.[7] This preferential prescribing can help explain the inconsistency between the results of the current study and those of previous studies that found an increased risk of diabetes with olanzapine compared to aripiprazole.[4,13,14] All of the prior studies used data from time periods ending in 2004–2005, when the variation among second-generation antipsychotics with regard to risk of diabetes was not well known; the hypothesized preferential prescribing may be a more recent trend. This hypothesis is supported by the finding in the present study of higher rates of new-onset diabetes mellitus with aripiprazole (19–20 events per 1,000 person-years) compared to the earlier studies, which found rates of 11.3 and 5.6 cases per 1,000 person-years.[4,14] The present study lacked data on metabolic outcomes that may be precursors or otherwise related to diabetes, such as weight gain, blood glucose, and lipid levels, and hence could not investigate differences among patients with respect to these factors at baseline. It is also possible that outcome rates and patterns of outcomes between drugs may have differed if a longer follow-up duration were available.

The patients included in this study, who were selected without regard to indication for antipsychotic use, represent the distribution of diagnoses in a commercially insured population of persons prescribed antipsychotics. Schizophrenia and bipolar disorder, which are the 2 primary indications for antipsychotics, comprised a minority of this patient population; major depressive disorder and other mental health conditions were more common among users of these drugs. While the mental health diagnosis was included in the propensity score and outcome modeling and was well balanced between matched groups, differences may exist in the patterns of results for each indication. The limited sample size with a diagnosis of schizophrenia precluded analysis stratified by indication.

The present study used propensity score matching to create comparison groups that were well balanced on the observed baseline characteristics. Confounding by indication, or preferential prescribing of a particular drug to patients with a specific diagnosis or disease severity, should be greatly reduced through the use of this technique. The potential remains, however, for residual confounding by variables such as the additional metabolic factors discussed above, as well as race and smoking status, which are not typically available through claims data. In addition, propensity score matching drops numerous patients from the analysis, including those patients who are in some way notably different from comparators, thereby limiting the generalizability of the analysis population. Claims data, which were the sole data source for this study, are also limited with regard to diagnostic accuracy, in that some claims may have been submitted with incorrect diagnoses or with diagnoses that were considered but ruled out. Algorithms were applied in an effort to exclude rule-out diagnoses, but some outcome events and indications for antipsychotics may be erroneously classified.

To ensure that patients had sufficient exposure to the study drug to be considered at risk of the outcomes, all patients were required to have a minimum duration of follow-up with drug exposure. That follow-up time was included in the at-risk time for outcome events, some of which can be fatal. Thus, if a patient experienced a fatal cardiovascular event within the first 6 months after treatment initiation, that patient would have been excluded from the analyses. If 1 or more of the drugs led to a higher risk of fatal events specifically, this could lead to underestimation of the event rate and hazard ratio for that drug. Fatal events, and sudden death in particular, are clearly related outcomes of interest in this study that could not be examined, because the database lacks information on death. The minimum follow-up duration also means that the results are not generalizable to individuals with shorter periods of health plan enrollment, although given that the requirement was applied to each of the cohorts equally, it is unlikely to have led to bias in the effect estimates.

Not known are the potential medications that subjects may have been exposed to prior to the look-back period employed in this study. In addition, the treatments received during the follow-up period were not modeled simultaneously with antipsychotic exposure; it is possible that other medication use during follow-up may have impacted the risk of new-onset diabetes mellitus and of cardiovascular outcomes.

Prior research suggests that the metabolic effects of second-generation antipsychotics may be dose-dependent,[34,35] which can lead to bias in comparisons of drugs that are not used at equivalent doses. The present study matched on drug dose but thereby restricted all doses to the medium range. The sensitivity analysis increasing the threshold for low doses for aripiprazole did lead to changes in the results, most notably a change in the olanzapine comparison for new-onset diabetes mellitus that suggested a reduced risk of diabetes with olanzapine relative to aripiprazole. Considering that these results run directly counter to the association found in most studies,[4,13,14,36] it is likely that the reclassified dose levels are further adding to the residual confounding (bias from preferential prescribing) that is suspected.

Despite these limitations, this study provides a robust comparison of the risk of new-onset diabetes mellitus and several cardiovascular events in users of second-generation antipsychotics taken from a real-world population of insured patients around the United States. The risk of cardiovascular events was shown to be lowest among patients treated with aripiprazole, compared to all other second-generation antipsychotics except ziprasidone. The risk of diabetes was found to be similar for aripiprazole compared to other second-generation antipsychotics, possibly due to a bias whereby patients at a higher risk of developing diabetes may have been preferentially prescribed aripiprazole.

***Drug names:*** aripiprazole (Abilify), asenapine (Saphris), clozapine (Clozaril, FazaClo, and others), iloperidone (Fanapt), lithium (Lithobid and others), lurasidone (Latuda), olanzapine (Zyprexa), paliperidone (Invega), phenytoin (Dilantin, Phenytek, and others), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

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***Potential conflicts of interest:*** **Dr Citrome** has been a consultant for Alexza, Alkermes, Bristol-Myers Squibb, Eli Lilly, Envivo, Forest, Genentech, Janssen, Lundbeck, Merck, Mylan, Novartis, Noven, Otsuka, Pfizer, and Sunovion; has been a speaker or member of an advisory board for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck, Novartis, Otsuka, Pfizer, and Sunovion; and is a shareholder of Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Merck, and Pfizer. **Ms Collins**, **Dr Nordstrom**, and **Mr Rosen** are employees of Evidera, which received funding from Bristol-Myers Squibb for this work. **Dr Baker** is an employee of Otsuka. **Dr Nadkarni** is an employee of and shareholder in Bristol-Myers Squibb. **Dr Kalsekar** is an employee of Bristol-Myers Squibb and a shareholder in Bristol-Myers Squibb and Eli Lilly.

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