# Risk of Cerebrovascular Adverse Events in Older Adults Using Antipsychotic Agents: A Propensity-Matched Retrospective Cohort Study

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***Objective:*** To compare the risk of cerebrovascular adverse events with second-generation antipsychotic users versus those taking first-generation antipsychotics in community-dwelling older adults.

***Method:*** A population-based retrospective cohort study matched on propensity score was used to examine the risk of cerebrovascular adverse events in second-generation antipsychotic users compared to first-generation antipsychotic users. IMS LifeLink Health Plan Claims Database was used to identify older adults (≥ 50 years) taking second-generation or first-generation antipsychotic agents from July 1, 2000, to December 31, 2007. Cox proportional hazards regression model stratified on matched pairs was used to examine the risk of hospitalization or emergency visits due to cerebrovascular adverse events within 1 year of follow-up (primary outcome measure). The covariates adjusted for include duration of therapy and exposure to other medication increasing risk of cerebrovascular adverse events.

***Results:*** A total of 11,160 older adults (5,580 second-generation and 5,580 first-generation antipsychotic users) matched on propensity score was obtained. Regression analysis revealed that no statistically significant difference exists between second-generation and first-generation antipsychotic users with respect to risk of cerebrovascular adverse events (hazard ratio [HR], 0.858; 95% CI, 0.689–1.446). However, duration of therapy between 30–90 days (HR, 1.707; 95% CI, 1.174–2.481) and more than 90 days (HR, 1.570; 95% CI, 1.132–2.176) was associated with increased risk of cerebrovascular adverse events compared to duration of therapy less than 30 days.

***Conclusions:*** The use of second-generation antipsychotic agents was found not to be associated with increased risk of cerebrovascular adverse events compared to first-generation agents in older adults. However, long-term use of second- and first-generation antipsychotic agents is associated with increased risk of cerebrovascular adverse events.

*J Clin Psychiatry 2010;71(6):689–698*



***Submitted:*** *November 4, 2009; accepted February 10, 2010 (doi:10.4088/JCP.09m05817yel).*

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Antipsychotics, especially second-generation agents, are widely used in older adults to treat various psychiatric disorders. Second-generation antipsychotic agents are often used in the elderly to treat behavioral and psychiatric symptoms even though there is little evidence regarding their efficacy[1] and safety.[2,3] Adverse events such as cerebrovascular events and mortality in the elderly have heightened the safety concerns of antipsychotic agents.[4–8] Several regulatory bodies, including US Food and Drug Administration (FDA), issued warnings underlining the increased risk of cerebrovascular adverse events due to second-generation antipsychotic drugs, such as risperidone, olanzapine, and aripiprazole, in elderly demented patients in 2002–2005 on the basis of data that emerged from clinical trials.[9]

Systematic reviews have found conflicting evidence from randomized and nonrandomized studies examining the link between antipsychotic use and cerebrovascular adverse events.[9,10] Emerging data from large observational studies from 1999 to 2006 have revealed negative association between use of second- and first-generation antipsychotic agents and risk of cerebrovascular adverse events.[11–18] A literature search found few observational studies suggesting increased risk of cerebrovascular adverse events with the use of first-generation antipsychotic medication compared to second-generation antipsychotic agents.[19–21] One self-controlled case series study reported an association of stroke with use of any antipsychotic agents.[22] There have been a few clinical trials[23,24] that have not been able to detect increased risk of cerebrovascular adverse events with antipsychotic use. However, none of the previously stated studies compared matched cohort after controlling for duration of therapy, a potential confounder in identifying the relationship.[25] There is a need to confirm the relative advantage of one antipsychotic class over the other. Therefore, a propensity-matched retrospective cohort study was conducted to compare the effect of second-generation antipsychotic agents versus first-generation antipsychotic agents on the risk of cerebrovascular adverse events in community-dwelling older adults.

## METHOD

### Data Source: The IMS LifeLink Health Plan Claims Database

The present study analyzed data from the IMS LifeLink Health Plan Claims Database (formerly known as PharMetrics). Medical claims records were obtained from 94 different managed-care organizations and encompass more than 60 million unique patients from January 2000 to June 2008. The database included patient's enrollment and pharmacy, medical, and institutional claims. Pharmacy data included claims for each drug prescription's date of dispensing, the quantity dispensed, and the length of the supply. Provider and facility claims included date of service,

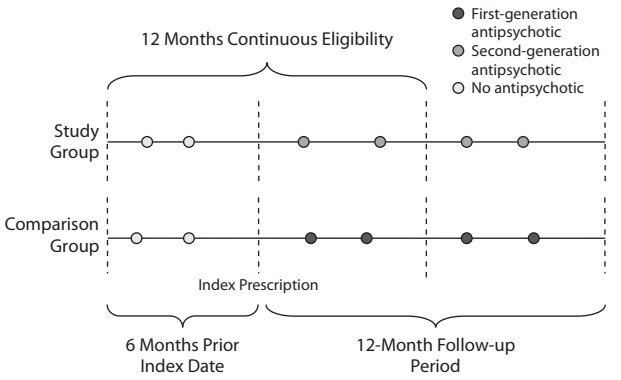
diagnoses codes (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] codes), and procedures based on the American Medical Association's Current Procedure Terminology codes and Center for Medicare and Medicaid Service's Health Care Common Procedure Coding System codes.

All claims in the database included a unique encrypted identifier for each patient. This identifier can be used to construct a longitudinal history of medical care utilization for each patient. Records in the IMS LifeLink Health Plan Claims Database are representative of the national, commercially insured population and include various demographic measures such as age, gender, and plan type.[26] The standard extract from the Health Plan Claims Database consists of 2 files: a claims detail file and an eligibility file. The claims detail file contains a number of claim-specific elements, carries a number of the output variables, and is the larger of the 2 files. The eligibility file contains the enrollment information for the specific individuals included in the claims detail file and meeting the requestor's criteria. Only health plans submitting data for all members are included in the database, which ensures complete data capture and representative samples. As data come from a number of different sources, data undergo a series of quality checks to ensure a standardized format. These factors enabled comparable analyses to be performed easily and confidently. The data are also longitudinal, with a mean member enrollment time of 2 years. The IMS LifeLink Health Plan Claims Database adheres to all Health Insurance Portability and Accountability Act requirements. This study was approved by the University of Houston Committees for the Protection of Human Subjects under exempt category number 4.

## Study Design

A retrospective cohort design was utilized to compare propensity score–matched older adults taking second-generation versus those taking first-generation antipsychotics to examine the risk of cerebrovascular adverse events. Claims details and enrollment data files were used to achieve the objectives of this study. The base population included all adults aged 50 years and above who were on antipsychotic medication anytime from July 1, 2000, to December 31, 2007. Figure 1 outlines the definitions used to construct treatment and comparison groups. *Therapy initiation* identified as index medication was defined as the first prescription fill date of antipsychotic medication after at least 6 months without a prescription fill date for these medications. Inclusion in the cohort required participants to have been continuously eligible 6 months before and at least 6 months after the index date. Thus, patients were followed till they were continuously eligible after the index date, with the minimum follow-up for 6 months and the maximum follow-up for up to 1 year.[27] Patients with the minimum eligibility of 6 months in the follow-up period were included because recent studies have revealed short-term mortality (180 days) risk due to adverse events with the use of first-generation and second-generation antipsychotic use in older adults.[28–30]

**Figure 1. Cohort Identification for Study Group and Comparison Group**




## Exposures and Outcome Definitions

Antipsychotic treatment exposure was measured using prescription claims data. The second-generation antipsychotic cohort involved users of clozapine, olanzapine, risperidone, quetiapine, ziprasidone and aripiprazole. The first-generation antipsychotic cohort involved users of loxapine, fluphenazine, trifluprom azine, chlorprothixene, haloperidol, chlorpromazine, thioridazine, prochlorperazine, promazine, trifluoperazine, thiothexene, molindone, perphenazine, acetophenazine, mesoridazine, carbamazepine, paliperidone, pimozide, and perphenazine-amitriptyline. Propensity score matching was applied to match these 2 cohorts. National Drug Code references were used to identify users of first- and second-generation antipsychotic.

The primary outcome measure was the occurrence of hospitalization or emergency room visit due to cerebrovascular adverse events within 1 year after the index date. The presence of acute cerebrovascular disease, occlusion and stenosis of precerebral arteries, transient cerebral ischemia, late effects of cerebrovascular disease, and other ill-defined cerebrovascular diseases were identified on the basis of hospital or emergency room visit claims with corresponding *ICD-9-CM* codes.[31] The *ICD-9-CM* codes selected to define cerebrovascular adverse events were chosen on the basis of the clinical classification of medical conditions provided by the Agency for Healthcare Research and Quality.[32] Patients were followed until hospitalization or emergency room visit due to cerebrovascular adverse events or until the end of their continuous eligibility, anytime after 6 months of index date. Maximum follow-up time was 1 year.

## Cohort Matching

Observational studies are a useful tool for determining causal relationship in real-world settings but suffer from the main criticism of absence of randomization of treatment assignment, which may lead to potential bias in the results due to uncontrolled confounding by unmeasured, unknown, or inadequately measured covariates.[33] As antipsychotic use was not randomly assigned in the study population, potential confounding and selection bias were addressed by matching



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the 2 groups on propensity score (predicted probability of getting 1 treatment versus another treatment).[34] The rationale for using propensity score matching technique was to minimize differences between the 2 groups so that they differ only on assignment to second-generation antipsychotic treatment versus first-generation antipsychotic treatment.[35,36]

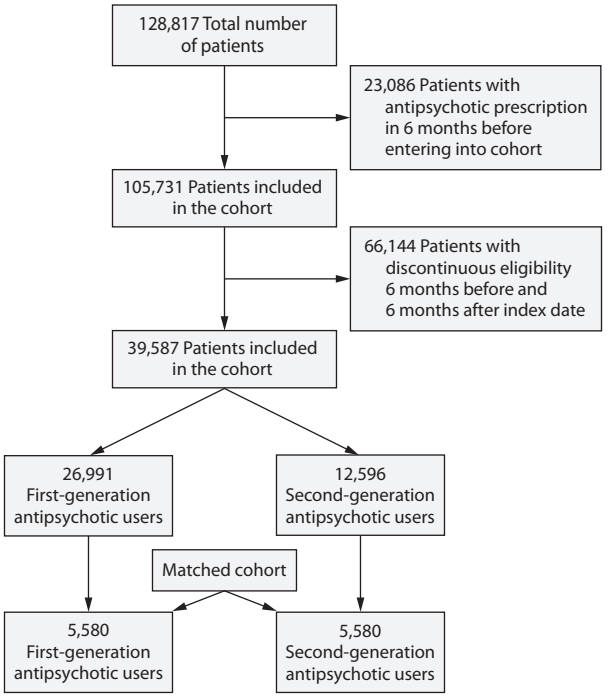
More than 60 covariates were included in the calculation of propensity score on the basis of previously published literature, expert opinions collected from experienced clinicians and pharmacists, and variable selection on the basis of its association with outcome.[37] Propensity scores were calculated from the large number of pretreatment characteristics (6 months before index date), which included clinical characteristics (comorbidities and co-medications), sociodemographics, year of cohort entry, and provider specialty. Severity of illness was also considered as one of the important predictors of treatment allocation measured as all-cause hospitalization in the previous 6 months before index date.[38]

The logistic regression model was developed using all baseline characteristics to obtain propensity scores. Using the resulting predicted probabilities, patients taking second-generation antipsychotics were matched with patients taking first-generation antipsychotics using Greedy 5→1 digit matching techniques.[39] This technique reduces matched-pair bias caused by incomplete and inexact matching. The 5→1 Digit Match indicates that cases are first matched to controls on the first 5 digits of the propensity score. For those that did not match, they are then matched on 4 digits. This process is continued down to a 1-digit match. If more than 1 control is found that matches to a case, the control is selected at random.

### Statistical Analysis

Differences between the 2 groups with respect to all the covariates used to calculate propensity score were evaluated using a $\chi^2$ test for categorical variables and *t* test for continuous variables before and after matching. The goodness of matched pairs was estimated by calculating percentage reduction in bias in the differences of explanatory variables before and after matching for the covariates, which remained significant after matching.[40] Survival analysis was then performed on the matched cohort to assess the risk of cerebrovascular adverse events between second- versus first-generation antipsychotic users. Kaplan-Meier survival plots were created to depict the crude (unadjusted) relationships between second-generation antipsychotic use versus first-generation antipsychotic use and time to hospitalization or emergency room visit due to cerebrovascular adverse event. Pairwise log-rank tests were used to compare survival curves for statistical difference. Cox proportional hazards regression model stratified on matched pairs was used to examine the risk of hospitalization or emergency room visit due to cerebrovascular adverse events between second-generation users and first-generation users, and hazard ratios were obtained. Stratified Cox proportional hazards regression model was applied using the STRATA option of PROC PHREG to account for matched pair design.[41–43] To address possible residual confounding even after matching, covariates that remained significant even after matching were adjusted for in the final regression model. The use of other medications during the follow-up period, such as cyclooxygenase 2 (COX-2) inhibitors,[44,45] vasoconstrictors,[46] anticoagulants,[47,48] and hormone replacement therapy,[49] which are also associated with the risk of cerebrovascular adverse events, were adjusted for in the Cox model to get unconfounded results. Another important covariate included in the model was duration of therapy, measured as "the duration of time from the initiation to discontinuation of therapy," with a maximum allowable gap of 30 days.[50] Duration of therapy was categorized as 0–30 days, 30–90 days, and more than 90 days as done in previous studies examining risk associated with duration of antipsychotic usage.[19,21] Patients were censored if they (1) lost their continuous eligibility before 1 year, (2) reached the end date of the follow-up period, or (3) switched from 1 class of antipsychotic medications to another class. Patients were followed until the end of their continuous eligibility. The proportional hazards assumption for the model was checked by including the interaction term between the independent variable and log of time. A *P* value of .05 was used to define statistical significance. SAS version 9.1 was used for analysis (SAS Institute Inc., Cary, North Carolina).

**Figure 2. Cohort Assembly for Second- and First-Generation Antipsychotic Users**




## RESULTS

### Matching Process and Patient Characteristics

Figure 2 shows the process of cohort assembly for second- and first-generation antipsychotic users. A total of 39,587



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Figure 3. Distribution of Propensity Scores Before Matching for Users of First- and Second-Generation Antipsychotics

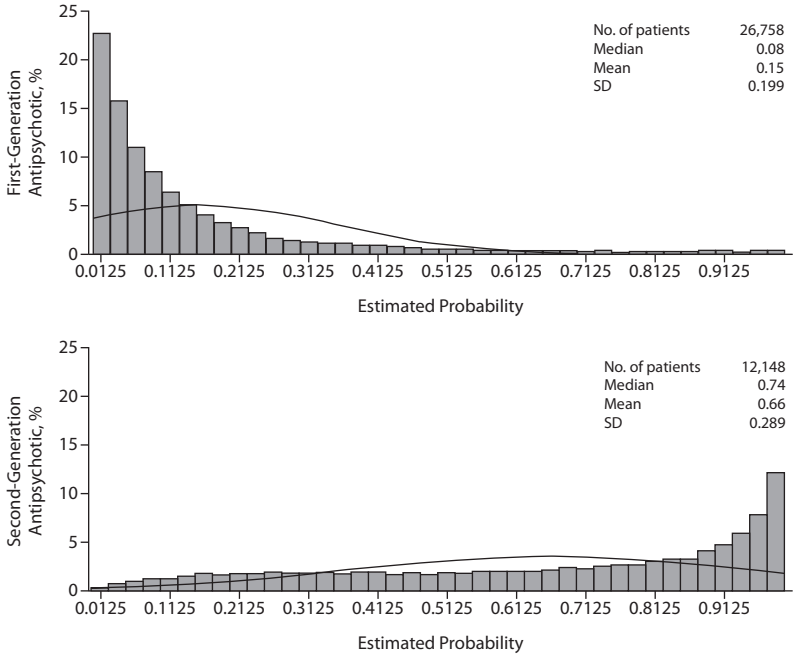
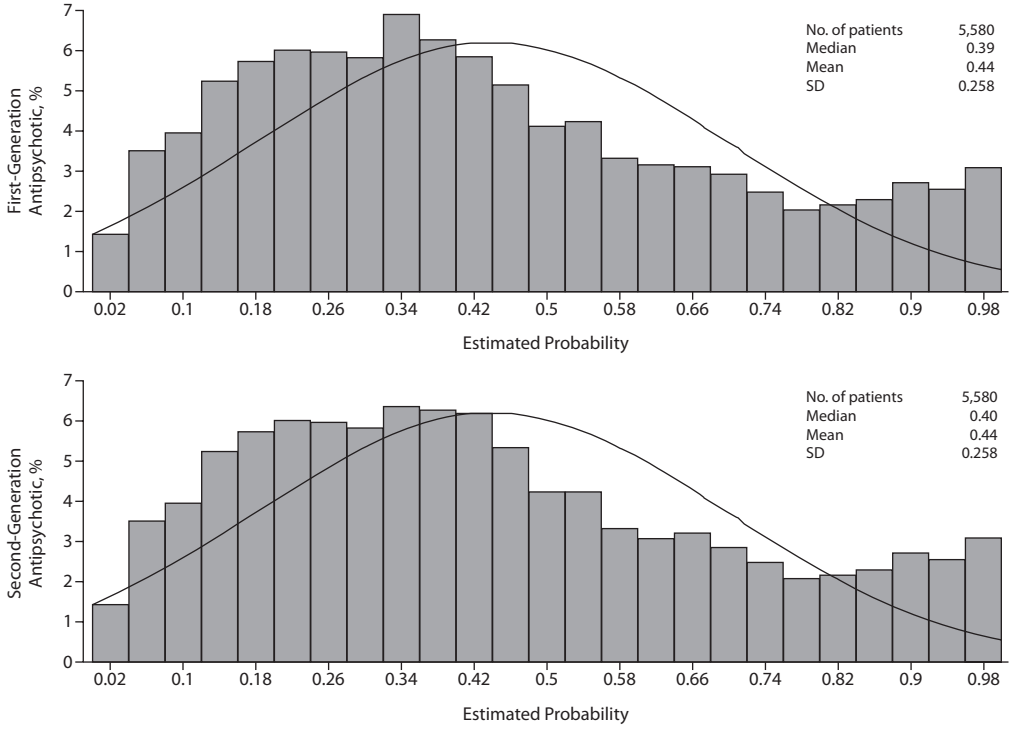



Figure 4. Distribution of Propensity Scores After Matching for Users of First- and Second-Generation Antipsychotics




new users of antipsychotic agents were obtained from July 1, 2000, to December 31, 2007, after applying the inclusion and exclusion criteria, of which 26,991 patients were first-generation antipsychotic users and 12,596 patients were second-generation antipsychotic users.

The distribution of propensity score for the 2 groups before matching reveals a good discrimination between the second-generation antipsychotic group and first-generation antipsychotic group (Figure 3). This underscores the importance of analytic approaches such as matching to reduce the influence of subjects with extreme propensity scores and thus avoid comparing the incomparable groups.[34,51] Figure 4 shows the distribution of the propensity scores of the 2 groups after matching. The statistics and distribution



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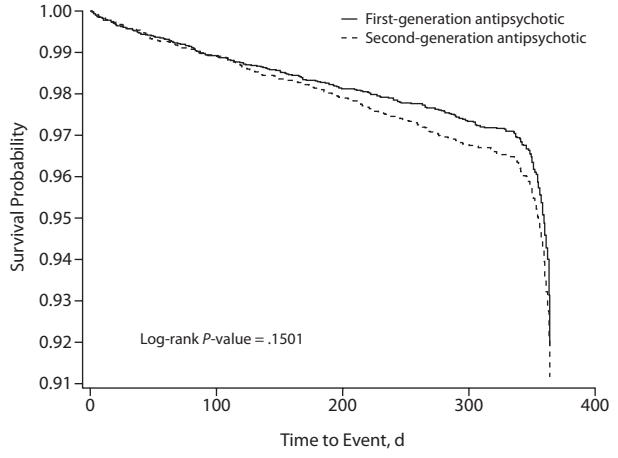
**Table 1. Descriptive Statistics of the Matched Cohort**

| Characteristic | Second-Generation Antipsychotic Users (n = 5,580) | First-Generation Antipsychotic Users (n = 5,580) |
|---|---|---|
| Duration of follow-up, mean ± SD, d | 331.71 ± 64.76 | 334.01 ± 63.10 |
| Time to event, mean ± SD, d | 279.70 ± 114.62 | 288.02 ± 114.73 |
| Hospitalization/ER visit due to cerebrovascular adverse event, n (%) | 416 (7.46) | 382 (6.85) |
| Duration of therapy, n (%)* | | |
| < 30 d | 2,089 (37.44) | 4,498 (80.61) |
| 30–90 d | 1,084 (19.43) | 470 (8.42) |
| > 90 d | 2,407 (43.14) | 612 (10.97) |
| Use of medication that probably could induce cerebrovascular adverse event, n (%) | | |
| COX-2 inhibitors | 1,653 (29.62) | 1,506 (26.99) |
| Vasoconstrictors | 2,029 (36.36) | 2,177 (39.01) |
| Anticoagulants | 973 (17.44) | 1,021 (18.30) |
| Hormone replacement therapy | 824 (14.77) | 820 (14.70) |

*Statistically significant at $P = .05$.
Abbreviations: COX-2 = cyclooxygenase 2, ER = emergency room.

**Figure 5. Kaplan-Meier Plot of Crude Association Between Users of Different Antipsychotics and Risk of Cerebrovascular Adverse Event**




suggests that the 2 matched groups are similar in nature and hence comparable.

A significant difference in the majority of baseline characteristics was found between the 2 groups before matching (see Appendix). The matching process used to match patients from the 2 groups produced a strong balance of baseline characteristics. After matching, a significant difference was still found between the 2 groups with respect to provider specialty, all-cause hospitalization, diagnosis of schizophrenia and cancer, and use of antidepressants in the 6 months before the initiation of treatment. However, the percentage reduction in bias calculated based on $(1 - D_i)/D_j \times 100\%$, where $D_i$ and $D_j$ are group differences in covariates means after matching and before matching, respectively, was more than 90% for all covariates, including those covariates that remained statistically significant after matching.[40]

**Table 2. Cox Proportional Hazards Regression Model for Risk of Cerebrovascular Adverse Event in Antipsychotic Users**

| Variable | Hazard Ratio | 95% CI | *P* Value |
|---|---|---|---|
| Antipsychotic | | | |
| First-generation | 1.00 | (Reference) | |
| Second-generation | 0.858 | 0.689–1.446 | .1728 |
| Duration of therapy† | | | |
| < 30 d | 1.00 | (Reference) | |
| 30–90 d | 1.707 | 1.174–2.481 | .0051 |
| > 90 d | 1.570 | 1.132–2.176 | .0068 |
| Other drugs used during follow-up | | | |
| COX-2 inhibitors | 1.091 | 0.824–1.446 | .5421 |
| Vasoconstrictors | 0.820 | 0.629–1.070 | .1432 |
| Anticoagulant† | 4.475 | 3.282–6.103 | < .0001 |
| Hormone replacement therapy | 0.624 | 0.413–0.942 | .0250 |
| Baseline characteristics that remained significant after matching | | | |
| Provider specialty† | | | |
| Geriatric/internist | 1.00 | (Reference) | |
| General/family physician | 1.018 | 0.605–1.715 | .9451 |
| Psychiatrist | 0.537 | 0.275–1.050 | .0691 |
| Other | 1.049 | 0.732–1.502 | .7957 |
| Hospitalization in past 6 mo† | | | |
| No | 1.00 | (Reference) | |
| Yes | 1.466 | 1.115–1.928 | .0061 |
| Diagnosis | | | |
| Schizophrenia | 0.875 | 0.521–1.470 | .6147 |
| Cancer | 1.033 | 0.704–1.518 | .8666 |
| Antidepressant use | 0.668 | 0.502–0.889 | .0057 |

†Statistically significant at $P = .005$.
Abbreviation: COX-2 = cyclooxygenase 2.

## Risk of Cerebrovascular Adverse Events

Table 1 presents the incidence of cerebrovascular adverse events by antipsychotic drug class. There were 798 cases of cerebrovascular adverse events with at least 1 hospitalization or emergency room visit following the use of antipsychotic agents. The risk of cerebrovascular adverse events was 7.46% for second-generation antipsychotic users and 6.85% for first-generation antipsychotic users. Figure 5 shows Kaplan-Meier survival curves evaluating the proportions of older adults experiencing cerebrovascular adverse events between those taking second-generation antipsychotics and first-generation antipsychotics. The graph demonstrates no significant association between antipsychotic use and risk of cerebrovascular adverse events ($P = .1501$ by log-rank test).

Table 2 presents results from the Cox proportional hazards regression model. This model adjusted for duration of therapy and other drugs that probably could induce cerebrovascular adverse events. Baseline characteristics that remained significant after matching were also adjusted for in this model. There was no statistically significant difference (HR, 0.858; 95% CI, 0.689–1.446) between second- and first-generation antipsychotic users with respect to risk of cerebrovascular adverse events. However, duration of therapy between 30–90 days (HR, 1.707; 95% CI, 1.174–2.481) and more than 90 days (HR, 1.570; 95% CI, 1.132–2.176) was associated with increased risk of cerebrovascular adverse events compared to duration of therapy less than 30 days. The other factors likely to influence the risk of cerebrovascular adverse events were anticoagulants use (HR, 4.475; 95% CI, 3.282–6.103), hormone replacement therapy (HR, 0.624; 95% CI, 0.413–0.942), and previous hospitalization (HR, 1.466; CI, 1.115–1.928).

## DISCUSSION

This population-based study involving adults 50 years old or more found that no significant difference exists between users of second- and first-generation antipsychotics with respect to cerebrovascular adverse events after controlling for duration of use and other medications in propensity score–matched cohorts based on the multivariate Cox proportional hazards regression model. Risk of cerebrovascular adverse events is associated with potential confounding by indication as older adults with severe mental illness such as Alzheimer's disease are more likely to die of cerebrovascular disease than nondemented elderly patients.[52,53] This study presents comparative safety of second-generation antipsychotic versus first-generation antipsychotics based on a propensity score–matched cohort, thus taking into account the issue of controlling cerebrovascular risk factors and confounding by indication. The main advantage of matching on propensity score is that it eliminates incomparable subjects in both exposed groups[34] and thus provides more precise and unbiased estimates of true treatment effects.[35,51,54] Several observational studies have found no association between use of second- and first-generation antipsychotics and cerebrovascular events.[11–16] The findings are consistent with previous observational studies,[11–16] and thus the study suggests that there is no significant differential risk of cerebrovascular adverse events with antipsychotic agents after controlling for duration and other factors in propensity-matched groups.

The major strength of the current study is the control of potential confounders in propensity-matched cohorts. Duration of therapy is an important factor to be considered while estimating causal relationship. Our study demonstrates that extent of antipsychotic exposure is associated with increased risk of cerebrovascular adverse events irrespective of the class of antipsychotic used. The risk of cerebrovascular adverse events was found to be increased in 30–90 days period of treatment (HR, 1.70; 95% CI, 1.17–2.48) and more than 90 days (HR, 1.57; 95% CI, 1.13–2.17) when compared to the initial 30 days of therapy. In contrast to our findings, Kleijer et al[21] reported that risk of cerebrovascular adverse events associated with antipsychotics in elderly patients is elevated, especially during the first week of treatment, and the risk decreases over time and is back to base level after 3 months of treatment. They stated that there is acute increase in risk, which is unlikely to be attributable to atherosclerotic effects of deregulation of glucose and lipid metabolism effects of antipsychotic agents which are chronic in nature.[21] Strong evidence is provided in the literature regarding several characteristics of metabolic syndrome (increased triglycerides and cholesterol levels, increased plasma glucose and leptin levels) known to be associated with a decreased fibrinolytic activity.[12,55,56] Our study suggests that there might be a correlation between atherosclerotic effect and risk of cerebrovascular events. Few recent observational studies have found significant increase in risk of cerebrovascular adverse events with antipsychotic treatment.[19–22,55] However, none of the studies had controlled for duration of therapy as a potential confounder.

The potential mechanism proposed earlier to explain the association between antipsychotic use and risk of cerebrovascular adverse events are similar for both first- and second-generation antipsychotic agents. Orthostatic hypotension, thromboembolic effects, excessive sedation resulting in dehydration and hemoconcentration, and hyperprolactinemia leading to atherosclerosis can lead to increased incidence of stroke with the use of antipsychotics in the elderly.[56–57] Orthostatic hypotension is induced by antipsychotics as a result of α-adrenergic receptor blockade.[12] An increased platelet aggregation is also possible with antipsychotic use.[58] Phenothiazines cause platelet aggregation due to serotonin induction, and second-generation antipsychotics are expected to increase platelet aggregation due to a high affinity for $5\text{-HT}_{2A}$ receptor.[12] Finally, both antipsychotics are associated with ventricular arrhythmias and venous thromboembolism that can lead to cerebral ischemia and stroke.[59–62] Thus, it can be argued that pharmacologic consequences of both second- and first-generation antipsychotics are similar, and thus the findings do not support any differential risk across antipsychotic drug classes.

The patients with vascular dementia are at increased risk of hospitalization due to cerebrovascular adverse events.[9] The FDA warnings are provided specifically for antipsychotic use in demented elderly. Thus, the interaction term between dementia and antipsychotic treatment was checked, which was found to be nonsignificant. This indicates that risk of stroke is not confined to only dementia patients. Patients with schizophrenia, depression, and bipolar disorders also present excess risk of cerebrovascular mortality.[20] An almost 3-fold increase in risk was found to be associated with concomitant anticoagulant use. This increased risk may be due to underlying risk factors for receiving anticoagulants or due to intracranial hemorrhage.[47] Consistent with previous research, baseline all-cause hospitalization was found to be an important predictor of risk of hospitalization or emergency room visits for cerebrovascular adverse events and thus demonstrates its importance as a measure of severity of illness.[38] Previous use of an antidepressant was also found to be associated with decreased risk of cerebrovascular events, which is consistent with the past literature.[63,64]

The limitations of this study should also be considered while interpreting the results. The use of computer-recorded information to capture data did not allow us to ascertain whether the subjects actually used their dispensed medicines. The diseases and outcome measurements were based on diagnostic data in medical claims. Incomplete, erroneous records submitted by health care providers; limited clinical detail in the *ICD-9-CM* system; and inaccurate demographic information may limit the accuracy of administrative data.[27] The population referred to in this study comprised community-dwelling older adults, and the results may not be generalized to other settings. Dose-response relationship was not examined, given the complexity of the study design and changes in dose over time.[28] Variables included in the propensity score



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are limited to those available in the data source and those used in the previous literature. There might be a possibility of some unmeasured confounder affecting the results. Because of unavailability in the dataset, racial variation and other stroke risk factors such as smoking and physical exercise were not controlled for in the multivariable analysis. Finally, all eligible patients available in the treatment group could not be matched, which may limit the generalizability of the results.

Study design and analytic approach were strengths of this study. There is a possibility that patients in the 2 treatment groups differed in terms of disease severity or that patients were preselected to receive 1 therapy over the other due to some unobservable characteristics, which can lead to selection bias. Matching based on propensity score tries to reduce the effect of selection bias. The calculation of propensity score by considering temporal details and individual characteristics can be useful in addressing causal relationship between exposure and outcome.[27] Only new users of antipsychotics were included in the study cohort to address the issue of prevalence bias. Researchers have demonstrated that randomly assigning thousands of individuals would be required to detect an important effect on risk due to exposure.[65] This study used population-based, large-sized retrospective data and applied pseudorandomization to provide validated results.

Drug-induced cerebrovascular events are an important public health concern. In recent years, second-generation antipsychotics have been rapidly replacing first-generation antipsychotics; the findings of this study can be beneficial for both health care professionals and policy makers to identify comparative safety of second- and first-generation antipsychotic agents. The findings suggest that no significant difference exists between second- and first-generation antipsychotic agents for increased risk of cerebrovascular adverse event. However, extent of antipsychotic treatment is associated with increased incidence of cerebrovascular adverse event. Health care professionals should systematically identify predisposed cerebrovascular risk factors when planning to treat patients for a longer period of time. Regular follow-up of patients and constant monitoring can be instrumental in minimizing risk of cerebrovascular adverse events associated with long-term use of antipsychotics. Large scale, prospective clinical trials are needed to strengthen the findings from observational studies. Future studies are also needed to evaluate comparative safety of individual antipsychotic treatment in older adults taking antipsychotics.

***Drug names:*** aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), molindone (Moban), olanzapine (Zyprexa), paliperidone (Invega), pimozide (Orap), prochlorperazine (Compro, Procomp, and others), quetiapine (Seroquel), risperidone (Risperdal and others), thiothixene (Navane and others), ziprasidone (Geodon).

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***Potential conflicts of interest:*** None reported.

***Funding/support:*** None reported.

***Acknowledgment:*** The statements, findings, conclusions, views, and opinions contained and expressed in this article are based in part on data obtained under license from the following IMS Health Incorporated information service(s): IMS LifeLink Health Plan Claims Database (1999-2003), IMS Health Incorporated. All rights reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities.

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**Appendix 1. Baseline Characteristics of Second- and First-Generation Antipsychotic Users**

| | Unmatched Cohort (n = 39,587) | | | Matched Cohort (n = 11,160) | | |
|---|---|---|---|---|---|---|
| Characteristic | Second-Generation Antipsychotic (n = 12,596) | First-Generation Antipsychotic (n = 26,991) | *P* Value | Second-Generation Antipsychotic (n = 5,580) | First-Generation Antipsychotic (n = 5,580) | *P* Value |
| Age, mean (SD), y | 70.77 (13.10) | 65.60 (10.17) | < .0001 | 69.84 (12.44) | 69.43 (12.85) | .09 |
| Gender, n (%) | | | | | | |
| Men | 4,986 (39.58) | 9,345 (34.62) | < .0001 | 2,164 (38.78) | 2,144 (38.42) | .69 |
| Women | 7,610 (60.42) | 17,646 (65.38) | | 3,416 (61.22) | 3,436 (61.58) | |
| Region, n (%) | | | | | | |
| West | 1,585 (12.58) | 2,847 (10.55) | < .0001 | 638 (11.43) | 652 (11.68) | .47 |
| Midwest | 5,285 (41.96) | 12,490 (46.27) | | 2,349 (42.10) | 2,268 (40.65) | |
| South | 3,027 (24.03) | 6,015 (22.29) | | 1,389 (24.89) | 1,434 (25.70) | |
| East | 2,699 (21.43) | 5,639 (20.89) | | 1,204 (21.58) | 1,226 (21.97) | |
| Year of cohort entry | | | | | | |
| 2000 | 1,106 (8.78) | 3,485 (12.91) | < .0001 | 543 (9.73) | 537 (9.62) | .55 |
| 2001 | 2,878 (22.85) | 7,785 (28.84) | | 1,403 (25.14) | 1,359 (24.35) | |
| 2002 | 2,978 (23.64) | 6,658 (24.67) | | 1,334 (23.91) | 1,322 (23.69) | |
| 2003 | 5,132 (40.74) | 8,927 (33.07) | | 2,180 (39.07) | 2,261 (40.52) | |
| 2004 | 242 (1.92) | 59 (0.22) | | 64 (1.15) | 45 (0.81) | |
| 2005 | 99 (0.79) | 36 (0.13) | | 22 (0.39) | 25 (0.45) | |
| 2006 | 97 (0.77) | 25 (0.09) | | 22 (0.39) | 20 (0.36) | |
| 2007 | 64 (0.51) | 16 (0.06) | | 12 (0.22) | 11 (0.20) | |
| Type of provider specialty, n (%)† | | | | | | |
| Geriatric/intern | 1,635 (12.98) | 3,929 (14.56) | < .0001 | 823 (14.75) | 856 (15.34) | < .0001 |
| General/family | 1,249 (9.92) | 2,478 (9.18) | | 631 (11.31) | 639 (11.45) | |
| Psychiatrist | 2,622 (20.82) | 250 (0.93) | | 369 (6.61) | 240 (4.30) | |
| Other | 7,090 (56.29) | 2,0334 (75.34) | | 3,757 (67.33) | 3,845 (68.91) | |
| Hospitalization in past 6 mo, n (%)† | | | | | | |
| Yes | 4,094 (32.50) | 8,502 (67.50) | .02 | 1,558 (27.92) | 1,448 (25.95) | .01 |
| No | 9,072 (33.61) | 17,919 (66.39) | | 4,022 (72.08) | 4,132 (74.05) | |
| Medical history in past 6 months, n (%) | | | | | | |
| Hypertension | 5,304 (42.11) | 1,1041 (40.91) | .02 | 2,297 (41.16) | 2,341 (41.95) | .39 |
| Coronary heart disease | 2,007 (15.93) | 4,127 (15.29) | .09 | 888 (15.91) | 925 (16.58) | .34 |
| Congestive heart failure | 1,398 (11.10) | 1,973 (7.31) | < .0001 | 582 (10.43) | 591 (10.59) | .78 |
| Acute myocardial infarction | 301 (2.39) | 468 (1.73) | < .0001 | 130 (2.33) | 130 (2.33) | > .99 |
| Cardiac arrhythmias | 2,032 (16.31) | 3,595 (13.32) | < .0001 | 848 (15.20) | 870 (15.59) | .56 |
| Circulatory disorder | 2,355 (18.70) | 5,156 (19.10) | .33 | 994 (17.81) | 1,014 (18.17) | .62 |
| Thromboembolic disorder | 382 (3.03) | 1,001 (3.71) | .0006 | 193 (3.46) | 185 (3.32) | .67 |
| Diabetes | 2,169 (17.22) | 4,845 (17.95) | .07 | 1,009 (18.08) | 1,032 (18.49) | .57 |
| Cerebrovascular disease | 1,917 (15.22) | 1,895 (7.02) | < .0001 | 714 (12.80) | 713 (12.78) | .97 |
| Hip/femur fracture | 354 (2.81) | 235 (0.87) | < .0001 | 100 (1.79) | 107 (1.92) | .62 |
| Chronic obstructive pulmonary disorder | 1,533 (12.17) | 3,513 (13.02) | .01 | 699 (12.53) | 716 (12.83) | .62 |
| Falls | 498 (3.95) | 332 (1.23) | < .0001 | 147 (2.63) | 144 (2.58) | .85 |
| Thyroid disorder | 1,457 (11.57) | 2,703 (10.01) | < .0001 | 568 (10.18) | 584 (10.47) | .61 |
| Renal failure | 492 (3.91) | 1,026 (3.80) | .61 | 237 (4.25) | 253 (4.53) | .45 |
| Other renal disorders | 3,122 (24.79) | 6,490 (24.05) | .10 | 1,319 (23.64) | 1,313 (23.53) | .89 |
| Liver disorder | 571 (4.53) | 3,235 (11.99) | < .0001 | 324 (5.81) | 281 (5.04) | .07 |
| Gastric disorder | 3,463 (27.49) | 11,489 (42.57) | < .0001 | 1,718 (30.79) | 1,669 (29.91) | .31 |
| Ulcers | 592 (4.70) | 941 (3.49) | < .0001 | 240 (4.30) | 259 (4.64) | .38 |
| Cancer (of any type)† | 1,296 (10.29) | 11,779 (43.64) | < .0001 | 833 (14.93) | 701 (12.56) | .0003 |
| Cataract | 1,201 (9.53) | 2,457 (9.10) | .16 | 551 (9.87) | 553 (9.91) | .94 |
| Glaucoma | 561 (5.25) | 1,412 (5.23) | .94 | 284 (5.09) | 283 (5.07) | .96 |
| Anemia | 1,517 (12.04) | 4,193 (15.53) | < .0001 | 699 (12.53) | 718 (12.87) | .58 |
| Osteoporosis | 630 (5.00) | 1,189 (4.41) | .008 | 262 (4.70) | 273 (4.89) | .62 |
| Rheumatoid arthritis | 185 (1.47) | 622 (2.30) | < .0001 | 86 (1.54) | 103 (1.85) | .21 |
| Back pain | 2,350 (18.66) | 5,610 (20.82) | < .0001 | 1,141 (20.45) | 1,153 (20.66) | .77 |
| Dyslipidemia | 2,372 (18.83) | 6,449 (23.99) | < .0001 | 1,113 (20.30) | 1,125 (20.30) | .85 |
| Obesity | 234 (1.86) | 658 (2.44) | .0003 | 114 (2.04) | 103 (1.85) | .45 |
| HIV infection | 19 (0.15) | 44 (0.16) | .77 | 9 (0.16) | 11 (0.20) | .65 |
| Pneumonia | 844 (6.70) | 1,802 (6.68) | .92 | 372 (6.67) | 399 (7.15) | .31 |
| Endocarditis | 321 (2.55) | 759 (2.81) | .13 | 168 (3.01) | 172 (3.08) | .82 |
| Suicide attempt | 53 (0.42) | 3 (0.01) | < .0001 | 7 (0.13) | 3 (0.05) | .20 |
| Alcohol and substance abuse disorder | 676 (5.37) | 361 (1.34) | < .0001 | 198 (3.55) | 178 (3.19) | .29 |
| Extrapyrimidal symptoms | 277 (2.20) | 237 (0.88) | < .0001 | 104 (1.86) | 111 (1.99) | .62 |
| Parkinson's disease | 594 (4.72) | 154 (0.57) | .57 | 150 (2.69) | 122 (2.19) | .08 |
| Psychotic disorder, n (%) | | | | | | |
| Dementia | 3,612 (28.68) | 923 (3.42) | < .0001 | 820 (14.70) | 761 (13.64) | .10 |
| Schizophrenia† | 1,930 (15.32) | 419 (1.55) | < .0001 | 413 (7.40) | 343 (6.15) | .008 |
| Anxiety disorder | 2,293 (18.20) | 1,288 (4.77) | < .0001 | 683 (12.24) | 665 (11.92) | .60 |
| Conduct disorder | 205 (1.63) | 41 (0.15) | < .0001 | 46 (0.82) | 33 (0.59) | .14 |
| Mood disorder | 5,443 (43.21) | 2,324 (8.61) | < .0001 | 1,495 (26.79) | 1,489 (26.68) | .89 |
| Other psychotic disorder | 1,496 (11.88) | 1,962 (7.27) | < .0001 | 477 (8.55) | 468 (8.39) | .75 |

*(continued)*

**Appendix 1 (continued). Baseline Characteristics of Second- and First-Generation Antipsychotic Users**

| | Unmatched Cohort (n = 39,587) | | | Matched Cohort (n = 11,160) | | |
|---|---|---|---|---|---|---|
| Characteristic | Second-Generation Antipsychotic (n = 12,596) | First-Generation Antipsychotic (n = 26,991) | *P* Value | Second-Generation Antipsychotic (n = 5,580) | First-Generation Antipsychotic (n = 5,580) | *P* Value |
| Other drugs used in past 6 mo, n (%) | | | | | | |
| Antihypertensive | 6,739 (53.50) | 13,851 (51.32) | < .0001 | 3,048 (54.62) | 3,111 (55.75) | .23 |
| Antianginal | 1,103 (8.76) | 2,007 (7.44) | < .0001 | 524 (9.39) | 558 (10.00) | .27 |
| Antiarrhythmic | 215 (1.71) | 462 (1.71) | .97 | 117 (2.10) | 113 (2.03) | .78 |
| Other cardiovascular drugs | 4,121 (32.72) | 7,979 (29.56) | < .0001 | 1,851 (33.17) | 1,905 (34.14) | .27 |
| Antidiabetic | 1,804 (14.32) | 4,099 (15.19) | .02 | 886 (15.88) | 920 (16.49) | .38 |
| Antihyperlipidemics | 2,963 (23.52) | 7,062 (26.16) | < .0001 | 1,450 (25.99) | 1,464 (26.24) | .76 |
| Antiobesity | 399 (3.17) | 275 (1.02) | < .0001 | 134 (2.40) | 133 (2.38) | .95 |
| Analgesics | 5,339 (42.39) | 17,564 (65.07) | < .0001 | 2,747 (49.23) | 2,749 (49.27) | .96 |
| Estrogen (hormone replacement therapy) | 1,711 (13.58) | 5,446 (20.18) | < .0001 | 864 (15.48) | 893 (16.00) | .45 |
| Antihistamines | 2,347 (18.63) | 6,950 (25.75) | < .0001 | 1,224 (21.94) | 1,258 (22.54) | .43 |
| Antigastric | 1,610 (12.78) | 4,694 (17.39) | < .0001 | 787 (14.10) | 803 (14.39) | .66 |
| Anticoagulant | 910 (7.22) | 2,406 (8.91) | < .0001 | 459 (8.23) | 464 (8.32) | .86 |
| Other hematologic agents | 949 (7.53) | 1,197 (4.43) | < .0001 | 418 (7.49) | 424 (7.60) | .82 |
| Hematopoietic agents | 626 (4.97) | 1,279 (4.74) | .31 | 269 (4.82) | 301 (5.39) | .16 |
| Corticosteroids | 1,147 (9.11) | 5,877 (21.77) | < .0001 | 658 (11.79) | 636 (11.40) | .51 |
| Vitamin D | 34 (0.27) | 110 (0.41) | .03 | 15 (0.27) | 20 (0.36) | .39 |
| Bronchodilators | 1,580 (12.54) | 3,673 (13.61) | .003 | 772 (13.84) | 834 (14.95) | .09 |
| Antimycotics | 12 (0.10) | 53 (0.20) | .02 | 8 (0.14) | 9 (0.16) | .80 |
| Anti-infective agents | 4,582 (36.38) | 14,680 (54.39) | < .0001 | 2,334 (41.82) | 2,341 (41.95) | .98 |
| Urinary anti-infective | 328 (2.60) | 676 (2.50) | .55 | 136 (2.44) | 165 (2.96) | .09 |
| Anti-cancer | 346 (2.75) | 2,391 (8.86) | < .0001 | 194 (3.48) | 164 (2.94) | .10 |
| Anti-ulcer | 3,766 (29.90) | 9,959 (36.90) | < .0001 | 1,880 (33.69) | 1,956 (35.05) | .12 |
| Alcohol drug dependency | 23 (0.18) | 6 (0.02) | < .0001 | 4 (0.07) | 5 (0.09) | > .99 |
| Ophthalmic | 1,457 (11.57) | 2,766 (10.25) | < .0001 | 624 (11.18) | 649 (11.63) | .45 |
| Thyroid agents | 2,055 (16.31) | 3,674 (13.61) | < .0001 | 857 (15.36) | 868 (15.56) | .77 |
| Hypnotics | 1,964 (15.59) | 3,157 (11.70) | < .0001 | 828 (14.84) | 823 (14.75) | .89 |
| Anticholinergic | 1,233 (9.79) | 4,061 (15.05) | < .0001 | 563 (10.09) | 534 (9.57) | .35 |
| Smoking deterrents | 61 (0.64) | 215 (0.80) | .09 | 35 (0.63) | 35 (0.63) | > .99 |
| Endocrine and metabolic agents | 1,089 (8.65) | 2,365 (8.76) | .70 | 488 (8.75) | 509 (9.12) | .48 |
| Antidepressants† | 7,794 (61.88) | 7,234 (26.80) | < .0001 | 2,898 (51.94) | 3,073 (55.07) | .0009 |
| Antianxiety | 4,141 (32.88) | 6,624 (24.54) | < .0001 | 1,669 (29.91) | 1,734 (31.08) | .18 |
| Anticonvulsant | 3,213 (25.51) | 2,509 (9.30) | < .0001 | 1,102 (19.75) | 1,155 (20.70) | .21 |
| Lithium | 725 (5.76) | 141 (0.52) | < .0001 | 151 (2.71) | 126 (2.26) | .12 |

Abbreviation: HIV = human immunodeficiency virus.
†Statistically significant at *P* = .005.



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