Antipsychotic Use and Myocardial Infarction in Older Patients With Treated Dementia

Antoine Pariente, MD, PhD; Annie Fourrier-Réglat, PharmD, PhD; Thierry Ducruet, MSc; Paddy Farrington, PhD; Sarah-Gabrielle Béland, PhD; Jean-François Dartigues, MD, PhD; Nicholas Moore, MD, PhD; Yola Moride, PhD

Background: Antipsychotic agents (APs) are commonly prescribed to older patients with dementia. Antipsychotic use is associated with an increased risk of ischemic stroke in this population. Our study aimed to investigate the association of AP use with the risk of acute myocardial infarction (MI).

Methods: A retrospective cohort of community-dwelling older patients who initiated cholinesterase inhibitor treatment was identified between January 1, 2000, and December 31, 2009, using the Quebec, Canada, prescription claims database. From this source cohort, all new AP users during the study period were matched with a random sample of AP nonusers. The risk of MI was evaluated using Cox proportional hazards models, adjusting for age, sex, cardiovascular risk factors, psychotropic drug use, and propensity scores. In addition, a self-controlled case series study using conditional Poisson regression modeling was conducted.

Results: Among the source cohort of 37 138 cholinesterase inhibitor users, 10 969 (29.5%) initiated AP treatment. Within 1 year of initiating AP treatment, 1.3% of them had an incident MI. Hazard ratios for the risk of MI after initiation of AP treatment were 2.19 (95% CI, 1.11-4.32) for the first 30 days, 1.62 (95% CI, 0.99-2.65) for the first 60 days, 1.36 (95% CI, 0.89-2.08) for the first 90 days, and 1.15 (95% CI, 0.89-1.47) for the first 365 days. The self-controlled case series study conducted among 804 incident cases of MI among new AP users yielded incidence rate ratios of 1.78 (95% CI, 1.26-2.52) for the 1- to 30-day period, 1.67 (95% CI, 1.09-2.56) for the 31- to 60-day period, and 1.37 (95% CI, 0.82-2.28) for the 61- to 90-day period.

Conclusion: Antipsychotic use is associated with a modest and time-limited increase in the risk of MI among community-dwelling older patients treated with cholinesterase inhibitors.

Arch Intern Med. 2012;172(8):648-653.
Published online March 26, 2012.
doi:10.1001/archinternmed.2012.28

Author Affiliations: Faculty of Pharmacy, Université de Montreal (Drs Pariente and Moride and Mr Ducruet), and Pharmacoepidemiology Unit, Research Center, University of Montréal Hospital Center (Dr Moride, Mr Ducruet, and Ms Béland), Montreal, Quebec, Canada; Unité 657 (Drs Pariente, Moride, Moore, and Fourrier-Réglat) and Unité 897 (Dr Dartigues), Institut National de la Santé et de la Récherche Médicale, Université Bordeaux Ségalen, and Centre Hospitalier Universitaire de Bordeaux, Pharmacology (Drs Pariente, Moore, and Fourrier-Réglat) and Neurology (Dr Dartigues) Departments, Bordeaux, France; and Department of Mathematics and Statistics, The Open University, Milton Keynes, England (Dr Farrington).

In 2005, the worldwide prevalence of dementia was estimated to be almost 24 million cases and is expected to reach 42.3 million in 2020 and 81.1 million in 2040, according to a Delphi consensus study.[1] Dementia may be accompanied by physical aggression, agitation, and hallucinations, which are referred to as behavioral and psychological symptoms of dementia.[2] Antipsychotic agents (APs) are often prescribed for the management of these symptoms.[3-5] For this indication, randomized controlled trials comparing the use of atypical APs vs placebo revealed an increased risk of stroke,[6,7] which resulted in regulatory warnings in various countries[8-10] and a subsequent influence on prescription practices.[11] Further studies[12-15] have shown that the risk was associated with the atypical and conventional AP classes. Studies[16-19] focusing on the risk of death from all causes led to similar conclusions (ie, an increased risk was observed for both classes of APs). Following these findings, safety warnings by regulatory agencies were extended to the entire drug class.[20] Among the causes of death, major cardiovascular events (such as stroke and ischemic events) were the most frequent. However, the mechanism by which APs, either conventional or atypical, may induce such events in older persons remains unclear,[21] despite the fact that dementia itself was described as being a potential cofactor.[13,14] To date, the effect of AP use on the risk of acute myocardial infarction (MI) in patients with treated dementia remains poorly examined. Therefore, we conducted a study to evaluate the risk of MI associated with the use of APs in a population of community-dwelling patients having dementia treated with cholinesterase inhibitors (ChIs).

See Invited Commentary at end of article

©2012 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 05/21/2013

METHODS

OVERALL STUDY DESIGN

We conducted a retrospective cohort study among community-dwelling patients having dementia who were treated with ChIs, comparing new AP users with nonusers. In addition, a self-controlled case series (SCCS) study was performed among all AP users who had an incident MI during the follow-up time.

Commercially available statistical software (SAS 9.1 for Windows; SAS Institute, Inc) was used for all analyses. All reported *P* values are 2-tailed, with significance set at .05. We assessed statistical uncertainty using 95% CIs.

Data Sources

The study data sources were the databases of the public prescription drug and medical services coverage programs of the province of Quebec, Canada (Régie de l'Assurance Maladie du Québec). The public drug plan includes more than 98% of older (≥65 years) residents of the province and covers all outpatient prescribed medications, provided that they are included in the list of reimbursed medications. Drugs acquired in hospital, over the counter, or out of pocket are excluded. The resulting prescription database includes information on the name of the drug, number of units dispensed, dosage, prescribed duration, and date of dispensing. The public medical services program is universal (ie, it covers all residents of the province regardless of age or income), and the resulting database includes all medical services and procedures billed on a fee-for-service basis, whether rendered in an outpatient, inpatient, or emergency department setting. For each service rendered, the database includes the type of service or procedure, date, location, and diagnostic code (*International Classification of Diseases, Ninth Revision* [*ICD-9*]). We restricted the study to patients 66 years or older to have at least 1 year of prescription history before inclusion in the study.

Study Population

Patients who were residing in institutions were not targeted by our study because no data are available for them in the Régie de l'Assurance Maladie du Québec prescription database. A sample comprising 55% of community-dwelling patients 66 years or older was randomly selected among all Quebec public drug plan members who were new users of ChIs (donepezil hydrochloride, rivastigmine, or galantamine hydrobromide) between January 1, 2000, and December 31, 2009. This random sample corresponds to the maximum allowable sample size for research purposes, as determined by access and confidentiality policies of the database custodian (Régie de l'Assurance Maladie du Québec). Given that dementia diagnoses are largely underreported in medical billing claims, we defined the cohort of older patients with dementia by the presence of at least 2 ChI dispensings during a given year. We considered new users only, defined as patients with the absence of ChI dispensing in the 365 days before the first ChI dispensing in the study period.

RETROSPECTIVE COHORT STUDY

Exposed and Unexposed Subcohorts of the Study Population

From the source cohort of ChI-treated patients, we created a subcohort of incident AP users (exposed subcohort) and a subcohort of nonusers (unexposed subcohort). Incident AP use was defined as at least 1 AP dispensing after the initiation of ChI treatment and no dispensing during the prior year. All APs (conventional or atypical) were considered. We defined the index date as the date of first AP dispensing.

The unexposed subcohort consisted of patients from the source population of patients with dementia who received no AP dispensing during the year before ChI initiation or during the study period. We randomly selected patients among all the unexposed subcohort and individually matched them with patients of the exposed subcohort on the date of the first ChI dispensing (date of entry in the source cohort with dementia) using a 1:1 ratio. Because 2 events were required for membership in the exposed subcohort (incident ChI dispensing and incident AP dispensing at a later date), there is potential for immortal time bias. Consequently, the follow-up time for each patient in the unexposed subcohort also started on the index date of the matched AP-exposed patient (date of first AP dispensing).

Follow-up Time and Outcome Definitions

For the retrospective cohort study, we followed up patients for up to 1 year after the index date. Follow-up surveillance was discontinued on the date of occurrence of the following events, whichever came first: death, institutionalization, 1 year after the index date, end of the study period (December 31, 2009), end of registration in the public health program, or MI (identified by *ICD-9* codes 410 and 410.9, with a location of service at an emergency department).

Potential Confounders and Effect Modifiers

In addition to sex and age category (66-69, 70-74, 75-79, 80-84, or ≥85 years), we considered as covariates dementia severity, markers of potential comorbidities, and known or suspected risk factors for MI or cardiovascular disease, all ascertained through claims data during the year preceding the index date. These included a history of MI (*ICD-9* codes 410, 410.9, 412, and 412.9 in the medical claims database), stroke (*ICD-9* codes 431-431.9, 432, 432.0, 432.1, 432.9, 436, 436.9, and 437), diabetes mellitus (*ICD-9* codes 250.0-250.7 and 250.9 or the use of insulin or oral antidiabetic agents), or hypertension or heart failure (*ICD-9* codes 401.0, 401.1, 401.9, 402.0, 402.1, 402.9, 403.0, 403.1, 403.9, 404.0, 404.1, 404.9, 428.0, 428.1, and 428.9 or dispensing of antihypertensive drugs), as well as the use of statins, sedatives, antidepressants, anxiolytic agents, acetylsalicylic acid, or nonsteroidal anti-inflammatory drugs.

Statistical Analysis

We conducted bivariate analyses to compare the characteristics of older patients having dementia who were treated vs untreated with APs and determined statistical significance using χ^2 test. We quantified the effect of exposure to APs on the risk of MI by hazard ratios (HRs) using multivariate Cox proportional hazards modeling. To determine if the risk varied according to time after treatment initiation, we estimated HRs specifically for the following time windows: the first 30 days, first 60 days, first 90 days, and first 365 days. We adjusted for potential confounders by 2 analytical strategies. First, a multivariate Cox proportional hazards model that included all the aforelisted covariates was used. Second, we developed a propensity score for exposure to APs using a multivariate conditional logistic regression model that included all the aforelisted covariates. In a sensitivity analysis, adjustment for confounding was performed using the propensity score only, which was characterized as a continuous variable in the Cox propor-

©2012 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 05/21/2013

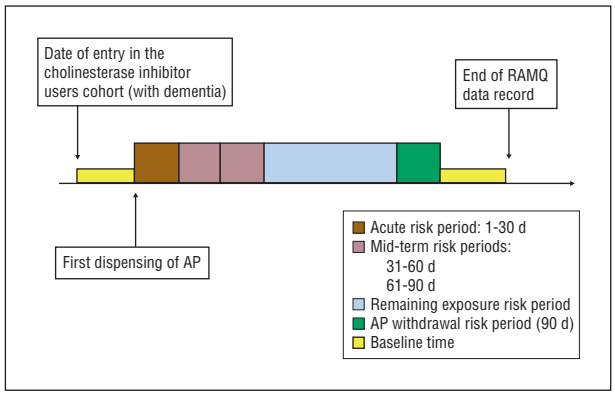


Figure 1. Risk periods for the self-controlled case series study. AP indicates antipsychotic agent; RAMQ, Régie de l'Assurance Maladie du Québec.

tional hazards model. Proportionality of hazards was assessed using Wald χ^2 test for all studied time windows. No test results were statistically significant; hence, proportionality of hazards was assumed.

To identify potentially high-risk patients, we included an interaction term in the multivariate model. We determined whether the association between AP use and MI was modified by the presence of a cardiovascular history at baseline (previous MI, previous stroke, hypertension or heart failure, or diabetes mellitus).

SCCS STUDY

Despite the inclusion of many potential confounders in the multivariate models, residual confounding by factors that are not measured in claims databases may remain. We performed an SCCS study to determine the effect of such unmeasured confounding. The SCCS design provides relative incidence estimates in high-risk periods compared with low-risk periods.[22] The study is performed using data from exposed cases only and relies on intraindividual comparison to eliminate interindividual confounding, such as the extent of coronary heart disease.

Study Population

In accord with the SCCS design, we included all patients from the exposed subcohort who experienced an incident MI during the entire study period. This contrasts with the retrospective cohort study approach, which restricted the follow-up time to 1 year.

Exposure

We extracted all data on drug dispensings that occurred before or after the first MI. We estimated acute, intermediate, prolonged, and withdrawal effects of APs by quantifying the incidence of the first MI in a predefined risk period relative to the incidence of MI in the reference period (**Figure 1**). Risk periods were acute (days 1-30 after the first AP dispensing), intermediate (days 31-60), or prolonged (days 61-90). The remaining exposure period was defined as day 91 until the end of the last AP dispensing. Finally, the residual risk period (withdrawal) covered the 90 days after the end date of the last AP dispensing (defined with regard to the date of dispensing and the prescribed duration). We considered all remaining periods as the reference period. Figure 1 shows how we classified the follow-up time for a given patient with respect to exposure to AP.

Follow-up Time and Outcome Definitions

By design, all available follow-up time is considered in the SCCS study (as opposed to a maximum of 1 year as already described for the retrospective cohort study). This included all periods from first AP dispensing to the earliest occurrence of death, end of coverage, institutionalization, or end of the study period.

Statistical Analysis

For each risk period, we used conditional Poisson regression models to estimate incidence rate ratios. In accord with the SCCS method, we adjusted for age at the first MI to account for the aging of the cohort. This was achieved by partitioning the observation time in 5 age groups.

RESULTS

During the study period, we identified 37 138 patients 66 years or older who initiated ChI treatment and comprised the main cohort of older patients with treated dementia. Of them, 10 969 (29.5%) initiated AP treatment during the study period and were included in the exposed subcohort. Among 97.8% of AP users, treatment was initiated with products of the atypical class (64.5% with risperidone, 21.6% with quetiapine fumarate, and 11.7% with olanzapine). In the remaining 2.2% of patients, products of the conventional class were prescribed, including prochlorperazine maleate (1.9% of exposed patients) and chlorpromazine hydrochloride (0.3%), with other products accounting for fewer than 5 patients. Patients from the exposed subcohort were matched by index date with 10 969 AP nonusers (unexposed subcohort).

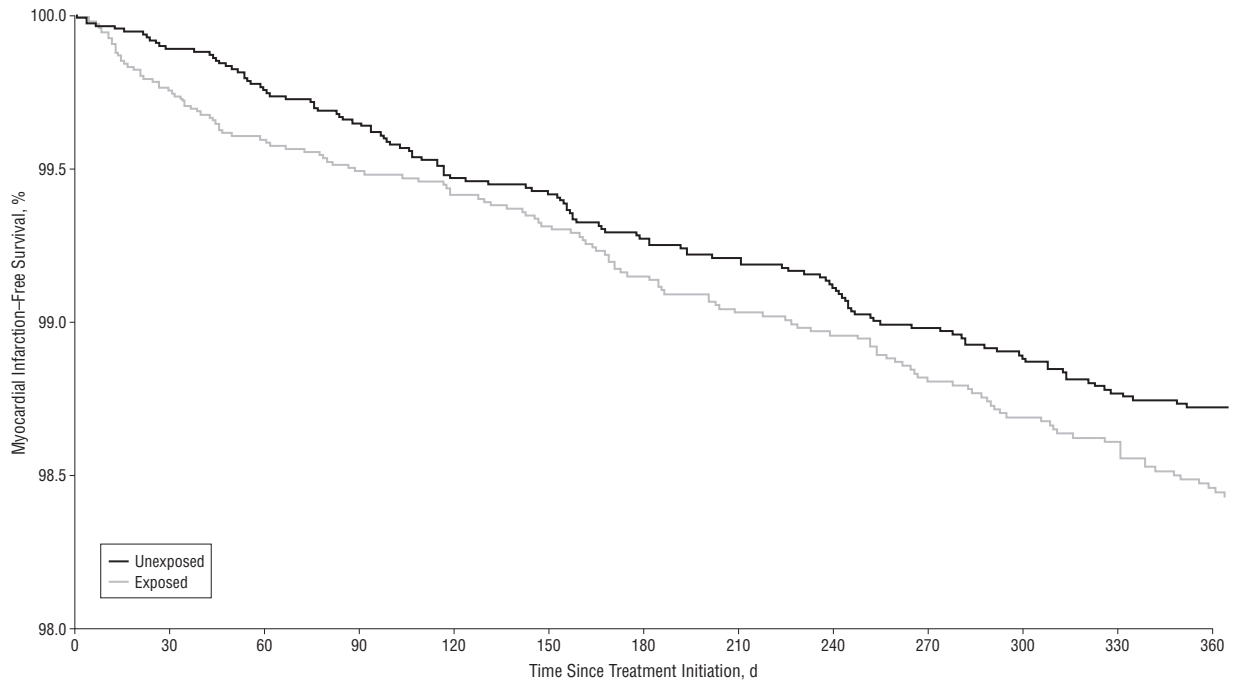
During the year following the index date, we identified 138 cases (1.3%) of incident MI among the exposed subcohort and 126 cases (1.2%) among the unexposed subcohort (**Figure 2**). The characteristics of patients exposed vs unexposed to APs are given in **Table 1**. Patients with dementia who initiated treatment with APs were less likely to be 80 years or older (50.1% vs 56.2%), more likely to have hypertension or heart failure (89.4% vs 76.4%), and more likely to use cardiovascular drugs (statins or acetylsalicylic acid), psychotropic agents (antidepressants and anxiolytics or sedatives), and nonsteroidal anti-inflammatory drugs.

For the SCCS study, our population consisted of 804 patients with incident MI who were identified during the entire study period among patients exposed to APs. The median follow-up time was 47 months.

Results of the multivariate Cox proportional hazards model used for the retrospective cohort study are given in **Table 2**, and results of the conditional Poisson regression model used for the SCCS study are given in **Table 3**. In the retrospective cohort study, the HRs for MI among AP users relative to nonusers were 2.19 for the first 30 days, 1.62 for the first 60 days, 1.36 for the first 90 days, and 1.15 for the first 365 days (Table 2). Propensity score–adjusted models produced similar HRs for MI: 2.00 (95% CI, 1.01-3.98) for the first 30 days (P=.047), 1.49 (95% CI, 0.90-2.45) for the first 60 days (P=.12), 1.27 (95% CI, 0.83-1.94) for the first 90 days

©2012 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 05/21/2013



Population size*		10 d	30 d	60 d	90 d	365 d
Exposed (n = 10 969)	No. at risk	10 969	10 203	9716	9312	7066
	No. of cases	…	26	16	10	86
	No. censored	…	740	471	394	2160
Unexposed (n = 10 969)	No. at risk	10 969	10 583	10 290	10 034	8470
	No. of cases	…	13	14	13	86
	No. censored	…	373	279	243	1478

*At the beginning of the interval.

Figure 2. One-year myocardial infarction–free survival and incidence of myocardial infarction among community-dwelling older patients with treated dementia in the exposed subcohort (incident users of antipsychotic agents) vs the unexposed subcohort (nonusers).

(P = .28), and 1.21 (95% CI, 0.95-1.53) for the first 365 days (P = .13). In the SCCS study, the incidence rate ratios for MI in the exposed period relative to the unexposed periods were 1.78 for the 1- to 30-day period, 1.67 for the 31- to 60-day period, 1.37 for the 61- to 90-day period, 1.18 for the remaining exposure period, and 0.80 for the withdrawal period (Table 3).

In the retrospective cohort study, effect modification by the presence of a cardiovascular history at baseline yielded HRs for MI of 0.98 (95% CI, 0.36-2.67) for patients with a history and 4.05 (95% CI, 1.48-11.10) for patients without a history. However, the interaction term did not reach statistical significance (P = .07). We obtained similar results in the SCCS study.

COMMENT

Our study results indicate that the use of APs is associated with a modest increase in the risk of MI among community-dwelling older patients with treated dementia. The increased risk seems to be highest at the beginning of treatment and seems to decrease thereafter, with the first month of treatment accounting for the highest period of risk. To our knowledge, this is the first study to document an increase in the risk of MI associated with AP use in this population. Because AP use is frequent in patients with dementia (29.5% in our study population), the increased risk of MI may have a major public health effect,[3-5] which highlights the need for communicating such risk and for close monitoring of patients during the first weeks of treatment. Although the risk of conventional vs atypical APs or of individual AP products may differ,[12,17,23] we could not investigate product differences in the present study because of limited statistical power (only 2.2% of patients were treated with conventional APs).

These findings are consistent with those of studies[6,7,12,14,16,17,19] reporting an increased risk of ischemic stroke shortly after AP treatment initiation in older patients with dementia; both of these outcomes are cardiovascular thrombotic events. Therefore, we can hypothesize that APs act through a common pathway, although the mechanism of occurrence of MI and ischemic stroke remains poorly defined because no obvious effect of APs on platelet function or coagulation has been demonstrated to date. An effect of AP use on body weight and on the development of metabolic syndrome, which supports the controversial association between AP use and MI in patients with schizophrenia,[24,25] seems unlikely in the context of our study. If such a pathway was involved, one would expect a risk that progressively increases over time when receiving treat-

©2012 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 05/21/2013

Table 1. Characteristics of Community-Dwelling Older Patients With Treated Dementia in the Exposed Subcohort (Incident Users of Antipsychotic Agents) vs the Unexposed Subcohort (Nonusers)

Characteristic	No. (%) Unexposed Subcohort (n = 10 969)	No. (%) Exposed Subcohort (n = 10 969)	*P* Value
Male sex	3762 (34.3)	3729 (34.0)	.64
Age category, y			
66-74	1963 (17.9)	2443 (22.3)	<.001
75-79	2832 (25.8)	3029 (27.6)	.003
80-84	3217 (29.3)	2991 (27.3)	<.001
≥85	2957 (27.0)	2506 (22.8)	<.001
Cardiovascular history at baseline and risk factors[a]			
Previous MI	312 (2.8)	362 (3.3)	.05
Previous stroke	673 (6.1)	645 (5.9)	.43
Hypertension or heart failure	8379 (76.4)	9800 (89.3)	<.001
Diabetes mellitus	1676 (15.3)	1658 (15.1)	.74
Other medication use[a]			
Statins	3279 (29.9)	3677 (33.5)	<.001
Acetylsalicylic acid	4524 (41.2)	5371 (49.0)	<.001
Nonsteroidal anti-inflammatory drugs	1216 (11.1)	1557 (14.2)	<.001
Antidepressants	1870 (17.0)	3086 (28.1)	<.001
Anxiolytics or sedatives	3100 (28.3)	4974 (45.3)	<.001

Abbreviation: MI, myocardial infarction.
[a] Assessed during the year before the index date.

Table 2. Retrospective Cohort Study of the Association Between Antipsychotic Use and Myocardial Infarction (MI)

Variable	No. of MI Cases	Multivariate-Adjusted Hazard Ratio (95% CI) for MI	*P* Value
Time window after initiation of antipsychotic treatment[a]			
Nonuse	. . .	1 [Reference]	. . .
1-30 d	26/39	2.19 (1.11-4.32)	.02
1-60 d	42/69	1.62 (0.99-2.65)	.06
1-90 d	52/92	1.36 (0.89-2.08)	.15
1-365 d	138/264	1.15 (0.89-1.47)	.28
Male sex	105	0.89 (0.44-1.77)	.73
Age category, y			
66-74	38	1 [Reference]	. . .
75-79	59	3.48 (0.75-16.12)	.11
80-84	84	4.27 (0.94-19.38)	.06
≥85	83	8.06 (1.83-35.44)	.006
Cardiovascular history at baseline and risk factors			
Previous MI	9	1.49 (0.20-10.99)	.70
Previous stroke	16	1.18 (0.36-3.88)	.79
Diabetes mellitus	61	3.06 (1.52-6.15)	.002
Other medication use			
Statins	95	0.84 (0.40-1.74)	.63
Acetylsalicylic acid	152	1.28 (0.66-2.51)	.47
Nonsteroidal anti-inflammatory drugs	28	1.01 (0.39-2.60)	.98
Antidepressants	67	1.81 (0.91-3.60)	.09
Anxiolytics or sedatives	116	0.64 (0.32-1.27)	.20

[a] Number of MI cases among patients exposed to antipsychotic agents per the total number of MI cases for the time window.

Table 3. Self-controlled Case Series Study of 804 Incident Cases of Myocardial Infarction (MI) Among New Users of Antipsychotic Agents

Time Window After Initiation of Antipsychotic Treatment	No. of MI Cases (n = 804)	Incidence Rate Ratio (95% CI) for MI	*P* Value
1-30 d	31	1.78 (1.26-2.52)	.001
31-60 d	21	1.67 (1.09-2.56)	.02
61-90 d	16	1.37 (0.82-2.28)	.23
Remaining exposure period	198	1.18 (0.92-1.51)	.19
Withdrawal period	68	0.80 (0.62-1.04)	.10
Unexposed period	470	1 [Reference]	. . .

ment rather than an acute risk that decreases thereafter. Recent literature suggests a possible drug-drug interaction between APs and ChIs, which may be an alternative explanation for the findings.[26,27]

Another possible reason for the observed association with MI is protopathic bias, whereby APs would be prescribed to treat initial symptoms of the disease or to treat symptoms of a disease associated with the outcome, such as delirium. The literature on the relationship between MI and delirium is scarce. To our knowledge, only case reports have been published of MI in patients manifesting delirium tremens[28] and in which severe illnesses (including MI or cardiac surgery) have been identified as predictors of delirium in hospitalized older patients.[29] However, data on the frequency of delirium as an early symptom of MI in older persons are absent from the literature. It is also possible that agitation, aggressiveness, or potentially exhausting motor behaviors associated with delusion might increase the risk of MI. Therefore, patients being prescribed APs could have higher risk of MI because of underlying delusion and associated symptoms. Such a hypothesis remains undocumented to date. Consequently, the potential importance of a protopathic bias in the association reported herein cannot be appraised.

A limitation of our study is that some AP treatments may have been initiated in a secondary care setting, which would have led to an error in the determination of the initiation date. Patients who had an MI during their secondary care admission would not have been included in the study, while those who did not would have been included. This potential error in initiation date assessment may have resulted in a depletion of susceptible effect and an underestimation of the HRs.[30]

To minimize misclassification of potential confounders owing to the nature of the data (claims databases), we used the presence of a diagnostic code combined with drug dispensing data to optimize the specificity of the indicators for the covariates. Although a possibility of misclassification remains, it is likely to be nondifferential between the exposed and unexposed subcohorts. Consistency of results obtained in the retrospective cohort study and the SCCS study suggests that unmeasured confounders minimally affected the results, although the SCCS study is prone to bias from reverse causation and MI-related deaths.

©2012 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 05/21/2013

Because of the nature of the drug plan in Quebec, the population that we studied is representative of older patients having dementia treated with ChIs, and these results should be generalizable to this population. However, the potential effect modification by a cardiovascular history at baseline that we observed, although not statistically significant, could indicate that the increased risk is not homogeneous for all patients. Further investigations with larger sample sizes should be undertaken to identify high-risk subpopulations.

Accepted for Publication: December 31, 2011.
Published Online: March 26, 2012. doi:10.1001/archinternmed.2012.28
Correspondence: Yola Moride, PhD, Faculty of Pharmacy, Université de Montréal, PO Box 6128, Succursale Centre-ville, Montreal, QC H3C 3J7, Canada (yola.moride@umontreal.ca).
Author Contributions: Dr Moride had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Pariente, Fourrier-Réglat, Dartigues, Moore, and Moride. *Analysis and interpretation of data:* Pariente, Fourrier-Réglat, Ducruet, Farrington, Béland, Dartigues, Moore, and Moride. *Critical revision of the manuscript for important intellectual content:* Pariente, Fourrier-Réglat, Ducruet, Farrington, Béland, Dartigues, Moore, and Moride. *Obtained funding:* Pariente, Ducruet, Béland, and Moride. *Administrative, technical, or material support:* Fourrier-Réglat, Moore, and Moride. *Study supervision:* Pariente, Fourrier-Réglat, and Moride.
Financial Disclosure: None reported.
Funding/Support: This study was funded by the Fonds de la Recherche en Santé du Québec and by the Réseau Québécois de Recherche sur l'Usage des Médicaments (Dr Moride).
Role of the Sponsors: The funding sources were not involved in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

REFERENCES

1. Ferri CP, Prince M, Brayne C, et al; Alzheimer's Disease International. Global prevalence of dementia: a Delphi consensus study. *Lancet*. 2005;366(9503):2112-2117.
2. Cohen-Mansfield J, Taylor L, Werner P. Delusions and hallucinations in an adult day care population: a longitudinal study. *Am J Geriatr Psychiatry*. 1998;6(2):104-121.
3. Lövheim H, Karlsson S, Gustafson Y. The use of central nervous system drugs and analgesics among very old people with and without dementia. *Pharmacoepidemiol Drug Saf*. 2008;17(9):912-918.
4. Gruber-Baldini AL, Stuart B, Zuckerman IH, Simoni-Wastila L, Miller R. Treatment of dementia in community-dwelling and institutionalized Medicare beneficiaries. *J Am Geriatr Soc*. 2007;55(10):1508-1516.
5. Valiyeva E, Herrmann N, Rochon PA, Gill SS, Anderson GM. Effect of regulatory warnings on antipsychotic prescription rates among elderly patients with dementia: a population-based time-series analysis. *CMAJ*. 2008;179(5):438-446.
6. De Deyn PP, Carrasco MM, Deberdt W, et al. Olanzapine versus placebo in the treatment of psychosis with or without associated behavioral disturbances in patients with Alzheimer's disease. *Int J Geriatr Psychiatry*. 2004;19(2):115-126.
7. Brodaty H, Ames D, Snowdon J, et al. A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. *J Clin Psychiatry*. 2003;64(2):134-143.
8. Committee on Safety of Medicines. *Atypical Antipsychotic Drugs and Stroke: Message From Professor Gordon Duff, Chairman* . London, England: Committee on Safety of Medicine; 2004. CEM/CMO/2004/1.
9. Food and Drug Administration. Pharmaceutica. J. revision of WARNINGS section for Risperdal (risperidone). April 16, 2003. http://www.fda.gov/Safety/MedWatch/SafetyAlertsforHumanMedicalProducts/ucm153478.htm. Accessed February 1, 2012.
10. Health Canada. Important drug safety information: RISPERDAL* (risperidone) and cerebrovascular adverse events in placebo-controlled dementia trials: Janssen-Ortho Inc. October 11, 2002. http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2002/risperdal_hpc-cps-eng.php. Accessed September 2, 2011.
11. Dorsey ER, Rabbani A, Gallagher SA, Conti RM, Alexander GC. Impact of FDA black box advisory on antipsychotic medication use. *Arch Intern Med*. 2010;170(1):96-103.
12. Gill SS, Rochon PA, Herrmann N, et al. Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study. *BMJ*. 2005;330(7489):e445. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC549652/?tool=pubmed. Accessed January 27, 2012.
13. Layton D, Harris S, Wilton LV, Shakir SA. Comparison of incidence rates of cerebrovascular accidents and transient ischaemic attacks in observational cohort studies of patients prescribed risperidone, quetiapine or olanzapine in general practice in England including patients with dementia. *J Psychopharmacol*. 2005;19(5):473-482.
14. Douglas IJ, Smeeth L. Exposure to antipsychotics and risk of stroke: self controlled case series study. *BMJ*. 2008;337:a1227. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2526549/?tool=pubmed. Accessed January 31, 2012.
15. Rochon PA, Normand SL, Gomes T, et al. Antipsychotic therapy and short-term serious events in older adults with dementia. *Arch Intern Med*. 2008;168(10):1090-1096.
16. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA*. 2005;294(15):1934-1943.
17. Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med*. 2005;353(22):2335-2341.
18. Gill SS, Bronskill SE, Normand SL, et al. Antipsychotic drug use and mortality in older adults with dementia. *Ann Intern Med*. 2007;146(11):775-786.
19. Trifirò G, Verhamme KM, Ziere G, Caputi AP, Ch Stricker BH, Sturkenboom MC. All-cause mortality associated with atypical and typical antipsychotics in demented outpatients. *Pharmacoepidemiol Drug Saf*. 2007;16(5):538-544.
20. Food and Drug Administration. Information for healthcare providers: antipsychotics. June 16, 2008. http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinfromationforpatientsandproviders/ucm124830.htm. Accessed February 1, 2012.
21. Herrmann N, Lanctôt KL. Do atypical antipsychotics cause stroke? *CNS Drugs*. 2005;19(2):91-103.
22. Whitaker HJ, Hocine MN, Farrington CP. The methodology of self-controlled case series studies. *Stat Methods Med Res*. 2009;18(1):7-26.
23. Parker C, Coupland C, Hippisley-Cox J. Antipsychotic drugs and risk of venous thromboembolism: nested case-control study. *BMJ*. 2010;341:c4245. http://www.bmj.com/content/341/bmj.c4245?view=long&pmid=20858909. Accessed January 27, 2012.
24. Lindenmayer JP, Czobor P, Volavka J, et al. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. *Am J Psychiatry*. 2003;160(2):290-296.
25. Meyer JM, Davis VG, Goff DC, et al. Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE Schizophrenia Trial: prospective data from phase 1. *Schizophr Res*. 2008;101(1-3):273-286.
26. Bentué-Ferrer D, Tribut O, Polard E, Allain H. Clinically significant drug interactions with cholinesterase inhibitors: a guide for neurologists. *CNS Drugs*. 2003;17(13):947-963.
27. Pariente A, Sanctussy DJ, Miremont-Salamé G, Moore N, Haramburu F, Fourrier-Réglat A; l'Association Française des Centres Régionaux de Pharmacovigilance (CRPV). Factors associated with serious adverse reactions to cholinesterase inhibitors: a study of spontaneous reporting. *CNS Drugs*. 2010;24(1):55-63.
28. Danenberg HD, Nahir M, Hasin Y. Acute myocardial infarction due to delirium tremens. *Cardiology*. 1999;92(2):144.
29. Inouye SK, Viscoli CM, Horwitz RI, Hurst LD, Tinetti ME. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. *Ann Intern Med*. 1993;119(6):474-481.
30. Moride Y, Abenhaim L. Evidence of the depletion of susceptibles effect in non-experimental pharmacoepidemiologic research. *J Clin Epidemiol*. 1994;47(7):731-737.

©2012 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 05/21/2013