Long-Term Antipsychotic Use and Major Cardiovascular Events: A Retrospective Cohort Study

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ABSTRACT

Objective: Chronic treatment with antipsychotics may result in both metabolic side effects and cardiovascular disease. Our aim was to evaluate the effect of antipsychotic medications categorized by their metabolic side effect profiles as low, intermediate, or high risk on major cardiovascular events.

Methods: A retrospective cohort study was conducted in adult outpatients aged 30 years or older initiating antipsychotic treatment from 2002 to 2007. Antipsychotic medications were divided into 3 groups (low-, intermediate-, and high-risk) according to the severity of their side-effect profiles in developing metabolic abnormalities associated with cardiovascular disease. The primary outcome measure was the time to the composite of acute myocardial infarction, acute coronary syndrome, ischemic stroke, peripheral artery disease, or a new revascularization procedure. Inverse probability weighting of a marginal structural Cox model was used to adjust for confounding.

Results: A total of 1,008 patients were included (mean age = 72.4 years, median follow-up = 36.5 months), and 19.6% of patients experienced the primary outcome. The adjusted hazard ratios of a major cardiovascular event for patients in the high- or intermediate-risk medication groups compared to the low-risk group were 2.82 (95% CI, 1.57–5.05) and 2.57 (95% CI, 1.43–4.63), respectively.

Conclusions: Older adult patients under antipsychotic regimens with high or intermediate risk of metabolic side effects may face a higher incidence of major cardiovascular events than those under a low-risk regimen during long-term follow-up.

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Patients with schizophrenia, bipolar disorder, and unipolar depressive disorders exhibit an increased prevalence of comorbid conditions such as obesity, type 2 diabetes mellitus, hyperlipidemia, and metabolic syndrome.[1–3] These coexisting conditions may largely explain the increased rate of cardiovascular disease and mortality seen in this population as compared to the general public.[4,5] Additionally, the antipsychotics used for the treatment of these disorders have significant side effects that may contribute to the development or worsening of these comorbid conditions.[6,7]

Second-generation antipsychotics have been shown to induce greater weight gain and cause more metabolic abnormalities as compared to first-generation antipsychotics.[8–10] However, within the first- and second-generation antipsychotics, differences in the severity of their side-effect profiles exist.[11,12] The latter is especially evident with induced metabolic abnormalities. Thus, a better understanding of the severity and clinical impact of the metabolic side-effect profiles of specific antipsychotics is paramount.

Many studies[13–18] have compared the risk of first- and second-generation antipsychotics on the rates of cardiovascular events or mortality and have yielded mixed results. To our knowledge, none have compared antipsychotics on the basis of their proneness to develop metabolic abnormalities such as weight gain, hyperlipidemia, and type 2 diabetes. Our aim is to better delineate the effects of antipsychotic medications with low-, intermediate-, or high-risk side-effect profiles on the development of cardiovascular events. We thus report on a cohort study that examined the risk of major cardiovascular events associated with antipsychotic treatment during long-term follow-up. Specifically, we hypothesized that high- and intermediate-risk antipsychotic treatment would be associated with a greater incidence of major cardiovascular events during follow-up when compared to low-risk medications.

METHODS

Study Design and Data Extraction

The present study is a retrospective cohort based on an electronic database of a tertiary teaching hospital in Buenos Aires, Argentina. The institutional review board provided approval for this study (protocol reference number: 2435), and it was developed in accordance to the amended declaration of Helsinki. Patients included belonged to a local health plan (that is, a private health insurance that allows patients who are enrolled to get their medical care and follow-up within the hospital from which the electronic database was retrieved). Health-plan data include drug prescriptions and their characteristics, including

Clinical Points

- Antipsychotic treatment is associated with higher rates of all-cause mortality in older adults; however, mechanisms underlying this association remain largely unknown.
- Antipsychotic medications with high or intermediate risk of metabolic abnormalities are associated with an almost 3-fold higher risk of major cardiovascular events.
- In patients at high risk of cardiovascular disease, consider using a "low-risk agent" (ie, aripiprazole, trifluoperazine, or ziprasidone), since medications in this group were associated with a lower incidence of major cardiovascular events during follow-up.

dispensing date, drug name, dose, quantity, and duration of supply, all of which have been shown to be reliable measures of drug treatment.[19–21] Moreover, it contains a fully integrated health care database containing both inpatient and outpatient information regarding baseline comorbidities, clinical outcomes, and laboratory measures. We used these health records to gather baseline information on demographics, clinical history and comorbidities, physical examination, and laboratory and radiologic data. We also used the registry to capture information on vital status and new cardiovascular events during follow-up.

Study Population

We identified 1,229 consecutive patients receiving for the first time antipsychotic medication from January 2002 to December 2007. Each patient was assigned an index date corresponding to the date of the first drug prescription. Patients were included if they were 30 years or older on the index date, if they had continuous information for at least 365 days preceding the index date, if they were continuously enrolled in the health plan for more than 6 months after the index date, and if they had at least 2 pharmacy claims during the first 6 months of treatment. Patients were excluded if they had received the antipsychotic medication during hospitalization (mainly associated with delirium) and did not continue drug treatment at hospital discharge. Those patients who were older than 90 years at index date or had been discharged during the preceding 60 days of treatment initiation with a diagnosis of acute myocardial infarction or stroke were also excluded. Additionally, the present report excludes patients that presented with any cardiovascular event that occurred during the first 6 months of follow-up, since this was likely to reflect a preexisting condition and the focus of our analysis was on long-term cardiovascular effects of treatment. Of the 1,229 initially assessed patients, 1,008 were included in this report (Figure 1).

Baseline Covariates

Demographic variables including age, sex, year of index date, and psychiatric diagnosis were recorded. Baseline characteristics regarding prior cardiovascular events (ischemic stroke, myocardial infarction, diagnosis of peripheral artery disease, atrial fibrillation) were included. Risk factors (sex, blood pressure, type 2 diabetes) and laboratory markers associated with cardiovascular disease (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total triglycerides, and fasting plasma glucose) were also evaluated. In addition, prevalent chronic pulmonary obstructive disease, heart failure, chronic renal failure, malignancy, and both tobacco and alcohol use were recorded. Finally, the number of hospitalizations during follow-up and number of suicide attempts were measured since a potential relationship between severity of serious mental illness and cardiovascular events has been reported.[22–24]

Regarding concomitant pharmacologic treatment, other claims for pharmacotherapy in addition to antipsychotic drugs were taken into consideration. These included cholesterol-lowering agents, antihypertensive medication, antithrombotic agents, lithium, anticonvulsants, benzodiazepines, antidepressants, cholinesterase inhibitors, corticosteroids, and antidiabetic agents.

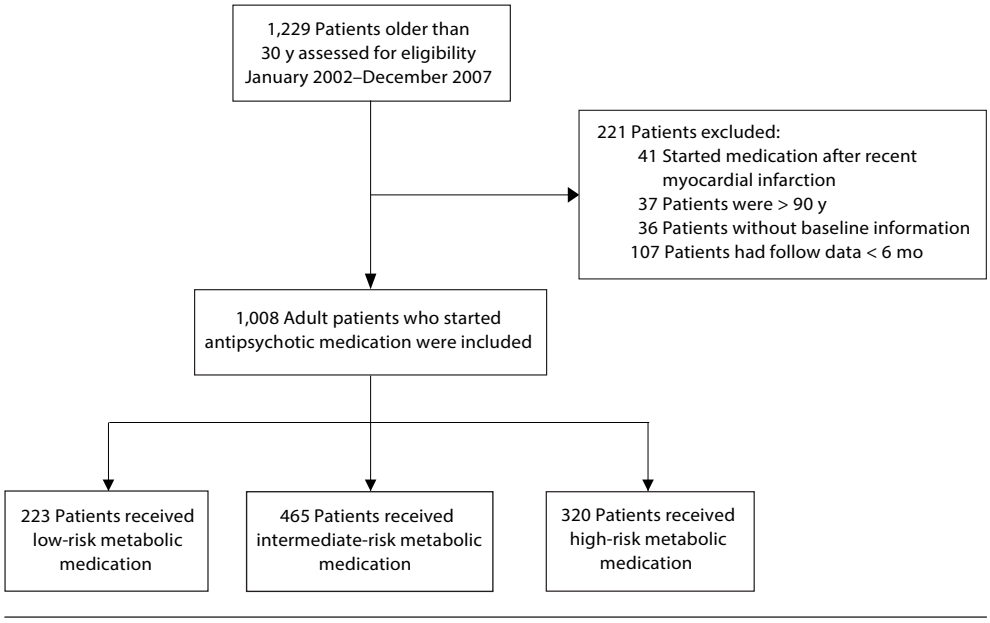
Explanatory Variables

Our primary exposure of interest was antipsychotic treatment, defined as any antipsychotic drug initiated by the patient for the first time in his or her life. Combination therapy was defined as any concomitant use of 2 or more antipsychotic drugs during the study follow-up. Antipsychotic medications were divided into 3 groups according to the severity of their side-effect profiles in developing metabolic abnormalities associated with cardiovascular disease (eg, weight gain, hyperlipidemia, diabetes mellitus).[8,10,11,25–28] Antipsychotics categorized as low risk included haloperidol, aripiprazole, ziprasidone, trifluoperazine, and levomepromazine. Antipsychotics categorized as intermediate risk were quetiapine and risperidone. Finally, those drugs categorized as high risk included thioridazine, olanzapine, and clozapine (see Supplementary eTable 1). Patients taking any combination of 2 or more antipsychotic drugs concomitantly were considered as being part of the high-risk group because of the increased severity of side-effect profiles associated with polypharmacy[29] and because they were most likely receiving at least 1 high-risk drug. Dosage was categorized as low, medium, or high on the basis of chlorpromazine equivalents.[30]

Follow-Up

Each patient was followed from the index date to disenrollment from health plan, end of the study period (December 31, 2013), development of a cardiovascular event, or death. Time to the occurrence of first composite outcome was recorded. For cases in which a patient switched to other antipsychotic medication during follow-up, the individual was censored after a 1-month grace period.[31] An approximation to an intention-to-treat analysis was performed in which patients taking at least 2 prescriptions of an antipsychotic drug were followed until disenrollment, end of follow-up, or primary outcome, regardless of discontinuation of index drug. Current users were defined as patients who received a prescription for an antipsychotic

Figure 1. Flowchart of Patients



drug within 2 months of the primary composite outcome. Past users were patients whose last prescription of the antipsychotic drug was more than 2 months away from the primary composite outcome.

Outcome Measures

The primary outcome measure was time to the composite of acute myocardial infarction, acute coronary syndrome, ischemic stroke, peripheral artery disease, or a new revascularization procedure (either coronary artery bypass grafting or percutaneous coronary intervention). Composite secondary outcome was time to the composite of the primary outcome plus all-cause mortality. In addition, onset of type 2 diabetes mellitus and all-cause mortality also served as secondary outcomes. Type 2 diabetes mellitus was defined as a fasting plasma glucose level during follow-up ≥ 200 mg/dL or 2 consecutive fasting plasma glucose values of 126 mg/dL or the addition of a glucose-lowering agent during follow-up.

Statistical Analysis

Quantitative variables are presented as mean and standard deviation or, in case of noticeably skewed data, as the median and interquartile range. Baseline differences between antipsychotic categories (low, intermediate, and high risk) were assessed using the χ^2 test for categorical variables and 1-way analysis of variance for continuous variables.

A multinomial logistic regression was fit to estimate the propensity of receiving each level of antipsychotic treatment based on all measured clinical characteristics including baseline disease, comorbidities, and laboratory measures (see Supplementary eFigure1). To adjust for confounding, we used inverse probability weighting of a marginal structural Cox proportional regression model with robust standard errors calculation to estimate the effect of antipsychotic medication on the occurrence of the primary composite outcome and all secondary end points. We used stabilized weights to improve statistical efficiency.

To evaluate the robustness of our findings, we also used a multivariate Cox proportional hazards model to compare the survival experience of the cohorts–using low risk of metabolic events as the reference group–conditional on the propensity score modeled as regression splines. Cubic-restricted splines were used to assess the linearity assumption for all continuous covariates, and a priori meaningful interactions were tested.

Finally, to investigate the potential mediatory effect of weight gain and diabetes on major adverse cardiovascular events, a mediation analysis was performed.[32,33] We used a threshold of .05 to declare statistical significance, and all presented tests are 2-sided. All analyses were performed using STATA v.14.1 (StataCorp LP, College Station, Texas).

RESULTS

A total of 1,008 patients were included in the present study. Of these, 223, 465, and 320 received low-, intermediate-, and high-risk antipsychotic medications, respectively (Figure 1). Among the high-risk group, only 31 patients were treated with combination therapy. Mean (SD) age overall was 68.7 years (15.7) for the low-risk group, 75.1 years (13.8) for the intermediate-risk group, and 71.0 years (14.6) for the high-risk group (Table 1). Median follow-up time for the full cohort was 36.5 months. Median follow-up and survival times for each cohort and crude incidence rates for each cohort are available in Supplementary eTable 2.

The most frequent diagnosis at baseline was dementia (63.4%), followed by schizophrenia (9.6%), major depression (12.4%), and bipolar disorder (11.6%). Users

Table 1. Baseline Characteristics of Patients

Characteristic	Category of Antipsychotics According to Severity of Metabolic Side Effect Profile[a]			
	Low-Risk Group (n = 223)	Intermediate-Risk Group (n = 465)	High-Risk Group (n = 320)	*P* Value[b]
Age, mean (SD), y	68.7 (15.7)	75.1 (13.8)	71.0 (14.6)	< .01
Male sex, n (%)	73 (32.7)	141 (30.3)	99 (30.9)	.81
Systolic blood pressure, mean (SD), mm Hg	125.1 (14.8)	127.9 (14.9)	132.8 (68.3)	.08
BMI (kg/m^2), mean (SD)	27.2 (5.4)	26.3 (6.1)	26.1 (4.5)	.12
Geriatric residence, n (%)	23 (10.3)	92 (19.8)	46 (14.4)	< .01
Antipsychotic dose (chlorpromazine equivalents), n (%)				.01
< 100 mg (low dose)	148 (66.4)	303 (65.2)	231 (72.2)	< .01
100–299 mg (intermediate dose)	53 (23.8)	126 (27.1)	49 (15.3)	.11
≥ 300 mg (high dose)	22 (9.9)	36 (7.7)	40 (12.5)	.09
Psychiatric characteristic, n (%)				
Schizophrenia	28 (12.6)	20 (4.3)	49 (15.3)	< .01
Bipolar disorder	21 (9.4)	44 (9.5)	52 (16.3)	< .01
Major depressive disorder	51 (22.9)	45 (9.7)	29 (9.1)	< .01
Dementia	113 (50.7)	340 (73.1)	186 (58.1)	< .01
Alcohol abuse	11 (4.9)	16 (3.4)	18 (5.6)	.32
Past suicidal attempt	3 (1.4)	17 (3.7)	6 (1.9)	.13
Past psychiatric hospitalization	13 (5.8)	48 (10.3)	39 (12.2)	.05
Use of concomitant medication, n (%)				
Cholesterol-lowering agents	59 (26.5)	123 (26.5)	70 (21.9)	.30
Antihypertensive	102 (45.7)	236 (50.8)	154 (48.1)	.45
Antithrombotic	53 (23.8)	158 (34.0)	74 (23.1)	.01
Antiepileptic	31 (13.9)	52 (11.2)	46 (14.4)	.36
Lithium	9 (4.0)	6 (1.3)	12 (3.8)	.04
Benzodiazepines	139 (62.3)	278 (59.8)	209 (65.3)	.29
SSRI	64 (28.7)	194 (41.7)	121 (37.8)	< .01
Cholinesterase inhibitors	32 (14.4)	176 (37.9)	87 (27.2)	< .01
Memantine	4 (1.8)	57 (12.3)	19 (5.9)	< .01
Corticosteroids	14 (6.3)	26 (5.6)	21 (6.6)	.84
Antidiabetics	21 (9.4)	35 (7.5)	22 (6.9)	.54
Tricyclic antidepressants	6 (2.7)	9 (1.9)	4 (1.3)	.48
Comorbid conditions, n (%)				
COPD	20 (9.0)	49 (10.5)	26 (8.1)	.51
Chronic renal failure	24 (9.9)	42 (9.0)	25 (7.8)	.69
Heart failure	17 (7.6)	55 (11.8)	36 (11.3)	.23
Atrial fibrillation	15 (6.7)	42 (9.0)	23 (7.2)	.48
Cancer	42 (18.8)	56 (12.0)	45 (14.1)	.06
Tobacco use	91 (40.8)	130 (28.0)	101 (31.6)	< .01
Previous cardiovascular events, n (%)				
Myocardial infarction	19 (8.5)	20 (4.3)	14 (4.4)	.05
Stroke	21 (9.4)	43 (9.3)	19 (5.9)	.19
Diabetes	24 (10.8)	42 (9.0)	20 (6.3)	.16
Peripheral artery disease	6 (2.7)	16 (3.4)	3 (0.94)	.08
Baseline laboratory measure, mean (SD), mg/dL				
LDL cholesterol	124.0 (31.3)	117.8 (31.7)	121.9 (29.8)	.54
HDL cholesterol	49.5 (13.9)	50.0 (13.7)	50.8 (14.8)	.59
Triglycerides	117.7 (51.4)	111.2 (51.8)	108.8 (43.1)	.02
Fasting plasma glucose	101.2 (26.5)	97.0 (22.3)	97.0 (19.7)	.05

[a]Antipsychotic medications were divided into 3 groups according to the severity of their side-effect profiles in developing metabolic abnormalities associated with cardiovascular disease (eg, weight gain, hyperlipidemia, diabetes mellitus). Antipsychotics categorized as low risk included haloperidol, aripiprazole, ziprasidone, trifluoperazine, and levomepromazine. Antipsychotics categorized as intermediate risk were quetiapine and risperidone. Finally, those drugs categorized as high risk included thioridazine, olanzapine, and clozapine.

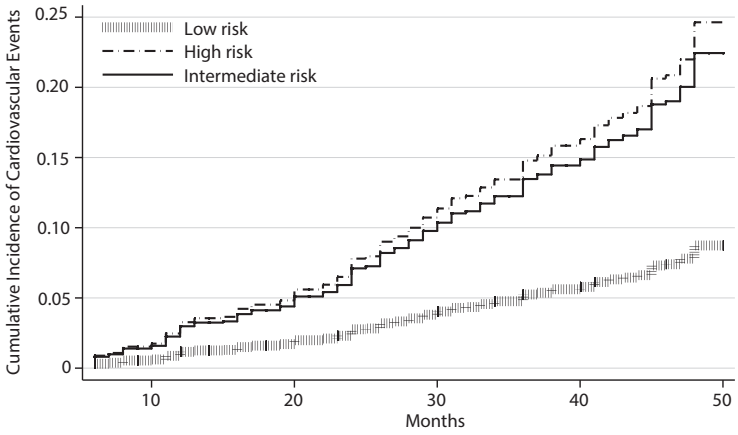
[b]Two-sided *P* values. Mean values are compared with 1-way analysis of variance and proportions with the χ^2 test.

Abbreviations: BMI = body mass index, COPD = chronic obstructive pulmonary disease, HDL = high-density lipoprotein, LDL = low-density lipoprotein, SSRI = selective serotonin reuptake inhibitor.

of intermediate-risk medications were less likely to have a diagnosis of schizophrenia compared to low-risk and high-risk antipsychotic users. Most patients (67% of the total sample) were treated with low doses of antipsychotic drugs (between 100 and 300 mg of chlorpromazine. Further, more than 50% of all patients received benzodiazepines as concomitant therapy. Regarding baseline severity of psychiatric disease, 5.8% of the low-risk, 10.3% of the intermediate-risk, and 12.2% of the high-risk groups had a previous psychiatric stay in the last 6 months, suggesting that patients receiving intermediate- and high-risk medications presented with greater baseline severity.

Patients receiving low-risk antipsychotics had higher cardiovascular comorbidity at baseline (more previous myocardial infarction and diabetes) than the intermediate- and high-risk groups. However, significantly more patients in the high-risk group (14.8%) compared to the low-risk group (2.4%) developed obesity with antipsychotic treatment.

Figure 2. Estimated Cumulative Cardiovascular Events for Patients Under High-, Intermediate-, or Low-Risk Antipsychotic Exposures[a]



[a]Inverse probability weighting of a marginal structural Cox proportional hazards model. Major cardiovascular event was a composite of myocardial infarction, stroke, peripheral artery disease, acute coronary syndrome, or new revascularization procedure.

Table 2. Major Cardiovascular Events During Follow-Up for High-, Intermediate-, and Low-Risk Antipsychotic Medication[a]

		Adjusted Hazard Ratio (95% CI)[c]		
Main Exposure	Crude Hazard Ratio (95% CI)[b]	Overall	< 2 y From Baseline	< 5 y From Baseline
High risk of metabolic side effect	3.05 (1.84–5.06)	2.82 (1.57–5.05)	2.59 (0.84–7.98)	2.22 (1.18–4.17)
Intermediate risk of metabolic side effect	3.15 (1.89–5.24)	2.57 (1.43–4.63)	2.06 (0.70–6.05)	1.90 (1.03–3.52)

[a]The primary outcome measure was time to composite of myocardial infarction, stroke, peripheral artery disease, acute coronary syndrome, or new revascularization procedure.
[b]Univariate Cox proportional hazards model. Exposure was modeled using low-risk medications as the reference group.
[c]Inverse probability weighting of a marginal structural Cox proportional model. Exposure was modeled using low-risk medications as the reference group.

Similar findings were evident with the development of type 2 diabetes mellitus (Supplementary eTable 3). A total of 15.9% and 6.7% of the high-risk and intermediate-risk groups, respectively, developed type 2 diabetes mellitus as compared to 5.8% in the low-risk group (Supplementary eTable3). Finally, concerning severity of mental illness during follow-up, no significant differences regarding the number of hospitalizations or suicide attempts were found between users of high-, intermediate-, or low-risk medications (see Supplementary eTable 4).

Major cardiovascular events occurred in 19.6% of the cohort population. Adjusted survival curves for low-, intermediate-, and high-risk drug users are shown in Figure 2. Patients in the low-risk group had fewer events during follow-up when compared to either intermediate- or high-risk groups (Table 2). Overall, for the intermediate-risk group, the hazard of major cardiovascular events was 2.57 times the hazard of the low-risk group during the study follow-up period (95% CI, 1.43–4.63). In addition, for the high-risk group, the hazard of the primary composite outcome was 2.82 times the hazard of the low-risk group during the study follow-up period (95% CI, 1.57–5.05). The effect of antipsychotic medication with either intermediate- or high-risk side effect profiles during follow-up appeared to be similar at both 2 and 5 years of follow-up (Table 2). The multivariate Cox proportional regression model adjusting for the propensity score yielded similar point estimates (see Supplementary eTables 5 and 6 and eFigure 2). Of note, 91.2% of patients were current users of antipsychotic medications at the moment of experiencing the primary outcome.

Sensitivity analyses, excluding the 31 patients taking more than 1 antipsychotic medication in the high-risk group, showed similar results as above. The overall hazard of a major cardiovascular event for high-risk group was 2.61 (95% CI, 1.44–4.71) times the hazard of the low-risk group during the follow-up period. Similarly, the overall hazard for the intermediate-risk group was 2.59 (95% CI, 1.43–4.69) times the hazard of the low-risk group during the follow-up period (Supplementary eTable 7). Moreover—to maximize ease of interpretation—when considering quetiapine as high risk and risperidone as low risk, the adjusted hazard ratio of the primary outcome for the high-risk versus the low-risk group was 1.57 (95% CI, 1.17–2.12; Supplementary eTable 8 and eFigure 3). Finally, a sensitivity analysis taking into account dosing strategies as a potential confounder yielded similar results to those previously reported (Supplementary eTable 9). No effect through either diabetes or weight gain was apparent in mediation analysis.

Table 3. Secondary Outcomes for High-, Intermediate-, and Low-Risk Antipsychotic Medication

Main Exposure	Crude HR (95% CI)	*P* Value[a]	Adjusted HR (95% CI)	*P* Value[b]
Composite secondary outcome[c]				
High risk of metabolic side effects	1.47 (1.09–1.98)	.01	1.31 (0.95–1.80)	.10
Intermediate risk of side effects	1.89 (1.41–2.54)	< .01	1.46 (1.06–2.00)	.02
All-cause mortality				
High risk of metabolic side effects	1.04 (0.73–1.49)	.81	0.95 (0.65–1.39)	.79
Intermediate risk of side effects	1.70 (1.21–2.39)	< .01	1.32 (0.92–1.92)	.14
Incident type 2 diabetes				
High risk of metabolic side effects	2.83 (1.54–5.21)	< .01	3.29 (1.66–6.51)	< .01
Intermediate risk of side effects	1.44 (0.75–2.75)	.27	1.76 (0.86–3.62)	.12

[a]Univariate Cox proportional hazards model. Exposure was modeled using low-risk medications as the reference group.
[b]Inverse probability weighting of a marginal structural Cox proportional model. Exposure was modeled using low-risk medications as the reference group.
[c]Composite secondary outcome was defined as myocardial infarction, stroke, peripheral artery disease, acute coronary syndrome, new revascularization procedure, or all-cause mortality.
Abbreviation: HR = hazard ratio.

Regarding the composite secondary outcome (all-cause mortality, myocardial infarction, stroke, peripheral artery disease, acute coronary disease, and new coronary revascularization), the hazard ratio for the high-risk group compared to the low-risk group was 1.31 (95% CI, 0.95–1.80), while the hazard ratio for intermediate-risk group versus the low-risk group was 1.46 (95% CI, 1.06–2.00) (Table 3). No apparent differences in time to all-cause mortality between groups were observed. Finally, only patients under treatment with high-risk medication presented with significantly more incident type 2 diabetes mellitus when compared to the low-risk group (adjusted hazard ratio = 3.29; 95% CI, 1.66–6.51).

DISCUSSION

The present study assessed the effect of initiating antipsychotic treatment on major cardiovascular events during long-term follow-up. We found an increased risk of major cardiovascular outcome presentations among those patients who started antipsychotic medications with an either intermediate or high risk of metabolic side effects. This finding appears to be mostly driven by the enhanced risk of stroke among our population, something that might be due to the high prevalence of patients with dementia in our sample or related to potential direct or indirect effects of antipsychotics.[34]

Our results agree with reports suggesting an increased risk of cardiovascular events with the use of quetiapine, risperidone, or olanzapine, although other studies[6,7,34,35] have shown inconsistent results. Most of the previous reports[4,16,31,36] on this subject informed their results on short-term outcomes probably reflecting the risk of sudden cardiac death and ventricular arrhythmias in the first weeks of treatment.[36] Conversely, we included events after a 6-month period so as to better evaluate the impact of antipsychotic medication on major cardiovascular events in a distinct fashion to overall toxicity related to initial treatment.

In addition, most of the previous studies[4,17,18,35] were nonexperimental, did not adequately control confounding by indication, and failed to classify the exposure according to the risk of developing metabolic abnormalities, thus blurring the implications on this matter with a potential mixture of effects. Our results may suggest that medications with distinct risk of inducing metabolic abnormalities may pose different overall cardiovascular risk during follow-up. However, we did not find differences between users of high- and intermediate-risk medication in the development of major cardiovascular events during follow-up, which might indicate that the difference in the induction of weight gain and metabolic abnormalities readily seen between these drugs does not necessarily imply differences in long-term cardiovascular morbidity. This observation is in keeping with the results of our mediation analysis. Moreover, this finding suggests the possibility that factors other than a metabolic side-effects profile might be involved in the development of cardiovascular events associated with the use of antipsychotics, which could be the focus of future studies. Finally, the fact that the great majority of patients experiencing cardiovascular events remained current users of antipsychotic drugs suggests that isolated past exposure to these drugs had no relevant impact in the results reported.

Notwithstanding this observation, the selection of the exposure as low, intermediate, or high risk instead of the usual typical versus atypical antipsychotic medication may prove useful in daily practice, where the particular effects (metabolic and other) of the drugs might drive the clinician's indication more than class itself. Likewise, findings in our study suggest that patients under long-term treatment with antipsychotics of intermediate or high risk (such as patients with schizophrenia or some patients with dementia or affective disorders) might need differential follow-up strategies and assessment, even in the absence of weight gain or metabolic syndrome.

On the other hand, no differences were found regarding all-cause mortality between antipsychotic groups. This result is in keeping with numerous epidemiologic studies[4,37] showing no major differences in all-cause mortality risk between distinct antipsychotics and may suggest that the net effect of metabolic abnormalities on major cardiovascular events induced by high- and intermediate-risk regimens

might be counterbalanced by other detrimental effects that low-risk drugs might have, such as bacterial infections, hip fractures, malignant neuroleptic syndrome, or exacerbations of preexisting congestive heart failure.[16,38,39] Furthermore, an important characteristic of our study is that we excluded patients that presented with recent events after antipsychotic medication initiation. So in fact, patients in our baseline, intermediate-, and high-risk groups may be considered as those that survived past the first months of treatment, the period in which most noncardiovascular toxicity has been previously reported. This was specifically done to evaluate separately the long-term cardiovascular impact but should certainly be taken into account when considering our results and evaluating the potential for toxicity of a specific medication.

Several limitations must be taken into consideration when interpreting the results of the present study. First, as our report relies on the use of electronic records information, the available data do not allow us to explicitly ascertain compliance. Second, given that allocation to treatment was nonrandomized, confounding by indication is warranted. Although we used robust methods to adjust for baseline imbalances with similar results when using different approaches, with sufficient data on a wide array of known cardiovascular risk factors and potential confounders, nonmeasured factors were not controlled for. For example, no data regarding cognitive status of patients were available other than dementia diagnosis at baseline, an absence possibly affecting the calculation of the propensity for treatment. Third, since our study included patients from only a single center in Argentina, the distribution of potential effect modifiers might be different from other populations, thus reducing the generalizability of our results. Finally, since included patients were older adults and most of them presented with a dementia diagnosis, generalization of these results to other populations may not be warranted.

In conclusion, patients who are prescribed antipsychotic medications considered to be of high or intermediate metabolic risk may face a higher risk of major cardiovascular outcomes during follow-up. Thus, the adequate control of major cardiovascular risk factors remains paramount. Our results warrant further confirmation and external validation.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Long-Term Antipsychotic Use and Major Cardiovascular Events: A Retrospective Cohort Study

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List of Supplementary Material for the article

Disclaimer

Long term antipsychotic use and major cardiovascular events: a retrospective cohort study

Supplementary appendix

Supplementary eTable 1. Side effect profile of selected antipsychotic medication

Medication	Weight gain	Lipids	Glucose	Other
High risk				
Olanzapine	+++	+++	+++	Sedation Hypotension CYP 1A2
Clozapine	+++	+++	+++	Agranulocitosis Myocarditis Lens opacities Sedation Hypotension CYP 1A2, 3A4, 2D6
Thioridazine	+++	++	++	QT prolongation Sedation Hypotension CYP 1A2, 2D6
Intermediate risk				
Quetiapine	++	+	+/-	Sedation CYP 3A4
Risperidone	++	+	+/-	Extrapiramidal effects CYP 2D6, 3A4
Low risk				
Haloperidol	+	-	-	QT prolongation Extrapiramidal effects CYP 3A4
Aripiprazole	+	-	-	CYP 2D6, 3A4
Ziprasidone	+	-	-	QT prolongation CYP 3A4
Trifluoperazine	+	-	-	Extrapiramidal effects
Levomepromazine	+	-	-	Sedation

Supplementary eTable 2. Participant follow-up and treatment information

	Low-Risk metabolic side effects (N=223)	Intermediate-risk metabolic side effects (N= 465)	High-risk metabolic side effects (N = 320)
Follow up information for primary outcome			
Median follow up time, months	39.0	33.0	41.5
Median survival time, months	NA	85	90
Incidence rate (events / 1000 person-year)	18.2	49.3	58.1

Supplementary eTable 3. Crude cumulative incidence of outcome measures in low, intermediate and high risk groups during study follow up.

Outcome - no. (%)	Low-risk group (N=223)	Intermediate-risk group (N= 465)	High-risk group (N = 320)	p value[1]
Myocardial infarction	4 (1.8)	14 (3.01)	16 (5.0)	0.11
Stroke	9 (4.0)	49 (10.5)	55 (17.2)	< 0.01
Peripheral artery disease	1 (0.5)	13 (2.8)	6 (1.9)	0.12
N-STEMI	6 (2.7)	11 (2.4)	15 (4.7)	0.17
CABG	0 (0.0)	1 (0.2)	4 (1.25)	0.06
All cause mortality	48 (21.5)	119 (25.6)	84 (26.3)	0.41
Diabetes	13 (5.8)	31 (6.7)	51 (15.9)	< 0.01
Weight gain*, BMI > 25 Kg/m^2	5 (2.4)	21 (4.9)	42 (14.8)	< 0.01

BMI: body mass index, N-STEMI: non ST elevation myocardial infarction, CABG: coronary artery bypass grafting.

1. Two sided p value, Chi squared test.

* N: low risk = 210, intermediate risk= 428, high risk = 284.

Supplementary eTable 4. Incidence rate ratios of suicide attempts and psychiatric hospitalizations during follow-up for high-, intermediate- and low-risk groups.

Main exposure	Incidence rate ratio (95% CI)[1]	p value[1]
Suicide attempts		
High risk of metabolic side effect antipsychotics	0.79 (0.38 - 1.81)	0.53
Intermediate risk of metabolic side effect antipsychotics	0.83 (0.38 - 1.81)	0.64
Psychiatric hospitalization		
High risk of metabolic side effect antipsychotics	1.07 (0.57 - 2.02)	0.83
Intermediate risk of metabolic side effect antipsychotics	1.36 (0.73 - 2.55)	0.33

1. P value based on Poisson regression with robust standard errors. Exposure modeled using low-risk group as baseline category.

Supplementary eTable 5. Crude and propensity score adjusted hazard ratios of primary composite outcome for main exposure

Main exposure	Crude HR (95% CI)[1]	Adjusted HR (95% CI)[2]		
		Overall	< 2 years from baseline	< 5 years from baseline
High risk of metabolic side effect antipsychotics	3.08 (1.85 - 5.11)	3.14 (1.87 - 5.26)	2.87 (1.06 - 7.78)	2.55 (1.43 - 4.56)
Intermediate risk of metabolic side effect antipsychotics	3.17 (1.90 - 5.29)	2.75 (1.62 - 4.65)	2.38 (0.89 - 6.35)	2.13 (1.20 - 3.78)

Abbreviations: HR: Hazard ratio, 95% CI: 95% confidence interval.
Primary composite outcome: myocardial infarction, stroke, peripheral artery disease, acute coronary syndrome or new revascularization procedure.
1. Univariate Cox proportional hazards model with exact method for ties. Exposure was modeled using low-risk medications as the reference group
2. Multivariate Cox proportional hazards model including main exposure and propensity score as regression splines. Exposure was modeled using low-risk medications as the reference group

Supplementary eTable 6. Crude and propensity score adjusted hazard ratios of secondary outcomes for main exposure

Main exposure	Crude HR (95% CI)	p value[1]	Adjusted HR (95% CI)	p value[2]
Composite secondary outcome				
High risk of metabolic side effects	1.48 (1.10 - 1.99)	0.01	1.41 (1.04 - 1.92)	0.03
Intermediate risk of side effects	1.91 (1.42 - 2.57)	< 0.01	1.55 (1.14 - 2.11)	< 0.01
All cause mortality				
High risk of metabolic side effects	1.04 (0.73 - 1.49)	0.81	0.95 (0.66 - 1.37)	0.78
Intermediate risk of side effects	1.72 (1.22 - 2.41)	< 0.01	1.32 (0.93 - 1.89)	0.13
Incident type 2 diabetes				
High risk of metabolic side effects	2.85 (1.55 - 5.24)	< 0.01	2.76 (1.45 - 5.25)	< 0.01
Intermediate risk of side effects	1.44 (0.75 - 2.76)	0.27	1.33 (0.67 - 2.66)	0.41

Abbreviations: HR: Hazard ratio, 95% CI: 95% confidence interval.
Composite secondary outcome: myocardial infarction, stroke, peripheral artery disease, acute coronary syndrome, new revascularization procedure and all cause mortality.
1. Univariate Cox proportional hazards model. Exposure was modeled using low-risk medications as the reference group
2. Multivariate Cox proportional hazards model including main exposure and propensity score as regression splines. Exposure was modeled using low-risk medications as the reference group

Supplementary eTable 7. Sensitivity analysis excluding patients under combination therapy

Main exposure	Crude HR (95% CI)[1]	Adjusted HR (95% CI)[2]		
		Overall	< 2 years from baseline	< 5 years from baseline
High risk of metabolic side effect antipsychotics	2.79 (1.67 - 4.67)	2.61 (1.44 - 4.71)	2.48 (0.79 - 7.79)	2.03 (1.07 - 3.87)
Intermediate risk of metabolic side effect antipsychotics	3.18 (1.91 - 5.31)	2.59 (1.43 - 4.69)	2.07 (0.71 - 6.07)	1.89 (1.02 - 3.51)

Abbreviations: HR: Hazard ratio, 95% CI: 95% confidence interval.
Primary composite outcome: myocardial infarction, stroke, peripheral artery disease, acute coronary syndrome or new revascularization procedure.
1. Univariate cox proportional hazards model. Exposure was modeled using low-risk medications as the reference group
2. Inverse probability weighting of a marginal structural cox model. Exposure was modeled using low-risk medications as the reference group

Supplementary eTable 8. Hazards ratio of major cardiovascular events during follow up for high and low risk antipsychotic medication

Main exposure	Crude HR (95% CI)[1]	Adjusted HR (95% CI)[2]		
		Overall	< 2 years from baseline	< 5 years from baseline
High risk of metabolic side effect antipsychotics	1.61 (1.20 - 2.15)	1.57 (1.17 - 2.12)	1.85 (1.05 - 3.27)	1.61 (1.14 - 2.27)

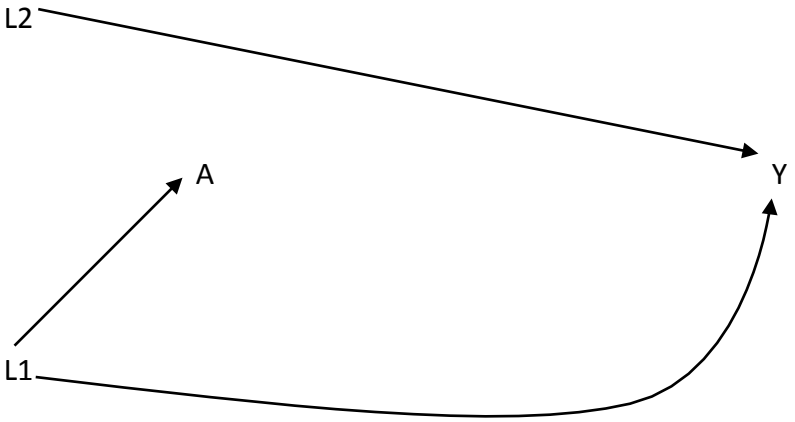
Abbreviations: HR: Hazard ratio, 95% CI: 95% confidence interval.
Primary composite outcome: myocardial infarction, stroke, peripheral artery disease, acute coronary syndrome or new revascularization procedure.
1. Univariate Cox proportional hazards model. Exposure modeled using low-risk group as baseline category
2. Inverse probability weighting of a marginal structural cox proportional model. Exposure modeled using low-risk group as baseline category

Supplementary eTable9. Hazards ratio of major cardiovascular events during follow up for high, intermediate and low risk antipsychotic medication including antipsychotic dose as a covariate.

Main exposure	Crude HR (95% CI)[1]	Adjusted HR (95% CI)[2]		
		Overall	< 2 years from baseline	< 5 years from baseline
High risk of metabolic side effect antipsychotics	3.05 (1.84 - 5.06)	2.67 (1.49 - 4.79)	2.50 (0.82 - 7.64)	2.12 (1.13 - 3.98)
Intermediate risk of metabolic side effect antipsychotics	3.15 (1.89 - 5.24)	2.57 (1.43 - 4.65)	2.11 (0.72 - 6.23)	1.91 (1.03 - 3.54)

Abbreviations: HR: Hazard ratio, 95% CI: 95% confidence interval.
Primary composite outcome: myocardial infarction, stroke, peripheral artery disease, acute coronary syndrome or new revascularization procedure.
1. Univariate Cox proportional hazards model. Exposure was modeled using low-risk medications as the reference group.
2. Inverse probability weighting of a marginal structural cox proportional model. Exposure was modeled using low-risk medications as the reference group.

Supplementary eFigure 1. Acyclic graph under the null (potential confounders included in propensity score calculation)



The figure represents the structural relationship of measured covariates in the setting of the present study. A represents the main exposure and Y the primary outcome. L1 and L2 are vectors of measured covariates. The relationships depicted are under the null since no a-priori relationship between A and Y is present.

Reference:

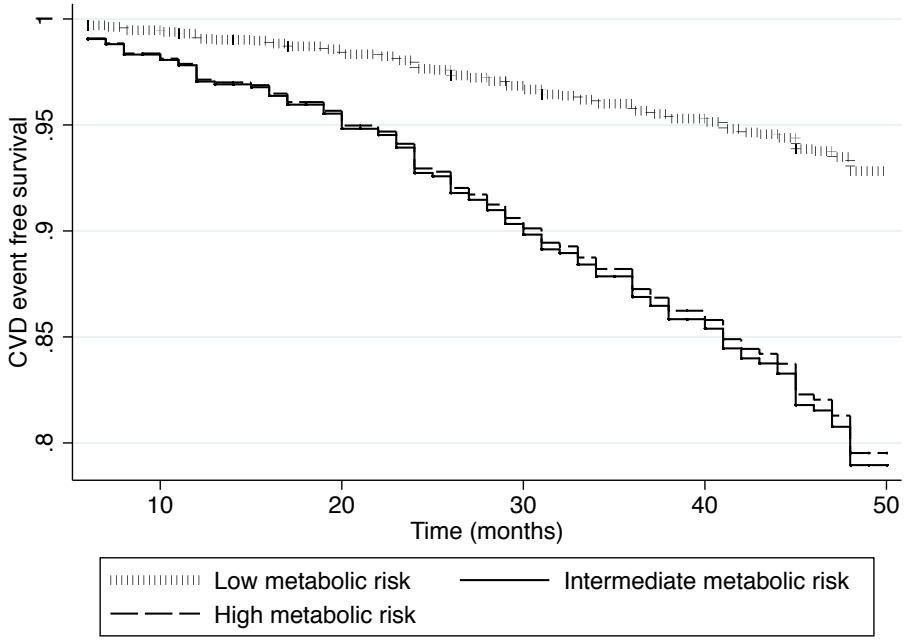
A: Antipsychotic treatment

Y: Major cardiovascular events

L1: age, nursing home, chronic heart failure, previous myocardial infarction, gender, baseline diabetes, previous stroke, previous arrhythmia, dementia, renal failure, statin use, cholinesterase inhibitors, treatment with antidepressants

L2: chronic obstructive pulmonary disease, smoking status, systolic blood pressure, aspirin/clopidogrel, steroids.

Supplementary eFigure 2. Estimated proportion of patients free of major cardiovascular events under either high, intermediate or low metabolic risk exposures[1].



Abbreviations: CVD: cardiovascular disease

Major cardiovascular events: composite of myocardial infarction, stroke, peripheral arterial disease or new revascularization procedure.

1. Multivariate proportional hazards model including propensity score as regression splines.

Supplementary eFigure 3. Estimated cumulative survival for high- and low-risk medication groups.